



Multicomponent reactions

Edited by Thomas J. J. Müller

Imprint

Beilstein Journal of Organic Chemistry
www.bjoc.org
ISSN 1860-5397
Email: journals-support@beilstein-institut.de

The *Beilstein Journal of Organic Chemistry* is published by the Beilstein-Institut zur Förderung der Chemischen Wissenschaften.

Beilstein-Institut zur Förderung der
Chemischen Wissenschaften
Trakehner Straße 7–9
60487 Frankfurt am Main
Germany
www.beilstein-institut.de

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Multicomponent reactions

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Editorial

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Beilstein J. Org. Chem. **2011**, 7, 960–961.
doi:10.3762/bjoc.7.107

Received: 11 July 2011
Accepted: 11 July 2011
Published: 13 July 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Chemistry as a central science is facing a steadily increasing demand for new chemical entities (NCE). Innovative solutions, in all kinds of disciplines that depend on chemistry, require new molecules with specific properties, and their societal consequences are fundamental and pioneering. However, NCE not only demand a realistic structural space but also their feasibility poses challenges to synthetic chemists. Nowadays the question of how to perform a synthesis has become most crucial.

What is the ideal synthesis [1,2]? Certainly it should be simultaneously simple, safe, short, selective, high yielding, environmentally benign, based on readily available starting materials, and highly diverse. Additionally, the criterion of selectivity has to be matched with increasing significance economical and ecological aspects. In particular multicomponent reactions (MCR) [3] are masterpieces of synthetic efficiency and reaction design. These one-pot processes consist of concatenations of elementary organic reactions under similar conditions. Most interestingly, multicomponent reactions have accompanied the field of organic chemistry since the early days, particularly in heterocyclic chemistry, but have not been recognized as a fundamental principle until Ugi's groundbreaking extension of the Passerini reaction and the conclusions he drew from this.

Now the major conceptual challenge comprises the engineering of novel types of MCR. Most advantageously and practically, MCR can often be extended into combinatorial, solid phase or flow syntheses promising manifold opportunities for developing novel lead structures of active agents, catalysts and even novel molecule-based materials.

This Thematic Series on multicomponent reactions represents a snapshot of a highly dynamic field and spans a broad range, from recent advances in isonitrile-based MCR to transition metal catalysis in MCR; from peptidic and depsi-peptidic to heterocyclic structures; from reactivity-based to property-based concepts. The sympathetic reader, expert or newcomer, will find a tremendous degree of dynamic and exciting new results in this compilation of multicomponent reaction chemistry.

As the guest editor of this Thematic Series I am very grateful to all authors for their excellent contributions and, in particular, to the staff of the Beilstein-Institut for their support and professional realization.

Thomas J. J. Müller

Düsseldorf, July 2011

References

1. Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 765, 767–769.
2. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, 75, 4657–4673.
doi:10.1021/jo1006812
3. Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.

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[doi:10.3762/bjoc.7.107](https://doi.org/10.3762/bjoc.7.107)

A practical two-step procedure for the preparation of enantiopure pyridines: Multicomponent reactions of alkoxyallenes, nitriles and carboxylic acids followed by a cyclocondensation reaction

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Full Research Paper

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Keywords:
allenes; enantiopure pyridines; ketoenamides; multicomponent
reactions; nonaflates

Beilstein J. Org. Chem. **2011**, *7*, 962–975.
doi:10.3762/bjoc.7.108

Received: 07 March 2011
Accepted: 06 June 2011
Published: 13 July 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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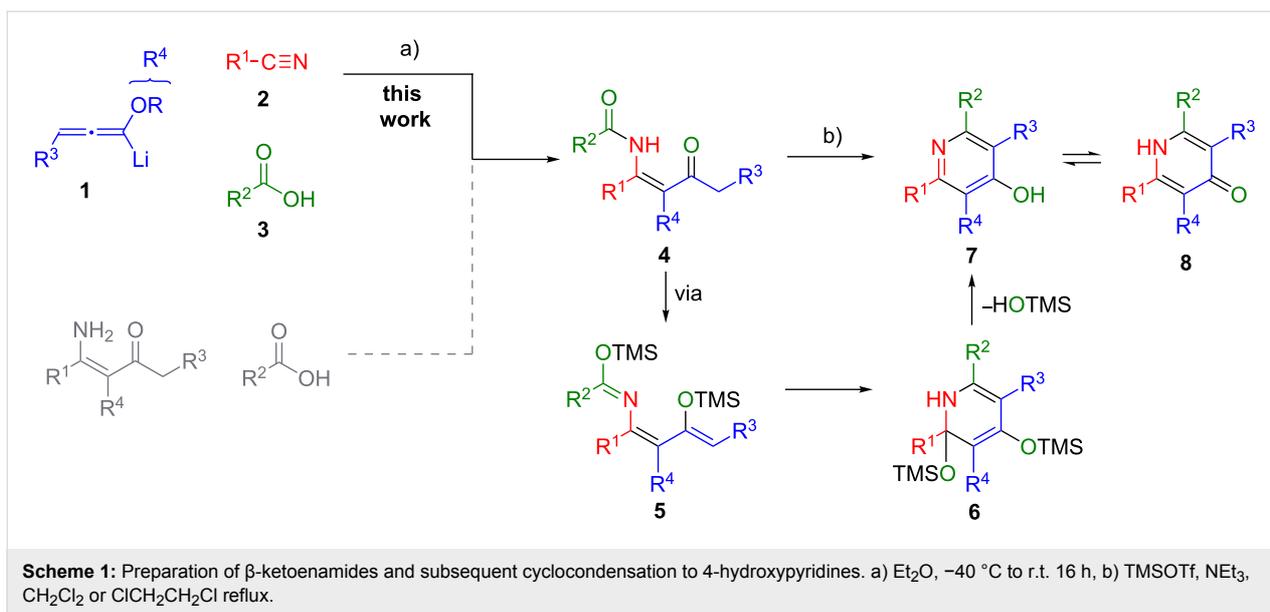
Abstract

A practical approach to highly functionalized 4-hydroxypyridine derivatives with stereogenic side chains in the 2- and 6-positions is described. The presented two-step process utilizes a multicomponent reaction of alkoxyallenes, nitriles and carboxylic acids to provide β -methoxy- β -ketoenamides which are transformed into 4-hydroxypyridines in a subsequent cyclocondensation. The process shows broad substrate scope and leads to differentially substituted enantiopure pyridines in good to moderate yields. The preparation of diverse substituted lactic acid derived pyrid-4-yl nonaflates is described. Additional evidence for the postulated mechanism of the multicomponent reaction is presented.

Introduction

The pyridine core is ubiquitous in pharmacologically active agents, agrochemicals and natural products [1-5]. The HMG-CoA reductase inhibitors Glenvastatin and Cerivastatin are exemplarily mentioned as pharmaceuticals that feature the pyridine nucleus [6-10]. Natural products that contain a pyridine ring include the 3-alkylpyridine alkaloid niphatesine C and the fuzanin family [11,12]. Moreover, the ability to form coordina-

tion compounds makes pyridines ideal ligands for transition metal-catalyzed processes and for the construction of supramolecular architectures [13]. Pyridines with chiral side chains are widely employed as ligands in asymmetric transformations, for instance, in the asymmetric hydrogenation of olefins, in enantioselective additions of metal organyls to aldehydes and enones, as well as in palladium-catalyzed allylic substitution



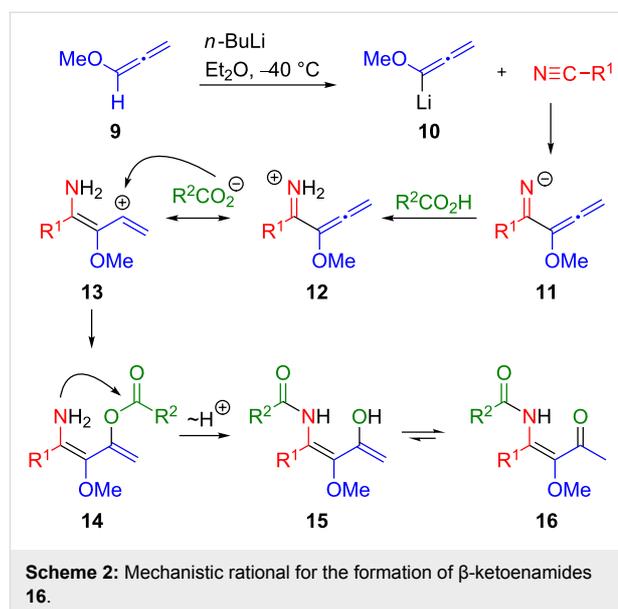
reactions [14–20]. Thus, the synthesis of specifically functionalized pyridines is of considerable interest, and many approaches toward this heterocyclic structure have been disclosed in the literature [21]. In addition to classical pyridine syntheses such as the Kröhnke reaction, many new approaches have recently been developed [22–26]. Despite the wide range of conceptually different syntheses, only few methods for introducing chirality into pyridine side chains have been described: Enantioselective reduction of pyridine carbonyl compounds, the addition of lithiated pyridine derivatives to chiral ketones or the resolution of racemates being the most common approaches. The preparation of chiral pyridine derivatives starting from simple enantiopure precursors is less common [27,28].

Recently, we reported a new synthesis of pyridines based on the trimethylsilyl trifluoromethanesulfonate (TMSOTf) induced cyclocondensation reaction of β -ketoenamides [29–34]. This cyclocondensation step can be rationalized as a 6π -electrocyclization of the disilylated intermediate **5** to provide dihydropyridine **6**. Elimination of trimethylsilanol and subsequent *O*-desilylation affords the 4-hydroxypyridine **7** (Scheme 1). The desired β -ketoenamides **4** are either accessible by acylation of enaminoketones or by a multicomponent reaction of lithiated alkoxyallenes, nitriles and carboxylic acids [35,36].

In the past, we devoted considerable interest to the synthesis of substituted pyridine derivatives by this route and investigated their use in subsequent transformations [37–39]. Broadening the scope of the process to functionalized, chiral starting materials is the subject of this report. Additionally, herein we disclose the full experimental data for compounds reported in a preliminary communication [40].

Results and Discussion

In continuation of our previous work, we addressed the question whether chiral starting materials react in the above sequence without loss of enantiopurity [40]. Chiral carboxylic acids are readily available and their use would allow for a rapid access to pyridines with side chains bearing stereogenic centers. In recent years we studied intensively the multicomponent reactions of lithiated alkoxyallenes with nitriles and carboxylic acids and could demonstrate that precursor compounds with alkyl, alkenyl or aryl substituents are smoothly converted into β -ketoenamides and subsequently transformed into the desired 4-hydroxypyridines. The mechanism of the multicomponent reaction is depicted in Scheme 2. In the first step, a lithiated



alkoxyallene such as **10** adds to a nitrile to yield an imino-allenyl anion **11**. Protonation of **11** then gives a resonance stabilized cation **12** which can be attacked in β -position by a carboxylate to afford an enol ester **14**. The β -ketoenamide **16** is then formed by transfer of the acyl group to the amino group and subsequent tautomerization.

In some cases we observed the formation of minor amounts of 4-hydroxypyridines along with the β -ketoenamides. Depending on the substitution pattern of the β -ketoenamide, a condensation to the corresponding pyridine can spontaneously occur. In most cases a second step is necessary and the cyclocondensation must be induced or completed by treatment with TMSOTf and an amine base in a suitable solvents at elevated temperatures. In order to minimize the operational effort, the process can be performed as quasi-one-pot procedure without purification of the intermediary β -ketoenamide.

Scope and limitations

Following the protocol mentioned before, we successfully prepared a series of 4-hydroxypyridines with chiral functional groups present in a side chain. As can be seen in Table 1 not merely chiral aliphatic carboxylic acids and nitriles such as **17** and **31** can be transformed into 4-hydroxypyridines, but rather complex substrates with appropriately protected functional groups. For instance, when lithiated methoxyallene was added to pivalonitrile and reacted with *O*-silylated mandelic acid **21**, pyridine derivative **22** was obtained in good yield over two steps. Furthermore, readily available *N,N*-dibenzylated amino acids, such as those derived from valine and phenylalanine, **23** and **25** gave the respective pyridines **24** and **26** in 45% and 50% yield, respectively. Carboxylic acids featuring aromatic units and branched side chains including quaternary α -carbon atoms were also tolerated. Besides chiral carboxylic acids, enantiopure nitriles were also successfully converted into pyridine

Table 1: Scope of the synthesis of 4-hydroxypyridine derivatives from lithiated methoxyallene, nitriles and carboxylic acids.

Carboxylic Acid R ² CO ₂ H	Nitrile R ¹ -CN	Product ^a	Yield ^b
 17		 18	24%
 19		 20	30%
 21		 22	50%

Table 1: Scope of the synthesis of 4-hydroxypyridine derivatives from lithiated methoxyallene, nitriles and carboxylic acids. (continued)

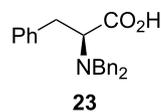
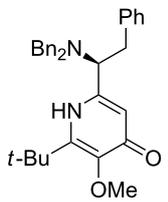
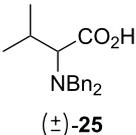
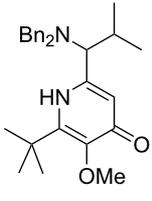
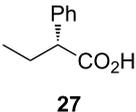
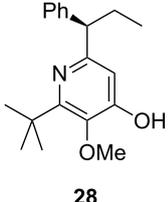
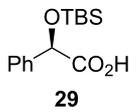
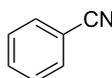
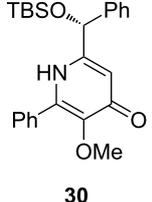
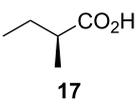
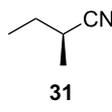
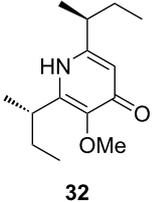
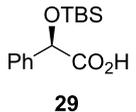
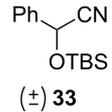
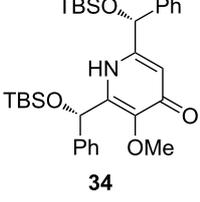
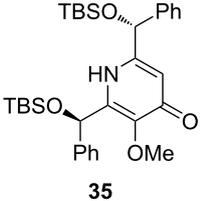
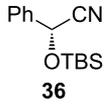
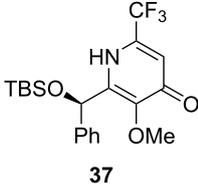
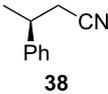
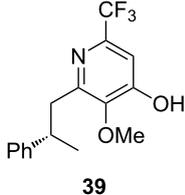
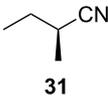
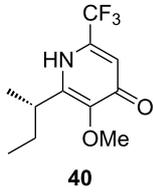
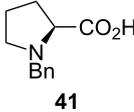
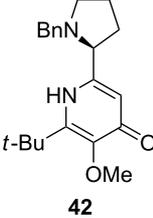
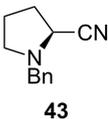
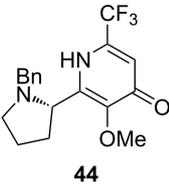
 <p>23</p>		 <p>24</p>	45%
 <p>(±)-25</p>		 <p>(±)-26</p>	50%
 <p>27</p>		 <p>28</p>	45%
 <p>29</p>		 <p>30</p>	24%
 <p>17</p>	 <p>31</p>	 <p>32</p>	85%
 <p>29</p>	 <p>(±) 33</p>	 <p>34</p>	26% (as a separable 1:1 mixture of diastereomers)
		 <p>35</p>	

Table 1: Scope of the synthesis of 4-hydroxypyridine derivatives from lithiated methoxyallene, nitriles and carboxylic acids. (continued)

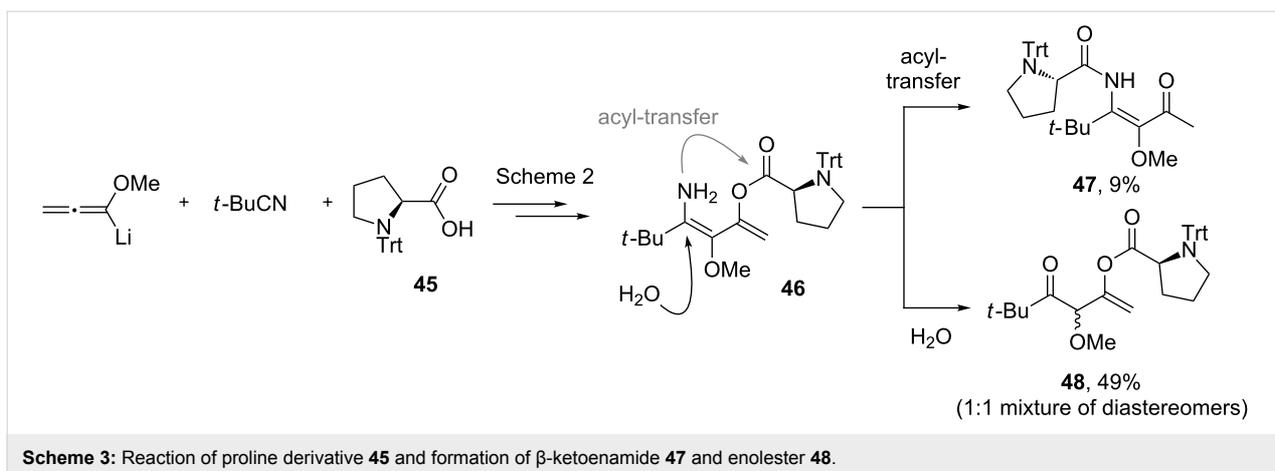
CF ₃ CO ₂ H			37%
CF ₃ CO ₂ H			28%
CF ₃ CO ₂ H			56%
			–
CF ₃ CO ₂ H			–

^aOnly the predominant tautomer in CDCl₃ is depicted; ^bAll yields are based on the nitrile.

derivatives in comparable yields. As an example, (*S*)-2-methylbutyronitrile (**31**) could be converted into compound **40** in good yield. The use of carboxylic acids and nitriles with structurally identical substituents allows a rapid access to pyridine derivatives such as **32** which almost has C₂-symmetry. Compound **32** is derived from nitrile **31** and carboxylic acid **17** and was obtained in high yield after two steps. Products **34** and **35** were prepared from enantiopure acid **29** and racemic *O*-TBS-mandelonitrile **33**. The diastereomeric pyridines obtained from this reaction are easily separable by column chromatography to give **34** and **35** in moderate yields. If not commercially available, the desired nitriles were prepared from the corresponding acids by an amide formation/dehydration sequence according to literature procedures [41,42]. Not all transformations proceeded in

very good yields, however, it should be noted that in only a few cases attempts to optimize the conditions have been undertaken. Hence, there may be room for improvement of yields in cases where the standard conditions led only to moderate yields.

Unfortunately, all attempts to incorporate proline-derived moieties failed. *N*-Benzylproline (**41**) turned out to be almost insoluble in ethereal solvents, which might explain why the desired β -ketoenamide was not formed [43]. To increase the solubility of the proline component, we changed the protective group from benzyl to the more lipophilic trityl group [44]. Surprisingly, the use of trityl-protected proline did not give the β -ketoenamide **47** as main product (Scheme 3). Instead, a diastereomeric 1:1 mixture of the β -keto-enolester **48** was



isolated in 49% yield together with minor amounts of the expected product **47**. The formation of **48** is additional evidence for our previously suggested mechanism (Scheme 2). We assume that the bulkiness of the trityl group hampers the transfer of the acyl group from intermediate **46** to **47**. Upon the addition of water, the enamine moiety of **46** was hydrolyzed to furnish enol ester **48**.

The pyridines in Table 1 are depicted in their predominant tautomeric form as found in CDCl_3 at ambient temperature. Interestingly, the pyridone/pyridinol equilibrium seems to depend on the substituents at the C-2 or C-6 side chains. In general, a hydrogen bond-acceptor seems to stabilize the pyridone tautomer, whereas the pyridinol tautomer is favored when a hydrogen bond-donor is present. Compound **37** exists exclusively as pyridone tautomer, but after desilylation the resulting product, with a free hydroxy group in the side chain, strongly prefers the pyridinol tautomer. It seems reasonable to assume that the pyridone tautomer is stabilized through an internal hydrogen bond between a silyl ether or a tertiary amine moiety of the side chain as observed for compounds **22** and **24**. Moreover, we found that the equilibrium is strongly influenced by the solvent. In CDCl_3 pyridine **40** exclusively exists in its pyridone form, but in methanol- d_4 the equilibrium shifts completely to the pyridinol tautomer.

Subsequent transformations of the prepared pyridine derivatives

To prove the enantiopurity of the pyridines derived from carboxylic acids and nitriles, which are prone to racemization, i.e., substrates with tertiary stereogenic centers in α -position, compounds **18**, **22** and **40** were transformed into esters **50**, **49** and **51**, respectively (Table 2). Treatment of the pyridones with Mosher acid chloride in a mixture of pyridine and dichloromethane as solvent afforded the desired esters in good yields. Comparison with the diastereomeric compounds

Table 2: Esterification of different pyridinol derivatives with the 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid.

Pyridine	Product	Yield
 22	 49	68% dr >95:5 ^a
 18	 50	55% dr >95:5 ^a
 40	 51	67% dr >95:5 ^a

^aDetermined by ^1H NMR spectroscopic analysis of the crude products.

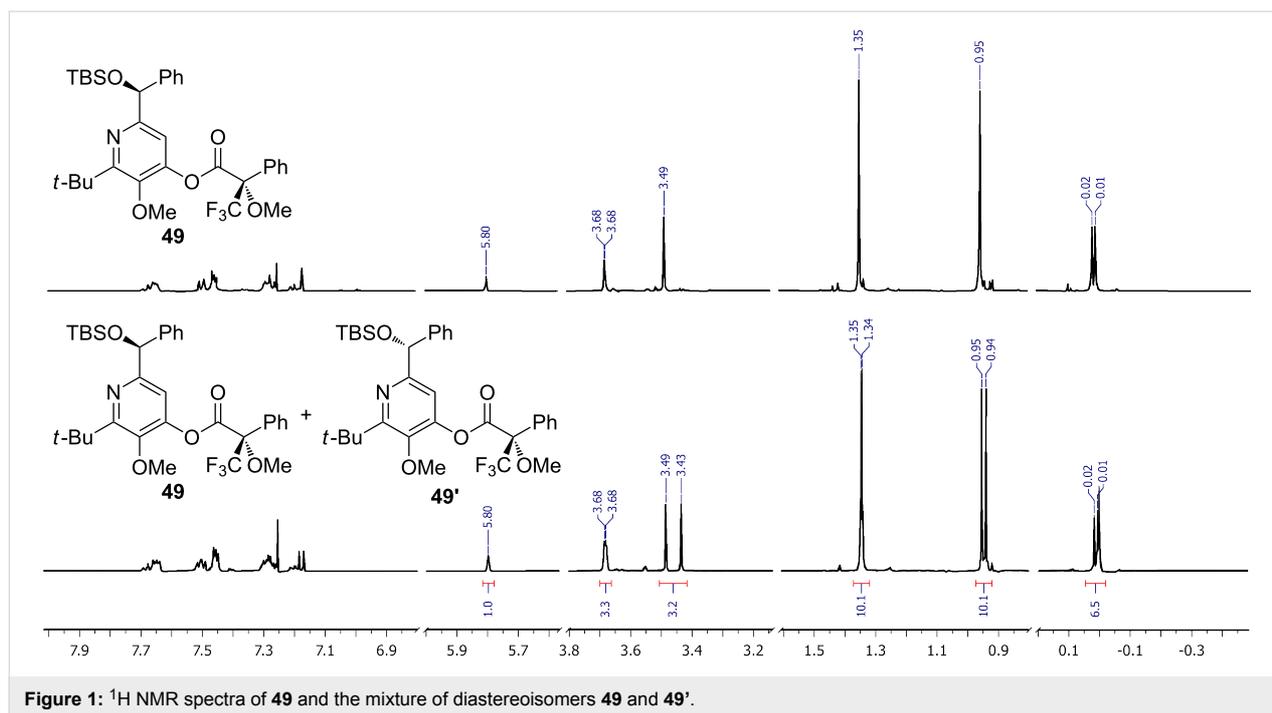
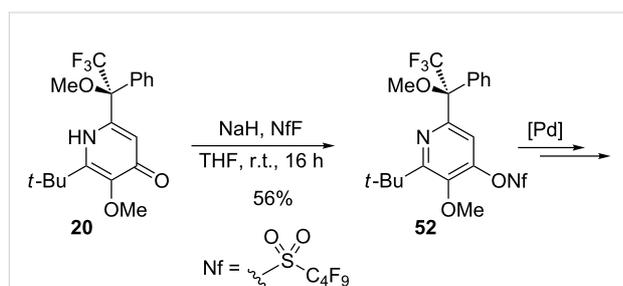


Figure 1: ^1H NMR spectra of **49** and the mixture of diastereoisomers **49** and **49'**.

obtained from racemic starting materials unambiguously shows that the sequence proceeds without noticeable racemization, since **49**, **50** and **51** were obtained in diastereomeric pure form (Table 2) as judged by ^1H NMR analysis (estimated error 3–5%). For instance, the signal of the methoxy group at C-3 of diastereomeric **49'** (obtained by starting with racemic mandelic acid) appears at 3.43 ppm in the ^1H NMR-spectrum, whereas this signal for **49** occurs at 3.49 ppm (Figure 1). In addition, the *tert*-butyl group of the OTBS groups of the two diastereoisomers **49** and **49'** show signals at different frequencies.

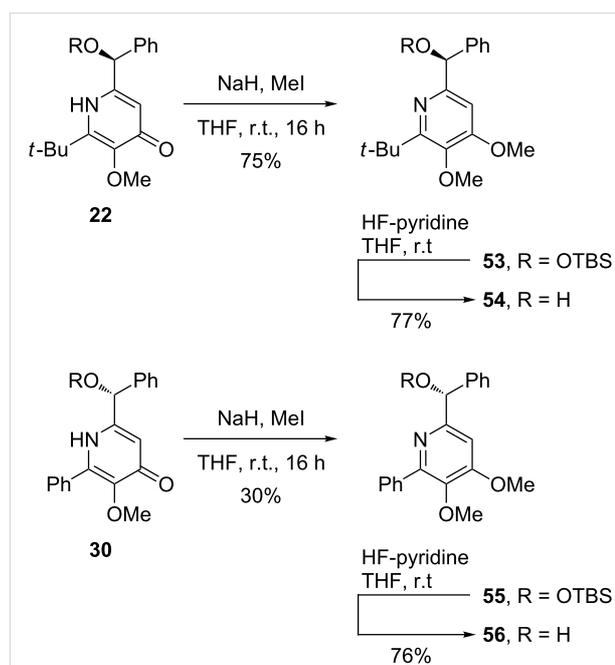
To explore the chemistry of the synthesized pyridine derivatives, we investigated the selective functionalization of the 4-hydroxy group. Pyridone **20** was nonaflated according to previously established conditions to provide **52** in 56% yield (Scheme 4). As we have already demonstrated, pyrid-4-yl nonaflates are excellent coupling partners in palladium-



Scheme 4: Synthesis of pyrid-4-yl nonaflate **52**.

catalyzed transformations such as Suzuki, Stille, Heck and Sonogashira reactions [45].

However, in contrast to the smooth nonaflation, the selective *O*-alkylation of the synthesized pyridines turned out to be more challenging (Scheme 5). Whereas pyridone **22** could be



Scheme 5: *O*-Methylation of pyridine derivatives **22** and **30** followed by desilylation.

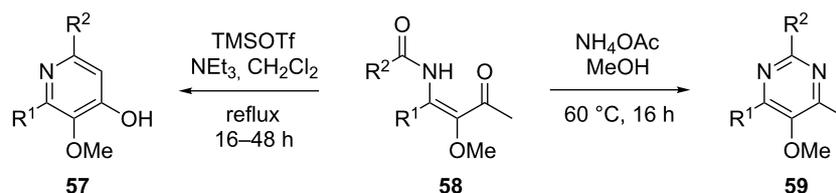
O-methylated in good yield with methyl iodide in THF, the same conditions converted **30** into **55** in a disappointing 30% yield. Desilylation of **53** and **55** with HF in pyridine gave the desired deprotected pyridine derivatives **54** and **56** in high yields. This type of enantiopure hydroxymethyl-substituted pyridine derivatives is of particular interest as they are known to be efficient catalysts for the asymmetric addition of zinc organyls to aldehydes [14,46].

Preparation of lactic acid derived pyrid-4-yl nonaflates

In the course of our investigations on the scope of the present procedure, we also discovered that easily available *O*-TBS-protected lactic acid and *O*-TBS-protected lactic nitrile are excellent reaction partners. We became interested in exploring the scope of this reaction with respect to lactic acid derived starting materials in more detail. In contrast to the previously described procedures, we decided to purify the reaction mixture

at the stage of the β -alkoxy- β -ketoenamides **58** obtained by the three-component reaction. Recently we demonstrated that β -alkoxy- β -ketoenamides are not only valuable intermediates in the synthesis of 4-hydroxypyridines **57**, but that they can also serve as precursors in the synthesis of 5-alkoxypyrimidines **59** (Scheme 6). When β -alkoxy- β -ketoenamides **58** were treated with an ammonia source such as NH₄OAc in MeOH, 5-alkoxypyrimidines with the general structure of **59** were formed in high yields [37,38,47]. By this simple change in the reaction conditions not only pyridine but also pyrimidine derivatives with lactic acid based side chains should be accessible.

O-TBS-protected lactic nitrile **63** was prepared following a literature procedure in four steps starting from enantiopure methyl lactate [48]. The scope of the multicomponent reaction with respect to lactic acid derived precursors is summarized in Table 3.



Scheme 6: Formation of 5-alkoxypyrimidines from β -alkoxy- β -ketoenamides.

Table 3: Scope of the synthesis of β -alkoxy- β -ketoenamides derived from lactic acid based precursors.

Carboxylic Acid R ² CO ₂ H	Nitrile R ¹ -CN	Product	Yield
 60		 61	58%
 60		 62	58%

Table 3: Scope of the synthesis of β -alkoxy- β -ketoenamides derived from lactic acid based precursors. (continued)

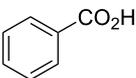
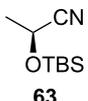
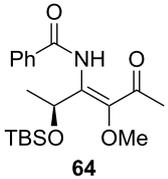
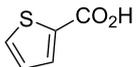
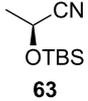
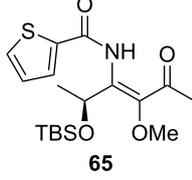
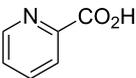
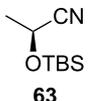
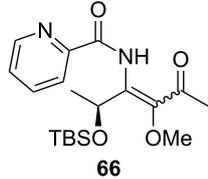
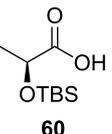
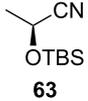
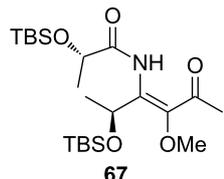
			73%
			73%
			51%
			25%

Table 3 shows that *O*-TBS-protected lactic acid **60** and *O*-TBS-protected lactic nitrile **63** gave the desired ketoenamides in moderate to high yields. When lithiated methoxyallene was reacted with pivalonitrile or benzonitrile followed by the addition of *O*-TBS-protected lactic acid, the corresponding ketoenamides **61** and **62** were isolated in 58% yield. Reaction of lithiated methoxyallene with *O*-TBS-protected lactic nitrile and benzoic acid furnished **64** in high yield. Heterocyclic moieties were also well tolerated as demonstrated by the efficient reaction of 2-thiophene carboxylic acid. The relatively low yield in the formation of **66** might be explained by the poor solubility of 2-picolinic acid in ethereal solvents rather than for reactivity reasons. In contrast to the other examples, enamide **66** was obtained as a 1:1 mixture of (*E*)- and (*Z*)-isomers. This may be due to alternative hydrogen bond formation with the NH unit to the pyridine nitrogen rather than to the carbonyl group. Subsequent cyclocondensation with TMSOTf and NEt₃ in 1,2-dichloroethane gave the expected pyridine derivatives, which were directly converted into pyrid-4-yl nonaflates in a second step. The results are depicted in Table 4.

In all examples the cyclization/nonaflation sequence provided the pyrid-4-yl nonaflates in good yields. Apparently, the reactivity in this sequence is not strongly governed by the struc-

ture of the original ketoenamide. Even the configuration of the enamide double bond seems to have no influence on the cyclization, since the (*E/Z*)-mixture of enamide **66** also gave the corresponding pyridine in good yield. Obviously, the diastereomers are in equilibrium under the cyclization conditions. Of particular interest are the pyrid-4-yl nonaflates **71** and **72**, possessing a chiral side chain as well as heteroaromatic units. 2,2'-Bipyridines with structures similar to **72** might show interesting properties when used as ligands in asymmetric transformations. The nonaflate moiety should allow electronic fine tuning of the ligand properties in palladium-catalyzed or nucleophilic substitution reactions.

Conclusion

We have demonstrated that enantiopure functionalized carboxylic acids and nitriles can be used without problems in our previously reported pyridine synthesis. The starting materials were successfully transformed into the corresponding pyridines without loss of enantiopurity to yield enantiopure 4-hydroxypyridine derivatives with stereogenic side chains at C-2 and C-6. The 4-hydroxy group allows further variations. Applications of the prepared pyridines as ligands or catalysts in asymmetric transformations will be studied and will be the subject of future reports.

Table 4: Cyclization and nonaflation of lactic acid derived β -alkoxy- β -ketoenamides.

β -Alkoxy- β -ketoenamide	Product	Yield ^a
 61	 68	56%
 62	 69	61%
 64	 70	63%
 65	 71	52%
 66	 72	72%
 67	 73	39%

^aYields over two steps based on the ketoenamide.

Experimental

General methods: Reactions were generally performed under an argon atmosphere in flame-dried flasks, and the components were added by syringe. Methanol was purchased in p.a. quality and stored under an argon atmosphere over molecular sieves (4 Å). Triethylamine was distilled from CaH₂ and stored over KOH under an atmosphere of argon. Pyridine was used as purchased and stored over KOH under an atmosphere of argon. 1,2-Dichloroethane was purchased in p.a. quality and stored over molecular sieves (4 Å) under an atmosphere of argon. Tetrahydrofuran, diethyl ether, toluene and dichloromethane were obtained from the solvent purification system MB-SPS-800 (M. Braun). Products were purified by flash chromatography on silica gel (230–400 mesh, Merck). Unless otherwise stated, yields refer to analytically pure samples. Internal standards: for ¹H NMR CDCl₃ (δ = 7.26 ppm), TMS (δ = 0.00 ppm), CD₃OD (δ = 3.31 ppm), C₆D₆ (δ = 7.16 ppm), for ¹³C NMR CDCl₃ (δ = 77.0 ppm), CD₃OD (δ = 49.0 ppm), C₆D₆ (δ = 128.1 ppm). NMR spectra were recorded on Bruker AC 250, ECP 400, AC 500, AVIII 700, or Jeol Eclipse 500 instruments in CDCl₃, CD₃OD, or C₆D₆ solution. Integrals are in accord with assignments; coupling constants are given in Hz. IR spectra were measured with a FT-IR spectrometer Nicolet 5 SXC or with a Nexus FT-IR equipped with a Nicolet Smart DuraSampIR ATR. MS and HRMS analyses were obtained with Finnigan Varian Ionspec QFT-7 (ESI-FT-ICR) and Agilent ESI-TOF 6210 (4 μL/min, 1 bar, 4000 V) instruments. Elemental analyses were obtained with “Elemental-Analyzers” (Perkin–Elmer or Carlo Erba). Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected. Optical rotations ([α]_D) were determined with a Perkin–Elmer 241 polarimeter at the temperatures given. Commercially available chemicals were used without further purification unless otherwise stated.

Typical procedure for the preparation of 3-methoxy-4-hydroxypyridines without isolation of the intermediate β-alkoxy-β-keto-enamide (Procedure 1)

A solution of *n*-BuLi (2.5 M in hexanes, 0.31 mL, 0.79 mmol) was added dropwise to a solution of methoxyallene (59 μL, 0.71 mmol) in diethyl ether (5 mL) at –40 °C. After stirring at that temperature for 15 min, pivalonitrile was added (59 mg, 0.71 mmol) and the resulting yellow solution stirred for 4 h at –40 °C. The solution was then cooled to –78 °C and (*S*)-2-methylbutyric acid (0.23 mL, 2.14 mmol) added. Stirring was continued overnight during which time the mixture was slowly allowed to reach r.t. The reaction was quenched by the addition of sat. aq. NaHCO₃ solution (10 mL) and the aqueous phase extracted with diethyl ether (2 × 20 mL). The combined organic

layers were washed with brine, dried with Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The residue was re-dissolved in CH₂Cl₂ (14 mL) and TMSOTf (0.41 mL, 2.1 mmol) and NEt₃ (0.30 mL, 2.1 mmol) were added. The mixture was heated under reflux under an atmosphere of argon for 2 d. After complete consumption of the starting material (by TLC), the reaction was quenched by the addition of aq. sat. NH₄Cl solution (20 mL) and the aqueous layer extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layers were dried with Na₂SO₄, filtered and evaporated. The residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 1:9) to afford **18** (41 mg, 24%) as colorless crystals.

(*S*)-6-*sec*-Butyl-2-*tert*-butyl-3-methoxypyridin-4-one (18**):** mp 109–110 °C; [α]_D²² +20.9 (*c* 2.3, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.90 (t, *J* ≈ 7 Hz, 3H, 4'-H), 1.24 (d, *J* = 6.9 Hz, 3H, 1'-H), 1.43 (s, 9H, *t*-Bu), 1.59 (quint, *J* ≈ 7 Hz, 2H, 3'-H), 2.47 (sext, *J* ≈ 7 Hz, 1H, 2'-H), 3.94 (s, 3H, OMe), 6.26 (s, 1H, 5-H), 7.74 (s, 1H, NH) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 11.8 (q, C-4'), 19.5 (q, C-1'), 28.4, 29.5 (2, s, *t*-Bu), 35.1 (t, C-3'), 39.9 (d, C-2'), 58.9 (q, OMe), 114.2 (d, C-5), 146.0, 146.4, 150.7 (3 s, C-2, C-3, C-6), 176.1 (s, C-4) ppm; IR (KBr) $\tilde{\nu}$: 3250 (N-H), 2965–2910 (=C-H, C-H), 1620 (C=O), 1580, 1540 (C=C) cm⁻¹; HRMS–ESI (*m/z*): [M + H]⁺ calcd for C₁₄H₂₄NO₂, 238.1807; found, 238.1803; Anal. calcd for C₁₄H₂₃NO₂: C, 70.85; H, 9.77; N, 5.90; found: C, 70.81; H, 9.79; N, 5.38.

Typical procedure for the preparation of β-alkoxy-β-ketoenamides (Procedure 2)

A solution of *n*-BuLi (1.30 mL, 3.28 mmol, 2.5 M in hexanes) was added to a solution of methoxyallene (0.30 mL, 3.28 mmol) in diethyl ether (20 mL) at –50 °C. After stirring for 30 min at –50 °C, the reaction mixture was cooled to –78 °C and (*S*)-TBS-lactic nitrile (200 mg, 1.14 mmol) in anhydrous diethyl ether (5 mL) was added to the mixture. After stirring for 4 h, a solution of benzoic acid (0.84 g, 6.88 mmol) in anhydrous DMF (10 mL) was added. The mixture was stirred overnight and slowly allowed to reach r.t. The reaction was quenched with sat. aq. NaHCO₃ solution (15 mL) and the product extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: hexane/EtOAc 3:1) to give **64** as a pale yellow oil (300 mg, 73%).

(*S*)-*N*-{1-[1-(*tert*-Butyldimethylsiloxy)ethyl]-2-methoxy-3-oxo-but-1-enyl}benzamide (64**)** ¹H NMR (500 MHz, CDCl₃) δ 0.07, 0.11, 0.88 (3 s, 3H, 3H, 9H, OTBS), 1.46 (d, *J* = 6.4 Hz,

3H, 2''-H), 2.32 (s, 3H, 4'-H), 3.51 (s, 3H, OMe), 5.33 (q, $J = 6.4$ Hz, 1H, 1''-H), 7.43–7.53, 7.85–7.87 (2 m, 3H, 2H, Ph), 10.10 (br s, 1H, NH) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ –4.8, –4.7 (2 q, OTBS), 18.2 (q, C-4'), 21.9 (q, C-2''), 25.9, 27.2 (2, q, OTBS), 60.9 (q, OMe), 65.6 (d, C-1''), 127.5, 128.8, 132.2, 134.2, 139.6, 141.9 (3 d, 3 s, Ph, C-1', C-2'), 165.0 (s, C-1), 200.2 (s, C-3') ppm; IR (ATR) $\tilde{\nu}$: 3315 (NH), 2955–2855 (=CH, C-H), 1720–1515 (C=O, C=C) cm^{-1} ; HRMS–ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{31}\text{NNaO}_4\text{Si}$, 400.1915; found, 400.1930.

Typical procedure for the cyclization of β -alkoxy- β -ketoenamides to 4-hydroxypyridines and subsequent nonaflation (Procedure 3)

Enamide **64** (40 mg, 0.11 mmol) was dissolved in 1,2-dichloroethane (2 mL) and placed in a sealable tube. Triethylamine (48 μL , 0.32 mmol) and TMSOTf (58 μL , 0.32 mmol) were added at r.t., and the resulting mixture was heated at 90 °C for 2 d. After complete consumption of the starting material (TLC), the reaction was quenched with sat. aq. NH_4Cl solution (2 mL). After extraction with dichloromethane (3×10 mL), the combined organic layers were dried with Na_2SO_4 filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , EtOAc/Methanol 10:1) to afford the respective pyridine derivative (36 mg, 94%) as a brown liquid.

The pyridine derivative (33 mg, 0.09 mmol) was dissolved in THF (3 mL) and NaH (6.6 mg, 0.28 mmol) added under an argon atmosphere. Nonafluorobutanesulfonyl fluoride (50 μL , 0.28 mmol) was added dropwise at room temperature. The mixture was stirred at the same temperature for 12 h and quenched by the slow addition of water. The resulting product was extracted with diethyl ether (3×10 mL), dried with Na_2SO_4 , filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (eluent: 2–5% EtOAc in hexane) to afford **70** (39 mg, 67%) as a colorless oil.

(S)-2-[1-(tert-Butyldimethylsiloxy)ethyl]-3-methoxy-6-phenylpyridin-4-yl nonaflate (70): $[\alpha]_{\text{D}}^{22}$ –21.2 (c 0.3, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.00, 0.05, 0.87 (3 s, 3H, 3H, 9H, OTBS), 1.60 (d, $J = 6.6$ Hz, 3H, 2'-H), 3.95 (s, 3H, OMe), 5.30 (q, $J = 6.6$ Hz, 1H, 1'-H), 7.42–7.48 (m, 3H, Ph), 7.51 (s, 1H, 5-H), 7.97–7.98 (m, 2H, Ph) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ –4.6, –4.4 (2 q, OTBS), 18.3 (q, C-2'), 25.9, 30.3 (2, s, OTBS), 62.6 (q, OMe), 68.8 (d, C-1'), 112.3, 126.9, 128.8, 129.5, 137.7, 144.4, 150.1, 153.7, 160.0 (4 d, 5 s, Ph, C-2, C-3, C-4, C-5, C-6) ppm; IR (ATR) $\tilde{\nu}$: 3310 (NH), 3010–2835 (=CH, C-H), 1685–1510 (C=O, C=C) cm^{-1} ; HRMS–ESI (m/z):

$[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{29}\text{F}_9\text{NO}_5\text{SSi}$, 642.1387; found, 642.1403.

Typical procedure for the esterification of 4-pyridones with 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (Procedure 4)

Pyridone **22** (22 mg, 0.06 mmol) was dissolved in anhydrous CH_2Cl_2 (0.3 mL) and anhydrous pyridine (0.3 mL), and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (17 μL , 0.09 mmol) added. The mixture was stirred under an atmosphere of argon at r.t. for 16 h. After complete consumption of the starting material (TLC), the mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was successively washed with sat. NaHCO_3 solution, 1 M HCl and H_2O (10 mL each). The organic layer was dried with Na_2SO_4 , filtered and the solvent was removed under reduced pressure to afford **49** (25 mg, 68%) as a colorless oil.

(S,S)-2-tert-Butyl-6-[(tert-butyldimethylsiloxy)phenylmethyl]-3-methoxy-4-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (49): $[\alpha]_{\text{D}}^{22}$ +14.0 (c 1.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.01, 0.02, 0.96 (s, 3H, 3H, 9H, OTBS), 1.35 (s, 9H, *t*-Bu), 3.49, 3.68 (2 s, 3H each, OMe), 5.80 (s, 1H, 1'-H), 7.17 (s, 1H, 5-H), 7.19–7.22, 7.27–7.31, 7.48–7.53, 7.61–7.71 (4 m, 10H, Ph) ppm; ^{19}F NMR (376 MHz, CDCl_3) δ –71.1 (s, CF_3) ppm; IR (neat) $\tilde{\nu}$: 2955–2930 (C-H), 1775 (C=O), 1570–1450 (C=C), 1170–1105 (=C-H), 780–700 (C-F) cm^{-1} ; HRMS–ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{43}\text{F}_3\text{NO}_5\text{Si}$, 618.2857; found, 618.2896.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-108-S1.pdf>]

Supporting Information File 2

^1H NMR and ^{13}C NMR spectra of synthesized compounds.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-108-S2.pdf>]

Acknowledgements

Generous support of this work by the Deutsche Forschungsgemeinschaft (SFB 765), the Studienstiftung des Deutschen Volkes (PhD fellowship to CE) and the Bayer Schering Pharma AG is most gratefully acknowledged. We thank Dr. R. Zimmer for help during the preparation of the manuscript.

References

- Newkome, G. R. In *Chemistry of Heterocyclic Compounds*; Newkome, G. R., Ed.; Wiley: New York, 1984; Vol. 15.
- McKillop, A.; Boulton, A. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, pp 67 ff.
- Kleemann, A.; Engel, J.; Kutscher, B. *Pharmaceutical Substances*; Thieme: Stuttgart, 2000.
- Spitzner, D. *Science of Synthesis*; Thieme: Stuttgart, 2004; Vol. 15.
- Jones, G. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A., Ed.; Pergamon Press: Oxford, 1996; Vol. 5, pp 167 ff.
- Wess, G.; Kessler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, O.; Kleine, H.; Schnierer, M. *Tetrahedron Lett.* **1990**, *31*, 2545–2548. doi:10.1016/0040-4039(90)80121-2
- Miyachi, N.; Yanagawa, Y.; Iwasaki, H.; Ohara, Y.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 8267–8270. doi:10.1016/S0040-4039(00)61407-7
- Beck, G. *Synlett* **2002**, 837–850. doi:10.1055/s-2002-31890
- Beck, G.; Kessler, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Granzer, E.; Jendralla, H.; Von Kerekjarto, B.; Krause, R. *J. Med. Chem.* **1990**, *33*, 52–60. doi:10.1021/jm00163a010
- Cattaneo, D.; Baldelli, S.; Merlini, S.; Zenoni, S.; Perico, N.; Remuzzi, G. *Expert Opin. Ther. Pat.* **2004**, *14*, 1553–1566. doi:10.1517/13543776.14.11.1553
- O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637–651. doi:10.1039/NP9971400637
- Aida, W.; Ohtsuki, T.; Li, X.; Ishibashi, M. *Tetrahedron* **2009**, *65*, 369–373. doi:10.1016/j.tet.2008.10.040
- Lehn, J.-M. *Supramolecular Chemistry - Concepts and Perspectives*; VCH: Weinheim, 1995.
- Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191–1203. doi:10.1002/cber.19921250529
- Kwong, H.-L.; Yeung, H.-L.; Yeung, C.-T.; Lee, W.-S.; Lee, C.-S.; Wong, W.-L. *Coord. Chem. Rev.* **2007**, *251*, 2188–2222. doi:10.1016/j.ccr.2007.03.010
- Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205–1215. doi:10.1002/cber.19921250530
- Bolm, C.; Ewald, M.; Zehnder, M.; Neuburger, M. A. *Chem. Ber.* **1992**, *125*, 453–458. doi:10.1002/cber.19921250224
- Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983. doi:10.1002/adsc.200800776
- Drury, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2003**, *116*, 72–76. doi:10.1002/anie.200352755
- Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411. doi:10.1021/ar700113g
- Henry, G. D. *Tetrahedron* **2004**, *60*, 6043–6061. doi:10.1016/j.tet.2004.04.043
- Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096–10097. doi:10.1021/ja073912a
- Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918–6919. doi:10.1021/ja8013743
- Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602–8603. doi:10.1021/ja803139k
- Xin, X.; Wang, Y.; Kumar, S.; Liu, X.; Lin, Y.; Dong, D. *Org. Biomol. Chem.* **2010**, *8*, 3078–3082. doi:10.1039/C001117G
- Hill, M. D. *Chem.–Eur. J.* **2010**, *16*, 12052–12062. doi:10.1002/chem.201001100
- Rahm, F.; Stranne, R.; Bremberg, U.; Nordstrom, K.; Cernerud, M.; Macedo, E.; Moberg, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1983–1990. doi:10.1039/b000269k
- Rahm, F.; Fischer, A.; Moberg, C. *Eur. J. Org. Chem.* **2003**, 4205–4215. doi:10.1002/ejoc.200300368
- Flögel, O.; Dash, J.; Brüdgam, I.; Hartl, H.; Reissig, H.-U. *Chem.–Eur. J.* **2004**, *10*, 4283–4290. doi:10.1002/chem.200400322
- Dash, J.; Lechel, T.; Reissig, H.-U. *Org. Lett.* **2007**, *9*, 5541–5544. doi:10.1021/ol702468s
- Lechel, T.; Dash, J.; Hommes, P.; Lentz, D.; Reissig, H.-U. *J. Org. Chem.* **2009**, *75*, 726–732. doi:10.1021/jo9022183
- Lechel, T.; Reissig, H.-U. *Pure Appl. Chem.* **2010**, *82*, 1835–1845. doi:10.1351/PAC-CON-09-09-06
- Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45–56. doi:10.1021/ar800011h
- Lechel, T.; Dash, J.; Brüdgam, I.; Reissig, H.-U. *Eur. J. Org. Chem.* **2008**, 3647–3655. doi:10.1002/ejoc.200800398
- Zimmer, R.; Reissig, H.-U. Donor-Substituted Allenes. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; pp 425–492.
- Reissig, H.-U.; Zimmer, R. Cumulenes and Allenes: Synthesis from Other Allenes. In *Science of Synthesis*; Krause, N., Ed.; Thieme: Stuttgart, 2007; Vol. 44, pp 301–352.
- Bera, M. K.; Reissig, H.-U. *Synthesis* **2010**, 2129–2138. doi:10.1055/s-0029-1218787
- Zimmer, R.; Lechel, T.; Rancan, G.; Bera, M. K.; Reissig, H.-U. *Synlett* **2010**, 1793–1796. doi:10.1055/s-0030-1258088
- Lechel, T.; Dash, J.; Eidamshaus, C.; Brüdgam, I.; Lentz, D.; Reissig, H.-U. *Org. Biomol. Chem.* **2010**, *8*, 3007–3014. doi:10.1039/B925468D
- Eidamshaus, C.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 1162–1166. doi:10.1002/adsc.200800789
- Couty, F.; David, O.; Larmanjat, B.; Marrot, J. *J. Org. Chem.* **2007**, *72*, 1058–1061. doi:10.1021/jo062221e
- Aureggi, V.; Frankevicius, V.; Kitching, M. O.; Ley, S. V.; Longbottom, D. A.; Oelke, A. J.; Sedelmeier, G. *Org. Synth.* **2008**, *85*, 72–87.
- Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151–3154. doi:10.1021/ol050814q
- Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *J. Org. Chem.* **1982**, *47*, 1324–1326. doi:10.1021/jo00346a031
- Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747–2763. doi:10.1002/adsc.200900566
- Liebehenschel, S.; Cvangroß, J.; Jacobi von Wangelin, A. *Synlett* **2007**, 2574–2578. doi:10.1055/s-2007-986630
- Lechel, T.; Möhl, S.; Reissig, H.-U. *Synlett* **2009**, 1059–1062. doi:10.1055/s-0028-1088220
- Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180–5182. doi:10.1021/jo00174a006

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[doi:10.3762/bjoc.7.108](https://doi.org/10.3762/bjoc.7.108)

Long-range diastereoselectivity in Ugi reactions of 2-substituted dihydrobenzoxazepines

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Letter

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Keywords:
benzoxazepines; cyclic imines; long range stereinduction;
multicomponent reactions; Ugi reaction

Beilstein J. Org. Chem. **2011**, *7*, 976–979.
doi:10.3762/bjoc.7.109

Received: 10 May 2011
Accepted: 22 June 2011
Published: 13 July 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

The Ugi reaction of 2-substituted dihydrobenzoxazepines was found to proceed with unexpectedly good diastereoselectivity (diastereoisomeric ratios up to 9:1), despite the large distance between the pre-existing stereogenic centre and the newly generated one. This result represents the first good 1,4 asymmetric induction in an Ugi reaction as well as the first example of diastereoselective Ugi reaction of seven membered cyclic imines. It allows the diversity-oriented synthesis of various tetrahydro[*f*][1,4]benzoxazepines.

Introduction

The Ugi reaction is probably the most renowned and widely used multicomponent reaction. Its great utility in the highly convergent and diversity-oriented synthesis of libraries of heterocyclic compounds, stemming from the possibility to introduce up to four diversity inputs in a single step, has been fully demonstrated [1-5]. However, a main drawback of this venerable reaction is the poor diastereoselectivity typically experienced when using chiral inputs. It is well known that chiral isocyanides, aldehydes/ketones and carboxylic acids always

bring about no or very little diastereoselectivity, whereas some relative asymmetric induction has been reported only with chiral amines as auxiliaries [6], or with chiral cyclic imines.

The use of cyclic imines (three-component Ugi–Joullié reaction) [7,8] is particularly useful, because the resulting Ugi products are necessarily nitrogen heterocycles. However, good diastereoselectivity has been obtained so far only with a few types of chiral substrates [9-15]. In most cases these are represented

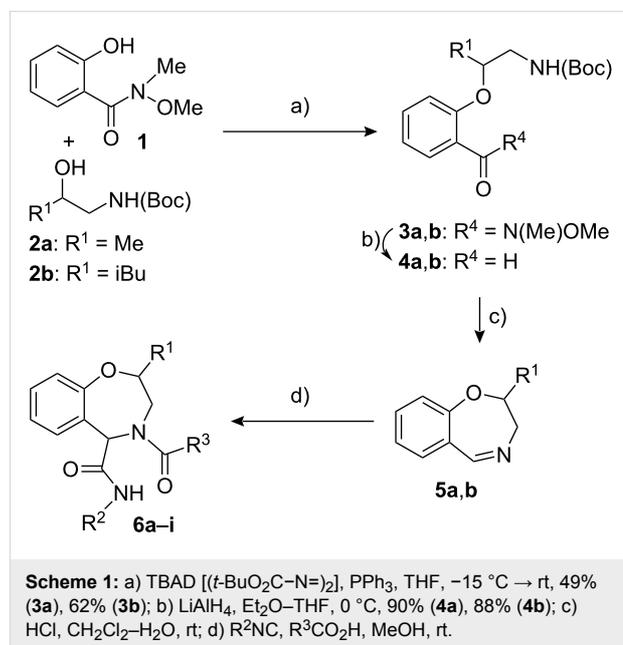
by five-membered imines (pyrrolines) with a stereogenic centre α to the imine carbon (1,2-induction), although this relative arrangement is not a guarantee of good stereoselectivity [8,14,16]. Examples of 1,3-induction on chiral imines with the stereocentre β to the carbon [14,16], or α to the nitrogen, of the C=N moiety [13,15,17] are rarer. More often, when the stereocentre is not in α , poor diastereoselectivity is observed [18,19]. This fact limits the diversity of heterocycles that can be accessed stereoselectively from the three-component Ugi–Joullié reaction of cyclic imines.

Results and Discussion

We report here some preliminary results disclosing a new family of chiral 7-membered cyclic imines that afford good levels of diastereoselectivity when submitted to an Ugi–Joullié reaction, despite the fact that the stereogenic centre is only γ to the imine carbon (1,4 relative induction). This is, to our knowledge, the first example of 1,4 asymmetric induction in an isocyanide based multicomponent reaction of chiral carbonyl compounds or imines, and the first example of diastereoselective Ugi reaction on chiral seven-membered imines [20,21].

The two imines **5a,b** (Scheme 1) have been convergently synthesized in three steps from Weinreb hydroxamate **1**, in turn prepared in one step from salicylic acid (Supporting Information File 1). The key step of the synthesis is the intramolecular condensation of **1** with racemic alcohols **2a,b** through a Mitsunobu reaction. The moderate yields are due to the consumption of alcohols **2**, which undergo side-reactions, resulting in incomplete transformation of **1**, even when using 1.3–1.5 equiv of **2**. The use of a larger excess of **2** would probably increase the yields, but this is not particularly convenient (especially if one plans to use enantiomerically pure **2**). In any case, unreacted **1** may be recovered. Alcohol **2b** behaves somewhat better than **2a** in this reaction. The other two steps proceeded with no problems to give imines **5a,b** in high yield. It

is worth noting that the Mitsunobu reaction is not effective on unprotected salicylaldehyde. 2,3-Dihydrobenzo[*f*][1,4]oxazepines similar to **5a,b** have been previously prepared, but through less general routes [22–24].



Compounds **5a,b** were reacted with a series of isocyanides and carboxylic acids to give, in good yields, nine different tetrahydro[*f*][1,4]benzoxazepines **6**, equipped with three diversity points.

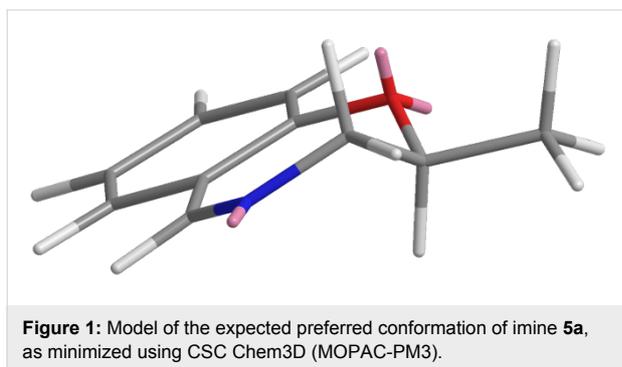
As shown in Table 1, all the tested Ugi reactions proceeded with remarkably high diastereoselectivity, if one considers that the R¹ substituent is quite far away from the imine carbon. This long range diastereoselectivity (from 5.25:1 up to 9:1) is completely unprecedented for an isocyanide based multicomponent reaction.

Table 1: Results of Ugi reactions of imines **5a,b**.

Product	R ¹	R ²	R ³	Yield ^a	dr ^b
6a	Me	Cy	Et	70%	85:15
6b	Me	<i>t</i> -Bu	MeOCH ₂	77%	87:13
6c	Me	Bn	BocNHCH ₂	71%	84:16
6d	<i>i</i> Bu	4-BnOC ₆ H ₄ CH ₂ CH ₂	MeOCH ₂	56%	90:10
6e	<i>i</i> Bu	Cy	Et	59%	86:14
6f	<i>i</i> Bu	<i>t</i> -Bu	Bn	64%	88:12
6g	<i>i</i> Bu	<i>n</i> -Bu	3-BrC ₆ H ₄	57%	88:12
6h	<i>i</i> Bu	<i>t</i> -Bu	5-Cl-2-thienyl	78%	89:11
6i	<i>i</i> Bu	<i>n</i> -Bu	Z-NH-CH ₂ CH ₂	70%	88:12

^aIsolated yields (after chromatography) from aldehydes **4a,b**. ^bDetermined by HPLC or by ¹H NMR (for **6f**, **6h**, **6i** only by NMR).

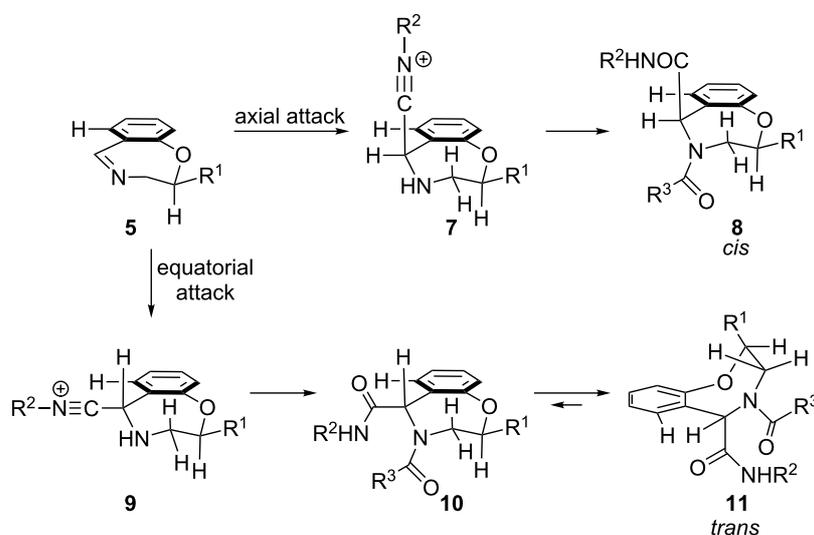
A slight increase in the *dr* was observed on passing from $R^1 = \text{Me}$ to bulkier $R^1 = \text{iBu}$. On the other hand the structure and the nature of both isocyanides and carboxylic acids seem to have little influence on the diastereoselectivity. NMR characterization of the products is reported in Supporting Information File 2. Minimization of the cyclic imine **5a** using CSC Chem3D (v10) indicates that there are only two significant conformations, and that the one with the substituent at C-2 in the equatorial position is strongly favored. In this situation (Figure 1), the substituent at C-2 should be quite far away from the site of isocyanide attack, being unable to discriminate the two diastereotopic faces.



Thus, rationalization of the observed stereoselectivity is not trivial, also because we have not yet proved unambiguously the relative configuration of the major adducts. Some authors have suggested, for six membered rings, a preferential axial attack of the isocyanide [14,16], since it relieves unfavorable steric strain in the forming tetrahedral adduct (Scheme 2). In our case, equatorial attack, leading to intermediate **9**, would experience steric

strain with the *peri* H-7. Therefore, if the preferred conformation of the imine is the one depicted in Figure 1, with R^1 equatorial, axial attack would give the *cis* adducts. The importance of the unfavorable *peri* interaction is confirmed by the fact that the isocyanide derived substituent prefers an axial position in both stereoisomers, as demonstrated by NOE experiments carried out on **6e** (Supporting Information File 2). Thus, after attack, the *trans* initial adduct **10** undergoes a conformational change to **11**. The two vicinal J_{2-3} (i.e., 2.1 and 9.3 Hz for **6h**) in the major diastereomers are in agreement with the chair-like conformation **8** of the *cis* adduct, whereas the same coupling constants in the minor diastereoisomer (i.e., 3.6 and 8.7 Hz. for **6h**) fit the boat-like conformation **11** of the *trans* adduct. However, the difference between these coupling constants for the two stereoisomers is not large enough to guarantee the undisputable assignment of the *cis* relative configuration to the major adduct. In the presented hypothesis, the function of the substituent at C-2 would therefore not be to shield one of the two diastereotopic faces, but only to fix the conformation by favoring an equatorial disposition of R^1 . We are planning to prove the relative configuration of the major adducts and to prepare analogues with further substituents in order to get more clues on this unusual diastereoselectivity and, hopefully, to further improve stereoselectivity.

In conclusion, the methodology presented herein appears particularly well suited for the stereoselective preparation of libraries of peptidomimetics based on the tetrahydrobenzoxazepine ring. Although structures of general formula **6** are unprecedented, other tetrahydrobenzoxazepines have shown interesting pharmacological properties [25,26]. The possibility to introduce up to 4 points of diversity (including also



substituents on the aromatic ring), and to obtain enantiomerically pure compounds, starting from enantiomerically pure alcohols **2a,b**, will be explored, too.

Supporting Information

Supporting Information File 1

Complete experimental procedures.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-109-S1.pdf>]

Supporting Information File 2

NMR characterization of products **6** and NMR spectra.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-109-S2.pdf>]

Acknowledgements

We wish to thank Benedetta Pollarolo for her collaboration to this work and Fondazione San Paolo for a contribution for the purchase of NMR and HPLC instruments.

References

- Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147. doi:10.3987/REV-07-SR(U)3
- Banfi, L.; Basso, A.; Riva, R. In *Synthesis of Heterocycles via Multicomponent Reactions I*; Orru, R. V. A.; Ruijter, E., Eds.; Springer: Berlin/Heidelberg, 2010; Vol. 23, pp 1–39.
- Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23–41. doi:10.1055/s-0029-1218527
- Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. doi:10.1021/cr0505728
- Hulme, C.; Dietrich, J. *Mol. Div.* **2009**, *13*, 195–207. doi:10.1007/s11030-009-9111-6
- Banfi, L.; Basso, A.; Guanti, R.; Riva, R. Asymmetric Isocyanide-Based MCRs. In *Multicomponent Reactions*; Zhu, J. P.; Bienaymé, H., Eds.; Wiley: Weinheim, 2005; pp 1–32. doi:10.1002/3527605118.ch1
- Nutt, R. F.; Joullié, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 5852–5853. doi:10.1021/ja00385a080
- Bowers, M. M.; Carroll, P.; Joullié, M. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 857–865. doi:10.1039/P19890000857
- Znabet, A.; Ruijter, E.; de Kanter, F. J. J.; Köhler, V.; Helllwell, M.; Turner, N. J.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 5289–5292. doi:10.1002/anie.201001592
- Bonger, K. M.; Wennekes, T.; Filippov, D. V.; Lodder, G.; van der Marel, G. A.; Overkleef, H. S. *Eur. J. Org. Chem.* **2008**, 3678–3688. doi:10.1002/ejoc.200800340
- Chapman, T. M.; Davies, I. G.; Gu, B.; Block, T. M.; Scopes, D. I. C.; Hay, P. A.; Courtney, S. M.; McNeill, L. A.; Schofield, C. J.; Davis, B. G. *J. Am. Chem. Soc.* **2005**, *127*, 506–507. doi:10.1021/ja043924l
- Timmer, M. S. M.; Risseeuw, M. D. P.; Verdoes, M.; Filippov, D. V.; Plaisier, J. R.; van der Marel, G. A.; Overkleef, H. S.; van Boom, J. H. *Tetrahedron: Asymmetry* **2005**, *16*, 177–185. doi:10.1016/j.tetasy.2004.11.079
- Maison, W.; Lützen, A.; Kosten, M.; Schlemminger, I.; Westerhoff, O.; Saak, W.; Martens, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1867–1871. doi:10.1039/B002258F
- Sperger, C. A.; Mayer, P.; Wanner, K. T. *Tetrahedron* **2009**, *65*, 10463–10469. doi:10.1016/j.tet.2009.10.020
- Zhu, D.; Chen, R.; Liang, H.; Li, S.; Pan, L.; Chen, X. *Synlett* **2010**, 897–900. doi:10.1055/s-0029-1219533
- El Kaïm, L.; Grimaud, L.; Oble, J.; Wagschal, S. *Tetrahedron Lett.* **2009**, *50*, 1741–1743. doi:10.1016/j.tetlet.2009.01.145
- Gröger, H.; Hatam, M.; Martens, J. *Tetrahedron* **1995**, *51*, 7173–7180. doi:10.1016/0040-4020(95)00365-F
- Banfi, L.; Basso, A.; Guanti, G.; Merlo, S.; Repetto, C.; Riva, R. *Tetrahedron* **2008**, *64*, 1114–1134. doi:10.1016/j.tet.2007.10.058
- Iizuka, T.; Takiguchi, S.; Kumakura, Y.; Tsukioka, N.; Higuchi, K.; Kawasaki, T. *Tetrahedron Lett.* **2010**, *51*, 6003–6005. doi:10.1016/j.tetlet.2010.09.026
- Gulevich, A. V.; Shevchenko, N. F.; Balenkova, E. S.; Roesenthaler, G. V.; Nenajdenko, V. G. *Synlett* **2009**, 403–406. doi:10.1055/s-0028-1087529
- Recently, a very high diastereoselectivity leading to seven-membered ring was obtained in an intramolecular Ugi reaction of an oxoacid endowed with axial chirality: Mehta, V. P.; Modha, S. G.; Ruijter, E.; Van Hecke, K.; Van Meervelt, L.; Pannecouque, C.; Balzarini, J.; Orru, R. V. A.; Van der Eycken, E. *J. Org. Chem.* **2011**, *76*, 2828–2839. doi:10.1021/jo200251q
- Del Buttero, P.; Molteni, G.; Papagni, A.; Miozzo, L. *Tetrahedron: Asymmetry* **2004**, *15*, 2555–2559. doi:10.1016/j.tetasy.2004.06.037
- Prabhu, K. R.; Sivanand, P. S.; Chandrasekaran, S. *Synlett* **1998**, *1998*, 47–48. doi:10.1055/s-1998-1057884
- Takács, M.; Vámos, J.; Tóth, G.; Mikó-Hideg, Z. *Arch. Pharm.* **2000**, *333*, 48–52. doi:10.1002/(SICI)1521-4184(200002)333:2/3<48::AID-ARDP48>3.0.CO;2-N
- Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J. A.; Marchal, J. A.; Aránega, A.; Gallo, M. Á.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2004**, *60*, 11547–11557. doi:10.1016/j.tet.2004.09.072
- Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 244–247. doi:10.1016/j.bmcl.2009.10.126

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Multicomponent reaction access to complex quinolines via oxidation of the Povarov adducts

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Full Research Paper

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Keywords:

manganese dioxide; multicomponent reactions; oxidation; Povarov; quinolines; tetrahydroquinolines

Beilstein J. Org. Chem. **2011**, *7*, 980–987.

doi:10.3762/bjoc.7.110

Received: 06 May 2011

Accepted: 22 June 2011

Published: 13 July 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

The tetrahydroquinolines obtained through the Povarov multicomponent reaction have been oxidized to the corresponding quinoline, giving access to a single product through a two-step sequence. Several oxidizing agents were studied and manganese dioxide proved to be the reagent of choice, affording higher yields, cleaner reactions and practical protocols.

Introduction

Heterocycles are ubiquitous scaffolds in pharmaceuticals, natural products and biologically active compounds. Quinoline systems in particular constitute a privileged substructure and are present in a large number of compounds with remarkable biological activity [1]. Although a variety of methods are used to prepare these heterocyclic compounds, the synthetic access to polysubstituted-polyfunctionalized derivatives remains a serious challenge [2]. Multistep sequences are widespread in the literature, but even in these cases the preparation of some substitution patterns and functional group combinations is particularly difficult. The recent introduction of multicomponent reactions (MCRs) into this field has brought interesting features typical of the ideal reaction, such as atom- and step economy, conver-

gence, and exploratory power, together with new avenues in connectivity, leading to the straightforward synthesis of previously unobtainable scaffolds [3]. In this context, it is possible to obtain a wide variety of complex tetrahydroquinolines through the Povarov MCR (the interaction of anilines, aldehydes and activated olefin inputs under acid catalysis) [4-8]. Interestingly, this process allows cyclic enol ethers and enamines to be used as electron-rich alkenes, leading to heterocycle-fused tetrahydroquinolines, usually as a mixture of stereoisomers [9-13]. Unfortunately, no general methods for enantioselective Povarov reactions have been developed (for examples of catalytic enantioselective transformations operating in particular systems, see [14,15]), and this constitutes a serious drawback in the use

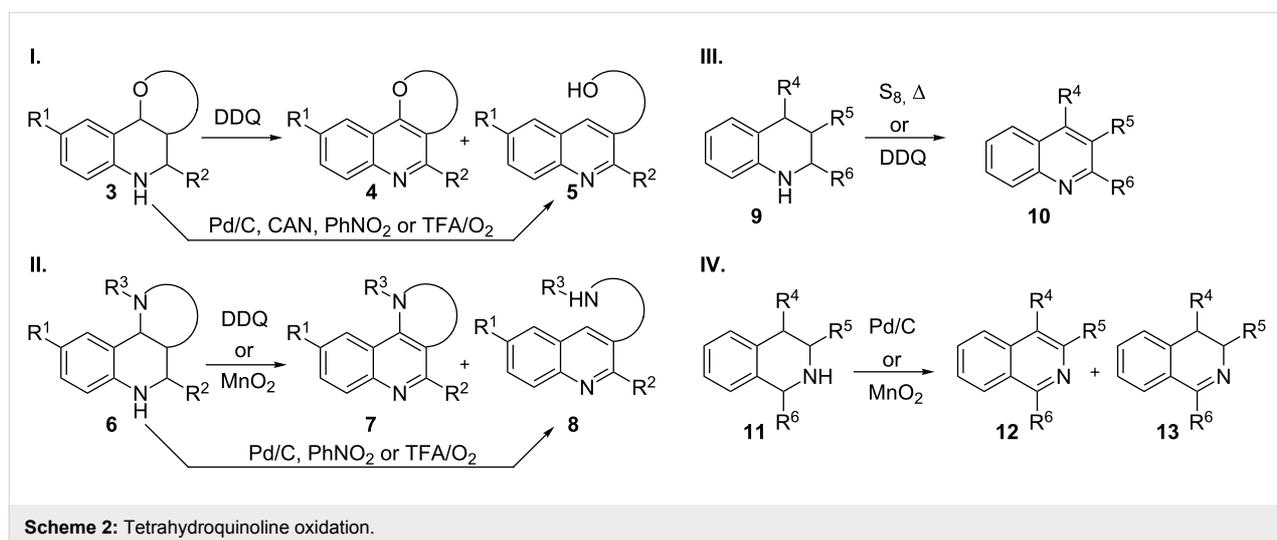
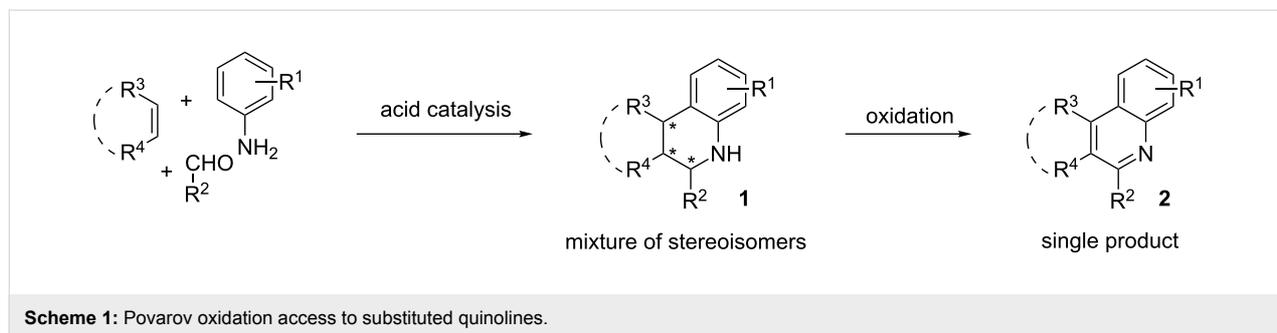
of this reaction for library preparation, as one reaction affords several products, when ideally it should give only one. However, these adducts can be subjected to oxidation, which will lead to the corresponding quinolines, preserving the substituents and functionalization already introduced in the preceding MCR. Despite the loss of all stereochemical information, in this way it would be feasible to obtain a single product from a multicomponent process (Scheme 1).

The oxidation step itself is challenging as it involves the formal removal of four hydrogens from a tetrahydroquinoline moiety to reach the fully aromatic species. The literature contains scattered reports of the use of oxidants for this transformation: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), ceric ammonium nitrate (CAN), nitrobenzene, elemental sulfur, palladium and manganese dioxide among others, all of them far from being ideally suited for these substrates.

One of the most commonly used is DDQ, which affords quinolines in acceptable yields. The main advantages of this oxidizing agent lie in its chemoselectivity and a requirement for relatively mild conditions, allowing it to be used in the presence of a wide range of substituents of the starting tetrahydro-

quinoline, such as O-, N- and C-linked residues (Scheme 2) [8,9,12,13,16–18]. Unfortunately, the alternative oxidation–elimination products (**5** and **8**) are often observed, therefore suggesting an acid catalyzed process. This would account for the elimination of alcohol and amine moieties, leading to dihydroquinoline intermediates that, after spontaneous oxidation in air, provide the final fragmented quinolines. The ability of DDQ to act as a Lewis acid and promote this alternative pathway has some precedent in the literature [19]. Furthermore, TFA treatment of Povarov adducts in oxygenated atmospheres also affords the oxidation–elimination products **5** and **8** (Scheme 2) [8,12,20].

The alternative oxidation–elimination pathway is predominant in some CAN-promoted oxidations of different Povarov adducts **3**. Incidentally, this reagent is also used as a catalyst in the Povarov MCR without oxidative interference [18]. The same trend (oxidation–fragmentation) can be observed using nitrobenzene [21] as the oxidant. Analogously, elemental sulfur and palladium, although requiring drastic conditions, also lead to the fragmented quinolines when the substrates bear O- and N-substituents [22–25] (for related isoquinoline oxidations, see [26,27]).



Related oxidative processes involve, for instance, a cascade Povarov–hydrogen transfer reaction using TF_2NH as a catalyst and the imine as an oxidant, as recently described [28]. In addition, Povarov adducts resulting from the reaction between 3-aminocoumarin, aldehydes and cyclic enol ethers have been oxidized with different types of reagents, such as bromide, palladium, DDQ, sodium periodate, manganese dioxide or CAN, but in all cases the main product was the elimination–oxidation compound [29].

Finally, chemical manganese dioxide (CMD) has been widely used in this type of transformations, and already in 1982 the oxidation of tetrahydroisoquinoline (**11**, Scheme 2) was reported to yield the corresponding isoquinoline **12**, the intermediate dihydroisoquinoline **13** being obtained as a by-product [26]. Later, Thompson et al. described the oxidation of fused pyrrolohydroquinolines (type **6**) using MnO_2 obtained from batteries. A kinetic competition between two processes was observed, and the desired double oxidation to the corresponding fused quinoline **7** took place, along with the oxidation–elimination sequence leading to **8**. A large excess of oxidant was required in order to obtain the desired quinoline **7** as the major product (Scheme 2) [30,31].

Results and Discussion

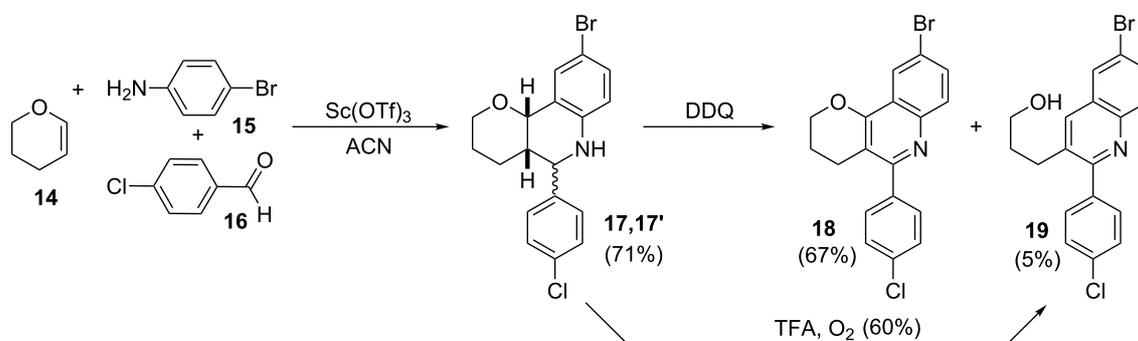
Experiments were performed with the goal of developing a general and practical protocol for the oxidation of Povarov adducts to furnish the corresponding fused quinolines, avoiding elimination by-products. After unsuccessful attempts using palladium on carbon (decomposition), CuCl (partial oxidative elimination), Fremy's salt (unreactive) and IBX (a complex reaction leading to unknown compounds), we focused our attention on MnO_2 as the oxidant of choice. A literature search revealed different reactivity patterns depending on the type and origin of the reagent, with the commercial source being particu-

larly important [32–36]. A systematic study was therefore conducted to determine the influence of different reaction conditions, commercial reagents and additives on the oxidation of an elimination-prone Povarov tetrahydroquinoline substrate.

In this way, tetrahydroquinolines **17,17'** were synthesized as a mixture of isomers from the enol ether **14**, *p*-bromoaniline (**15**) and *p*-chlorobenzaldehyde (**16**) under $\text{Sc}(\text{OTf})_3$ catalysis using standard reaction conditions (Scheme 3) [9]. Subsequently, these adducts **17,17'** were oxidized with DDQ by the standard protocol [9], to isolate the desired quinoline **18** and its fragmented derivative **19**, and they could also be subjected to an acid treatment to obtain selectively the latter product [8]. All compounds were purified and unequivocally characterized by NMR and HPLC methods.

Taking into account that the oxidation of thiazolidines to thiazoles with MnO_2 (25 equiv) in toluene (55 °C) in the presence of pyridine (1.25 equiv) is a clean and efficient method [35], a first experiment was set up to test these conditions with an old (≈ 40 years) MnO_2 sample of unknown origin (particle size 11.46 μm , see below). A promising result was obtained, achieving a 39% conversion to the desired product **18**, albeit with a high ratio of the elimination–oxidation compound **19**. Next, the equivalents of oxidant and pyridine were increased to 100 and 6, respectively, and under these optimized conditions, a 72% isolated yield of quinoline **18** was obtained, and no starting material or elimination–oxidation compound was detected.

Unfortunately, we were not able to reproduce the above results when using brand new samples of MnO_2 . It was decided to test different commercially available MnO_2 sources (Aldrich, Acros and Wako) of distinct activation degrees (particle size, powder or activated reagent, Table 1) in order to find a suitable reagent leading to comparable results.



Scheme 3: Synthesis of the Povarov adducts and their oxidation products.

μm) were inefficient in promoting the desired oxidation. On the other hand, medium size samples (Wako and the old sample of unknown origin) were the most selective oxidants (see Supporting Information File 1).

Using this reliable reagent, different reaction conditions were tested in order to optimize the process, especially regarding reagent consumption (Figure 1). The effects of varying the amounts of Wako MnO_2 (from 10 to 100 equiv) and pyridine (from 2 to 20 equiv) in the standard solvent (toluene), reaction time and temperature (2 h, 55 °C) were studied. The gradual increment in the amount of oxidant resulted in a progressive increase in the yield of compound **18** and the simultaneous decrease of the elimination quinoline **19**. No productive transformation to quinoline **18** was observed using 10 equiv of oxidant, the fragmented compound **19** being the predominant species. It is worth noting that the conversion of the starting material was only complete when at least 80 equiv of MnO_2 were used, but even in these conditions the elimination pathway could not be completely avoided, despite the huge excess of

pyridine (up to 20 equiv). As such large amounts of pyridine were not beneficial, the use of 6 equiv of this reagent was a practical compromise, leading to the same essential outcome. In an attempt to disaggregate the Wako MnO_2 powder, and in this way reduce the amount of reagent, the reaction was performed in an ultrasonic bath under the general conditions, but no improvement was observed in the reaction profile.

The optimized oxidation conditions were applied to another class of tetrahydroquinolines, which contain a fused lactam ring (**20,20'**, Scheme 4) [12]. These new substrates were prepared through the Povarov MCR from the corresponding unsaturated lactam, aldehyde and aniline. The oxidation and elimination products (**21** and **22**, respectively) were independently prepared with DDQ under acid catalysis in an oxygenated atmosphere (O_2 -TFA), and characterized by NMR and HPLC methods. The optimized conditions with the Wako reagent were productive and selectively afforded the corresponding quinolines **21** in high yields, and the elimination product **22** was not detected. The processes were slower (5–8 h) than those involving the pyran-

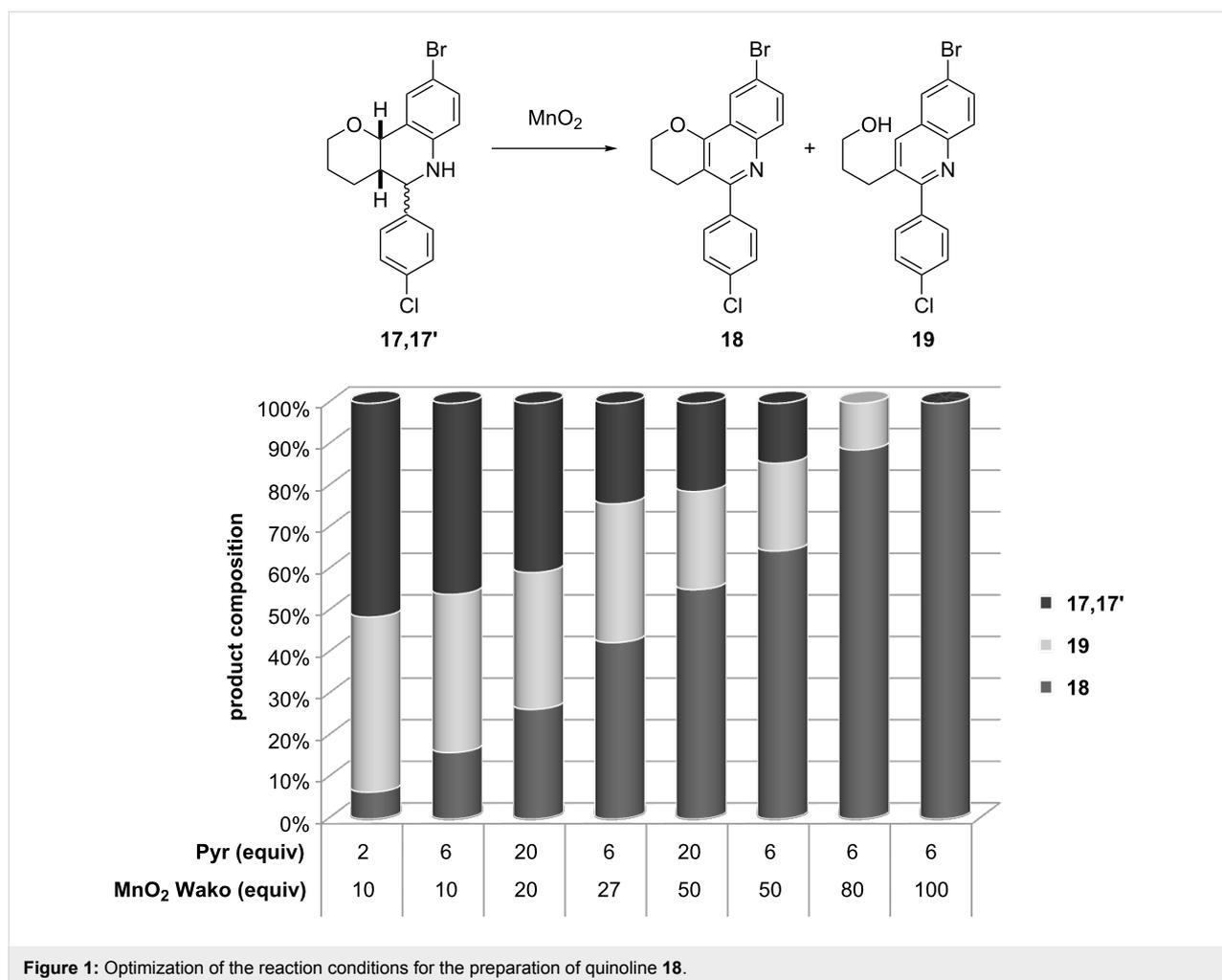
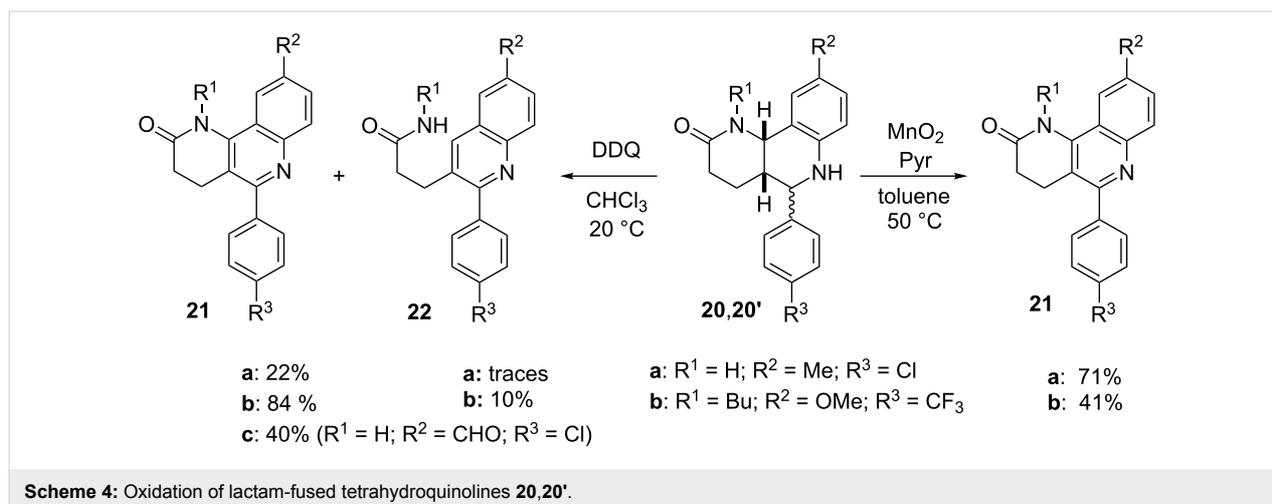


Figure 1: Optimization of the reaction conditions for the preparation of quinoline **18**.



fused substrates **17,17'** (Scheme 3). Interestingly, although DDQ is also capable of promoting these transformations, it is not as selective as Wako MnO₂, and apart from yielding the fragmented quinolines **22**, it also oxidizes the benzylic hydrogens (**a** series, R² = Me) leading to the corresponding aldehyde derivative **21c** [12]. Studies are ongoing to expand this set of transformations to fused oxygenated and nitrogenated 5-membered ring systems.

Conclusion

In conclusion, we have described a fast, practical and reliable methodology to oxidize complex polysubstituted tetrahydroquinolines, arising from Povarov MCRs, to the corresponding quinolines, using MnO₂. The influence of the reagent source, stoichiometry, additives and reaction conditions has been determined. Wako CMD is the oxidant of choice and the presence of pyridine is critical to avoid the fragmentation pathway, a side reaction often found in this type of transformation. This process enables the selective preparation of heterocycle-fused quinolines arising from a single combination of aldehydes, anilines and activated alkenes in a short sequence, involving Povarov MCR and oxidation steps.

Experimental

General

¹H and ¹³C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Unless otherwise stated, NMR spectra were recorded in CDCl₃ solution with TMS as an internal reference. Data for ¹H NMR spectra are reported as follows: Chemical shift (δ ppm), multiplicity, integration and coupling constants (Hz). Data for ¹³C NMR spectra are reported in terms of chemical shift (δ ppm). Signals were assigned by means of two-dimensional NMR spectroscopy: ¹H,¹H-COSY, ¹H,¹³C-COSY (HSQC: heteronuclear single quantum coherence) and long-range ¹H,¹³C-COSY (HMBC: heteronuclear multiple bond

connectivity). IR spectra were recorded using a Thermo Nicolet Nexus spectrometer and are reported in wavenumbers (cm⁻¹). High resolution mass spectrometry was performed by the University of Barcelona Mass Spectrometry Service.

General procedure A [9,12]

To a solution of compound **17,17'** or **20,20'** (1 mmol) in 15 mL of CHCl₃, DDQ (2 mmol) was added and the mixture was stirred for 24 h in an open vessel at room temperature. An aqueous saturated NaHCO₃ solution (10 mL) was added, and the resulting mixture was extracted with CHCl₃ (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The reaction mixture was purified by flash chromatography (hexane–EtOAc) to afford the desired product.

General procedure B [9,12]

To a solution of compound **17,17'** or **20,20'** (1 mmol) in CH₃CN/H₂O or CHCl₃/H₂O (1:1, 6 mL), TFA (2 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, quenched with an aqueous saturated NaHCO₃ solution (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give a residue which was purified by flash chromatography (hexane–ethyl acetate) to afford the desired product.

General procedure C

To a solution of compound **17,17'** or **20,20'** (1 mmol) in 50 mL of toluene, pyridine (6 mmol) and MnO₂ Wako (100 mmol) were added and the mixture was stirred in an open vessel at 55 °C. The progress of the reaction was controlled by TLC or HPLC, until the starting material completely disappeared or no evolution was observed. The crude mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The reaction

mixture was purified by flash chromatography (hexane–EtOAc) to afford the desired product.

9-bromo-5-(4-chlorophenyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline (18)

Following the general procedure A, the oxidation of **17**, **17'** afforded compound **18** as a white solid (68%). Following the general procedure C for 2 h with Wako MnO₂, the oxidation of **17**, **17'** afforded compound **18** as a white solid (66%). ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J* = 2.2 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 1H), 7.70 (dd, *J* = 2.3, 8.9 Hz, 1H), 7.53–7.48 (m, 2H), 7.45–7.40 (m, 2H), 4.46–4.39 (m, 2H), 2.72 (t, *J* = 6.3 Hz, 2H), 2.03–1.97 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 159.91, 156.71, 145.86, 138.58, 134.58, 132.71, 130.76, 130.24, 128.54, 123.91, 121.18, 119.46, 111.35, 67.21, 23.80, 21.75; IR (film): 3319, 3058, 2987, 2949, 2917, 2859, 1905, 1585, 1476, 1392, 1348, 1322, 1162, 1123, 1085, 989 cm⁻¹; HRMS (ESI+, *m/z*): [M + H]⁺ calcd for C₁₈H₁₄BrClNO, 373.9942; found, 373.9933.

3-(6-bromo-2-(4-chlorophenyl)quinolin-3-yl)propan-1-ol (19)

Following the general procedure B, the oxidation of **17**, **17'** afforded compound **19** as a white solid (60%). ¹H NMR (400 MHz, CDCl₃) δ 7.92–7.87 (m, 3H), 7.67 (dd, *J* = 2.2, 8.9 Hz, 1H), 7.44–7.37 (m, 4H), 3.51 (t, *J* = 6.2 Hz, 2H), 2.85–2.77 (m, 2H), 1.75–1.65 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 159.9, 145.2, 139.0, 135.3, 134.8, 134.3, 132.8, 131.2, 130.3, 129.2, 128.9, 128.9, 120.8, 62.0, 33.3, 29.4; IR (film): 3353, 2924, 2847, 1783, 1732, 1598, 1476, 1431, 1393, 1258, 1188, 1085, 1059, 1009, 919, 823 cm⁻¹; HRMS (ESI+, *m/z*): [M + H]⁺ calcd for C₁₈H₁₆BrClNO, 376.0098; found, 376.0090.

Supporting Information

Supporting information features the characterization data of compounds **18**, **19**, **21** and **22**, copies of their ¹H NMR and ¹³C NMR spectra, and the particle size analyses of MnO₂ samples.

Supporting Information File 1

Experimental details.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-110-S1.pdf>]

Acknowledgements

This work was supported by DGICYT – Spain (project BQUCTQ2009-07758), Generalitat de Catalunya (project 2009SGR 1024) and Barcelona Science Park. Grupo Ferrer (Barcelona, Spain) is thanked for financial support. We thank

Dr. Pedro Grima (Grupo Ferrer, R+D center, Barcelona) for useful comments.

References

- Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003; pp 316–336. doi:10.1002/352760183X
- Larsen, L. D.; Cai, D. Quinolines. In *Six-Membered Heterocycles with One Nitrogen or Phosphorus Atom*; Black, D., Ed.; Science of Synthesis, Vol. 15; Georg Thieme Verlag: Stuttgart, Germany, 2005; pp 551–660.
- Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
- Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656–670. doi:10.1070/RC1967v036n09ABEH001680
- Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721–2750. doi:10.1016/j.tet.2008.12.059
- Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2008**, *77*, 137–159. doi:10.1070/RC2008v077n02ABEH003749
- Bello, D.; Ramón, R.; Lavilla, R. *Curr. Org. Chem.* **2010**, *14*, 332–356. doi:10.2174/138527210790231883
- Smith, C. D.; Gavriyuk, J. I.; Lough, A. J.; Batey, R. A. *J. Org. Chem.* **2010**, *75*, 702–715. doi:10.1021/jo9021106
- Jiménez, O.; de la Rosa, G.; Lavilla, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6521–6525. doi:10.1002/anie.200501548
- Camps, P.; Formosa, X.; Galdeano, C.; Muñoz-Torrero, D.; Ramírez, L.; Gómez, E.; Isambert, N.; Lavilla, R.; Badia, A.; Clos, M. V.; Bartolini, M.; Mancini, F.; Andrisano, V.; Arce, M. P.; Rodríguez-Franco, M. I.; Huertas, O.; Dafni, T.; Luque, F. J. *J. Med. Chem.* **2009**, *52*, 5365–5379. doi:10.1021/jm900859q
- Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916. doi:10.1021/ol026293d
- Vicente-García, E.; Catti, F.; Ramón, R.; Lavilla, R. *Org. Lett.* **2010**, *12*, 860–863. doi:10.1021/ol902913j
- Stevenson, P. J.; Graham, I. *ARKIVOC* **2003**, *vii*, 139–144.
- Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599. doi:10.1021/ja900806q
- Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357–7360. doi:10.1016/0040-4039(96)01655-3
- Rano, T. A.; Sieber-McMaster, E.; Pelton, P. D.; Yang, M.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2456–2460. doi:10.1016/j.bmcl.2009.03.051
- Spaller, M. R.; Thielemann, W. T.; Brennan, P. E.; Bartlett, P. A. *J. Comb. Chem.* **2002**, *4*, 516–522. doi:10.1021/cc020027+
- Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2009**, *65*, 2087–2096. doi:10.1016/j.tet.2008.12.077
- Oku, A.; Kinugasa, M.; Kamada, T. *Chem. Lett.* **1993**, *22*, 165–168. doi:10.1246/cl.1993.165
- Borrione, E.; Prato, M.; Scorrano, G.; Stivanello, M.; Lucchini, V. *J. Heterocycl. Chem.* **1988**, *25*, 1831–1835. doi:10.1002/jhet.5570250644
- Zaitsev, V. P.; Mikhailova, N. M.; Orlova, D. N.; Nikitina, E. V.; Boltukhina, E. V.; Zubkov, F. I. *Chem. Heterocycl. Compd.* **2009**, *45*, 308–316. doi:10.1007/s10593-009-0271-1
- Kouznetsov, V. V.; Bohórquez, A. R. R.; Saavedra, L. A. *Synthesis* **2009**, 4219–4225. doi:10.1055/s-0029-1217049
- Fadel, F.; Titouani, S. L.; Soufiaoui, M.; Ajamay, H.; Mazzah, A. *Tetrahedron Lett.* **2004**, *45*, 5905–5908. doi:10.1016/j.tetlet.2004.05.127

24. Saavedra, L. A.; Vallejos C., G.; Kouznetsov, V. V.; Gutierrez C., M.; Meléndez Gómez, C. M.; Vargas Méndez, L. Y.; Bermúdez Jaimes, J. H. *Synthesis* **2010**, 593–600. doi:10.1055/s-0029-1218613
25. Kouznetsov, V. V.; Meléndez Gomez, C. M.; Bermúdez Jaimes, J. H. *J. Heterocycl. Chem.* **2010**, *47*, 1148–1152. doi:10.1002/jhet.441
26. Kashdan, D. S.; Schwartz, J. A.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 2638–2643. doi:10.1021/jo00134a025
27. Teske, J. A.; Deiters, A. *J. Org. Chem.* **2008**, *73*, 342–345. doi:10.1021/jo7020955
28. Shindoh, N.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *J. Org. Chem.* **2008**, *73*, 7451–7456. doi:10.1021/jo8009243
29. Kudale, A. A.; Kendell, J.; Miller, D. O.; Collins, J. L.; Bodwell, G. J. *J. Org. Chem.* **2008**, *73*, 8437–8447. doi:10.1021/jo801411p
30. Hadden, M.; Nieuwenhuyzen, M.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron* **2001**, *57*, 5615–5624. doi:10.1016/S0040-4020(01)00466-5
31. Kajino, M.; Hird, N. W.; Tarui, N.; Banno, H.; Kawano, Y.; Inatomi, N. Fused quinoline derivative and use thereof. PCT WO2005/105802 A1, Nov 10, 2005. *Chem. Abstr.* **2005**, *143*, 440393.
32. Lulinski, P.; Krassowska-Swiebocka, B.; Skulski, L. *Molecules* **2004**, *9*, 595–601. doi:10.3390/90700595
33. Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. *Synlett* **1998**, 35–36. doi:10.1055/s-1998-1583
34. Bhatnagar, I.; George, M. V. *J. Org. Chem.* **1968**, *33*, 2407–2411. doi:10.1021/jo01270a052
35. Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252–1255. doi:10.1021/jo00383a014
36. Sekine, Y. *Atmos. Environ.* **2002**, *36*, 5543–5547. doi:10.1016/S1352-2310(02)00670-2

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The definitive version of this article is the electronic one which can be found at: [doi:10.3762/bjoc.7.110](https://doi.org/10.3762/bjoc.7.110)

A practical route to tertiary diarylmethylamides or -carbamates from imines, organozinc reagents and acyl chlorides or chloroformates

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Letter

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Keywords:

acyliminium; amides; carbamates; multicomponent reactions; organozinc reagents

Beilstein J. Org. Chem. **2011**, *7*, 997–1002.

doi:10.3762/bjoc.7.112

Received: 07 April 2011

Accepted: 22 June 2011

Published: 20 July 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

A practical route to tertiary diarylmethylamides or -carbamates from imines, organozinc reagents and acyl chlorides or chloroformates is described. This route involves the formation of an imine, which is used without isolation, followed by its activation by the carbonyl-containing electrophile and the trapping of the acyliminium by an organozinc reagent. Most steps are conducted concomitantly to render the procedure as practical and straightforward as possible. Therefore, the whole experimental protocol takes less than two hours.

Introduction

Diarylmethylamines constitute an important class of nitrogen-containing compounds displaying antihistaminic, anti-arrhythmic, diuretic, antidepressant, laxative, anesthetic and anticholinergic properties [1,2]. In this context, diarylmethylamides and -carbamates represent reliable *N*-protected diarylmethylamine derivatives and should thus serve as valuable precursors in the preparation of compounds of pharmaceutical interest. Several procedures enabling the construction of the diarylmethylamide and -carbamate core have been described. However, with respect to the substitution pattern of the expected final compound, available methods differ notably.

Indeed, while the synthesis of secondary *N*-protected diarylmethylamines generally relies on the addition of organometallic reagents to electron-deficient (activated) imines [3-7], the preparation of tertiary diarylmethylamides or -carbamates may be conducted through the addition of aromatic nucleophiles onto *N*-acyliminium intermediates, formed in situ by reaction of imines with carbonyl-containing electrophiles. In this latter area, several studies have shown that some electron-enriched arenes can be used as nucleophiles and add efficiently onto the iminium carbon, either inter- or intramolecularly [8-16]. However, an increased range of aromatic moieties can be intro-

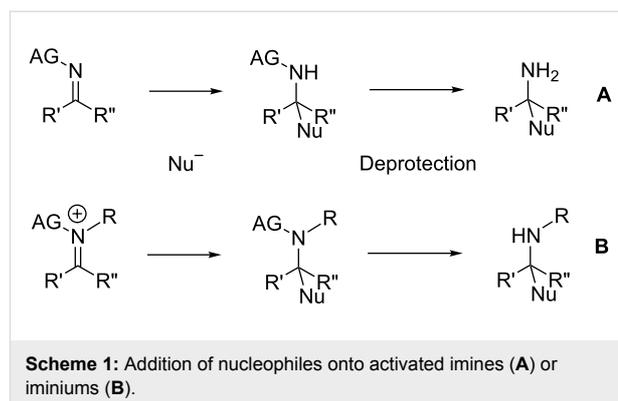
duced through the use of organometallic compounds. The most commonly employed reagents are organoindium [17,18], organolithium [19,20], organomagnesium [21,22], organotin [23], or organozinc compounds [24,25]. However, although these are recognized as mild multi-purpose reagents, sole examples of their use in nucleophilic additions on acyliminium salts consist, to the best of our knowledge, of the phenylation of quinolinium salts using diphenylzinc [26,27].

Recently, our group has been involved in various projects pertaining to the development of multicomponent reactions (MCRs) involving organometallic reagents, in particular organozinc reagents, due to their ability to react in very mild conditions and generally preserve most common functional groups. Moreover, used in stoichiometric amounts, organozinc reagents are more cost-effective and produce less toxic wastes than other common nucleophiles, such as, e.g., organoindium or organotin reagents. Our main contribution to the field was with regards to the use of arylzinc reagents in Mannich-type reactions with secondary amines and aldehydes to furnish tertiary diarylmethylamines [28–33]. However, while a large range of starting compounds could be used successfully in the process, we noticed that primary amines are ineffective, probably due to a weaker electrophilicity of the in situ-formed imines compared to iminium ions. Consequently, we report herein the use of primary amines in a sequential one-pot process, based on the preliminary activation of an aldimine with an acyl chloride or a chloroformate, and the subsequent trapping of the resulting acyliminium ion with an aromatic organozinc reagent, to generate a range of diarylmethylamides and -carbamates in satisfactory to good yields.

Results and Discussion

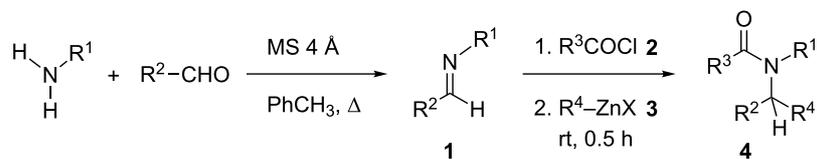
The limited intrinsic reactivity of imines towards the addition of nucleophiles has long been recognized as a major issue in nitrogen chemistry, but one which can be circumvented through several strategies, mainly intended to withdraw electrons and render the carbon more electrophilic [3–7]. Depending on the substitution pattern of the expected final amines, the increase of the electrophilicity should be implemented through the use of activated imines (Scheme 1, pathway A) or by quaternarization of the nitrogen atom with an electrophilic species (Scheme 1, pathway B). The activating group (AG) should then be released by a final deprotection to deliver the free amine (Scheme 1).

During the course of preceding works, we noticed that the addition of aromatic organozinc reagents onto *N*-substituted aldimines, formed in situ upon reaction of primary amines with aromatic aldehydes, cannot be undertaken under our established conditions. Thus, we intended to activate the C=N double bond by rendering the carbon more electrophilic and we



initially envisaged the use of Lewis acid catalysis. Indeed, we assumed that under these conditions, the formation of N-AG (AG = activating group) bonds would be reversible, thus cleavage would be effective in situ and only relatively small amounts of the Lewis acid would be necessary. While several common Lewis acids (TiCl₄, AlCl₃, CeCl₃ and BF₃·Et₂O) were trialled unsuccessfully, a different strategy based on the formation of solid bonds indicated that carbonyl derivatives such as acetyl chloride or methyl chloroformate were, in contrast, efficient activators of the C=N double bond, albeit used in stoichiometric amounts. This result is consistent with some previous studies reporting the activation of imines under an acyliminium form and the subsequent addition of either aromatic [17–23,26,27] or non-aromatic [34,35] organometallic nucleophiles onto carbon.

Our preliminary investigations were then conducted on *N*-benzylidenepropan-1-amine, taken as a model aldimine, which was preformed and purified prior to use. This compound was subjected to consecutive reactions with acetyl chloride and phenylzinc bromide, furnishing the corresponding diarylmethylamide in good yield (80%). However, as supplementary experiments indicated that the starting imine **1** can be used without preliminary purification, we chose to simplify the process by operating from the crude imine, although slightly lower yields (10–15% decreasing) were hence obtained. Thus, in a typical experiment, the amine and the aldehyde were heated in toluene in the presence of 4 Å molecular sieves for a few minutes. After cooling to room temperature, the toluene solution containing the imine **1** was transferred into another flask in which a slight excess of the electrophile (acyl chloride or chloroformate **2**) was added. After a limited period under heating, the arylzinc reagent **3**, prepared in parallel via a cobalt-catalyzed procedure [36] was added and the resulting solution was stirred for 30 minutes at ambient temperature. The chromatographic purification of the crude oil afforded the expected diarylmethylamide or -carbamate **4**. Representative experimental results are reported in Table 1.

Table 1: Formation of diarylmethylamides and -carbamates.^a

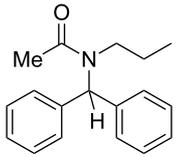
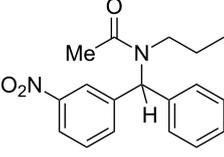
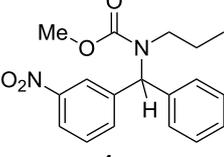
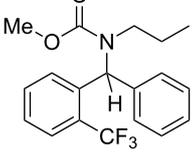
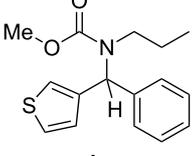
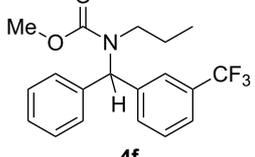
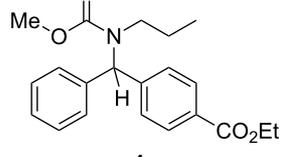
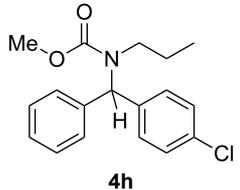
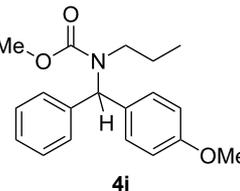
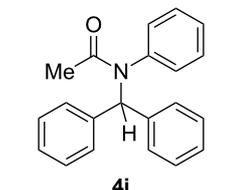
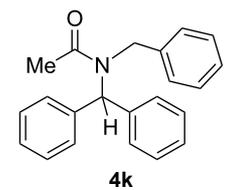
Entry	R ¹	R ²	R ³	R ⁴	Product	Isolated yield (%)
1	<i>n</i> -Pr	Ph	Me	Ph	 4a	64
2	<i>n</i> -Pr	3-O ₂ N-C ₆ H ₄ -	Me	Ph	 4b	55
3	<i>n</i> -Pr	3-O ₂ N-C ₆ H ₄ -	MeO	Ph	 4c	59
4	<i>n</i> -Pr	2-F ₃ C-C ₆ H ₄ -	MeO	Ph	 4d	67
5	<i>n</i> -Pr	thiophen-3-yl	MeO	Ph	 4e	42
6	<i>n</i> -Pr	Ph	MeO	3-F ₃ C-C ₆ H ₄ -	 4f	68
7	<i>n</i> -Pr	Ph	MeO	4-EtO ₂ C-C ₆ H ₄ -	 4g	57

Table 1: Formation of diarylmethylamides and -carbamates.^a (continued)

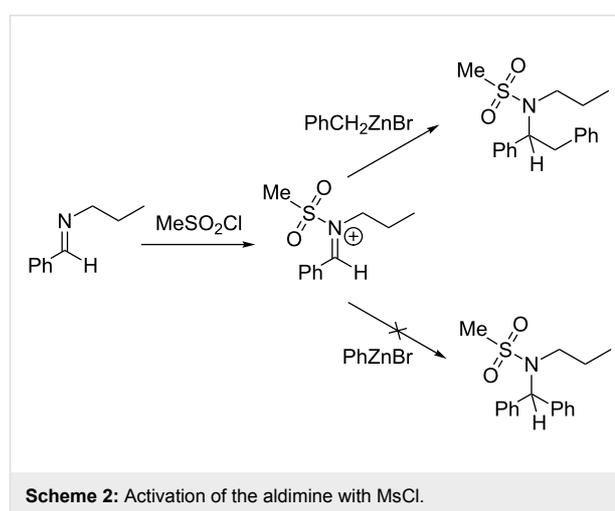
8	<i>n</i> -Pr	Ph	MeO	4-Cl-C ₆ H ₄ -	 4h	71
9	<i>n</i> -Pr	Ph	MeO	4-MeO-C ₆ H ₄ -	 4i	63
10	Ph	Ph	Me	Ph	 4j	69
11	Bn	Ph	Me	Ph	 4k	36

^aExperiments were conducted with ~10 mmol of imine, 12 mmol of acyl chloride or chloroformate, 13–16 mmol of the organozinc reagent, prepared from 20 mmol of aryl bromide.

Under these conditions, coupling products **4** are formed in low to high yields. The use of acetyl chloride (Table 1, entries 1, 2, 10 and 11) provided similar results to those observed with methyl chloroformate (Table 1, entries 3–9). It can be seen that more limited yields were obtained when a thiophene-derived aldehyde (Table 1, entry 5) or benzylamine was employed as the starting amine (Table 1, entry 11). However, these last two results could not be explained.

We next tried to extend the reaction to other electrophilic compounds that are known to easily form N–AG bonds with imines and furnish analogous iminium salts. The case of methanesulfonyl chloride (MsCl) was dealt with first (Scheme 2).

Unfortunately, while the reaction of benzylzinc bromide proved efficient under MsCl activation, phenylzinc bromide did not undergo the coupling at all [37]. This was also the case with trimethylsilyl chloride as an activator, whose reaction with the model aldimine and phenylzinc bromide did not afford the expected compound. On the other hand, a preliminary experiment indicated that trifluoroacetic anhydride was a very reliable activator of the imine towards phenylzinc bromide addition.



These results, combined with the above reported observations with common Lewis acids, may indicate that acylating reagents are particularly reliable for the activation of aldimines toward arylzinc additions. However, the use of carbonyl-containing electrophiles obviously constitutes an important drawback of the procedure. Indeed, although TBAF has been reported to

constitute a mild deprotection reagent for a range of carbamates [38,39], the cleavage of the N–C=O bond, which is formed during the process, might be commonly achieved under rather harsh conditions. This is not the case with other potential activating agents such as sulfinic or phosphinic chloride derivatives (ClS(O)R and ClP(O)R₂), whose N–AG bond might be cleaved easily upon acidic work-up. In addition, chiral versions of such activators would be of further interest for potential asymmetric couplings (at least with benzylzinc reagents), as the stereogenic center would be located very close to the impending asymmetric carbon and may thus serve as a valuable chiral auxiliary. Consequently, we envisage the implementation a further study which would be dedicated to the evaluation of well-recognized chiral inductors such as Ellman- [40,41] or Davis-type [42,43] sulfinyl derivatives in the process.

Conclusion

In conclusion, the results reported in this study indicate that the formation of acyliminium cations constitutes a very convenient approach to the activation of imines toward the addition of aromatic organozinc reagents. Indeed, we could prepare a range of diarylmethylamides or diarylmethylcarbamates by a sequential multicomponent process involving the preliminary formation of an imine, which can be used without isolation, its activation by an acyl chloride or a chloroformate and the final trapping of the resulting acyliminium salt by an arylzinc reagent. However, the harsh conditions which would probably be required for the deprotection of the amide or carbamate function prompt us to undertake complementary experiments dedicated to the assessment of easier-to-cleave activating groups. Consequently, the evaluation of sulfinyl- or phosphinyl derivatives in the process has been undertaken recently and will be reported in due course.

Experimental

Typical procedure for the preparation of diarylmethylamides and carbamates

The aldimine (~10 mmol) was prepared from the aromatic aldehyde (12 mmol) and the amine (12 mmol) in toluene (10 mL) in the presence of 4 Å molecular sieves (10 g) and *para*-toluene-sulfonic acid (10 mg). After 30 min stirring at 80 °C and cooling to rt, the solution was taken-up with a syringe and the sieves washed with 5 mL toluene. The combined toluene fractions were placed in another flask, which was flushed with argon prior to addition, and acetyl chloride or methyl chloroformate (12 mmol) was added. The resulting mixture was stirred at rt (ClCOCH₃) or at 50 °C (ClCOOCH₃) for 30 min, a period during which the aromatic organozinc reagent (13–16 mmol, depending on the starting halide) was prepared concomitantly as follows: A 100 mL round bottom flask was flushed with argon, then acetonitrile (20 mL), zinc dust (3 g), TFA (0.2 mL) and

BrCH₂CH₂Br (0.2 mL) were added consecutively under vigorous (~500 rpm) stirring. The mixture was heated until gas was evolved (at 50–70 °C), then allowed to cool to rt under continuous stirring. The aryl bromide (15 mmol) and anhydrous cobalt bromide (330 mg) were then added to the mixture, which was stirred at rt for additional 20 min. Stirring was then stopped and the surrounding solution was taken-up with a syringe. The solution was then added to the flask containing the imine/carbonyl-containing compound mixture and the resulting mixture was stirred at rt for 30 min. The solution was poured into a sat. NH₄Cl solution (100 mL), extracted with diethyl ether (2 × 75 mL) and the combined organic fractions were dried with magnesium sulfate, filtrated and then concentrated under reduced pressure. The crude oil was purified by column chromatography over silica gel with a pentane/diethyl ether mixture (1:0 to 0:1) as an eluant to afford the diarylmethylamide or carbamate **4**.

NMR data for selected compounds

Methyl phenyl(2-(trifluoromethyl)phenyl)methyl(propyl)carbamate (**4d**) ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.37–7.25 (m, 4H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.94 (s, 1H), 3.71 (s, 3H), 3.45–3.31 (m, 1H), 3.23–3.11 (m, 1H), 1.27–1.11 (m, 1H), 0.79 (br s, 1H), 0.56 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.9, 139.9, 139.5, 131.7, 131.0, 129.5 (q, *J* = 30.3 Hz), 128.4, 128.0, 127.9, 127.4, 126.4 (q, *J* = 6.0 Hz), 124.2 (q, *J* = 274.4 Hz), 59.4, 52.7, 47.5, 21.9, 11.11.

N-Benzhydryl-*N*-phenylacetamide (**4j**) ¹H NMR (400 MHz, CDCl₃) δ 7.19–7.10 (m, 15H), 6.74 (s, 1H), 1.86 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 140.9, 139.2, 130.2, 129.7, 128.9, 128.1, 128.0, 127.4, 64.1, 23.7.

N-Benzhydryl-*N*-benzylacetamide (**4k**) ¹H NMR (400 MHz, CDCl₃) δ 7.15–6.96 (m, 14H), 6.67–6.64 (m, 2H), 4.57 (s, 2H), 2.04 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.2, 139.3, 137.4, 129.2, 128.5, 128.2, 127.9, 127.6, 125.8, 66.4, 48.0, 22.8.

Acknowledgements

Financial support of this work by the CNRS and the University Paris-Est (PhD grant) is gratefully acknowledged.

References

- Spencer, C. M.; Faulds, D.; Peters, D. H. *Drugs* **1993**, *46*, 1055–1080.
- Sakurai, S.; Ogawa, N.; Suzuki, T.; Kato, K.; Ohashi, T.; Yasuda, S.; Kato, H.; Ito, Y. *Chem. Pharm. Bull.* **1996**, *44*, 765–777.
- Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. doi:10.1016/S0957-4166(97)00208-5
- Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438. doi:10.1021/cr940474e
- Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094. doi:10.1021/cr980414z

6. Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569. doi:10.1016/j.tet.2006.11.076
7. Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem.* **2002**, *114*, 3844–3846. doi:10.1002/1521-3757(20021004)114:19<3844::AID-ANGE3844>3.0.CO;2-R
8. Zhang, Y.; Kindelin, P. J.; DeSchepper, D. J.; Zheng, C.; Klumpp, D. A. *Synthesis* **2006**, 1775–1780. doi:10.1055/s-2006-942387
9. Kitabatake, M.; Saitoh, T.; Sano, T.; Horiguchi, Y. *Heterocycles* **2009**, *78*, 1177–1181. doi:10.3987/COM-08-11621
10. Zhang, Y.; DeSchepper, D. J.; Gilbert, T. M.; Sai, K. K. S.; Klumpp, D. A. *Chem. Commun.* **2007**, 4032–4034. doi:10.1039/b708760h
11. Romero, M.; Caignard, D.-H.; Renard, P.; Pujol, M. D. *Tetrahedron* **2008**, *64*, 11020–11027. doi:10.1016/j.tet.2008.09.097
12. Klumpp, D. A.; Zhang, Y.; O'Connor, M. J.; Esteves, P. M.; de Almeida, L. S. *Org. Lett.* **2007**, *9*, 3085–3088. doi:10.1021/ol0711570
13. Venkov, A. P.; Statkova-Abeghe, S. *Synth. Commun.* **1996**, *26*, 127–134. doi:10.1080/00397919608003871
14. Venkov, A. P.; Statkova, S. M.; Ivanov, I. I. *Synth. Commun.* **1992**, *22*, 125–134. doi:10.1080/00397919208021083
15. Venkov, A. P.; Statkova, S. M. *Synth. Commun.* **1991**, *21*, 1511–1520. doi:10.1080/00397919108016425
16. Venkov, A. P.; Molloy, N. M. *Synthesis* **1982**, 216–217. doi:10.1055/s-1982-29752
17. Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 1991–1993. doi:10.1021/ol060277p
18. Beveridge, R. E.; Black, D. A.; Arndtsen, B. A. *Eur. J. Org. Chem.* **2010**, 3650–3656. doi:10.1002/ejoc.201000231
19. Lamblin, M.; Couture, A.; Deniau, E.; Grandclaude, P. *Tetrahedron: Asymmetry* **2008**, *19*, 111–123. doi:10.1016/j.tetasy.2007.11.014
20. Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117–2122. doi:10.1016/S0957-4166(02)00531-1
21. Venkov, A. P.; Statkova-Abeghe, S. M. *Synth. Commun.* **1995**, 1817–1824. doi:10.1080/00397919508015425
22. Pegoraro, S.; Lang, M.; Dreker, T.; Kraus, J.; Hamm, S.; Meere, C.; Feurle, J.; Tasler, S.; Prütting, S.; Kuras, Z.; Visan, V.; Grissmer, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2299–2304. doi:10.1016/j.bmcl.2009.02.077
23. Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2005**, *70*, 5133–5138. doi:10.1021/jo0503557
24. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188. doi:10.1021/cr00022a008
25. Knochel, P.; Jones, P., Eds. *Organozinc Reagents, A Practical Approach*; The Practical Approach in Chemistry Series; Oxford University Press: Oxford, 1999.
26. Ludwig, M.; Polborn, K.; Wanner, K. T. *Heterocycles* **2003**, *61*, 299–326. doi:10.3987/COM-03-S40
27. Bender, C.; Liebscher, J. *ARKIVOC* **2009**, (vi), 111–136.
28. Haurena, C.; Le Gall, E.; Sengmany, S.; Martens, T. *Tetrahedron* **2010**, *66*, 9902–9911. doi:10.1016/j.tet.2010.10.058
29. Le Gall, E.; Haurena, C.; Sengmany, S.; Martens, T.; Troupel, M. *J. Org. Chem.* **2009**, *74*, 7970–7973. doi:10.1021/jo901704s
30. Sengmany, S.; Le Gall, E.; Troupel, M. *Synlett* **2008**, 1031–1035.
31. Sengmany, S.; Le Gall, E.; Le Jean, C.; Troupel, M.; Nédélec, J.-Y. *Tetrahedron* **2007**, *63*, 3672–3681. doi:10.1016/j.tet.2007.02.086
32. Le Gall, E.; Troupel, M.; Nédélec, J.-Y. *Tetrahedron* **2006**, *62*, 9953–9965. doi:10.1016/j.tet.2006.08.008
33. Le Gall, E.; Troupel, M.; Nédélec, J.-Y. *Tetrahedron Lett.* **2006**, *47*, 2497–2500. doi:10.1016/j.tetlet.2006.02.056
34. Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107–1110. doi:10.1021/ol036462+
35. Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497–1499. doi:10.1021/ol049578u
36. Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870. doi:10.1021/ja0289494
37. The more important reactivity of benzylzinc vs arylzinc reagents has been noticed on several occasions. For instance, we have already shown that benzyl bromides react, under Barbier-like conditions, with aldehydes and primary amines whereas aryl bromides do not undergo the coupling at all. This result is consistent with a possible nucleophilic addition of benzylzinc reagents onto imines without mandatory activation of the latter. See ref. [29] for details.
38. Routier, S.; Saugé, L.; Ayerbe, N.; Coudert, G.; Mérour, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 589–591. doi:10.1016/S0040-4039(01)02225-0
39. Jacquemard, U.; Bénétou, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039–10047. doi:10.1016/j.tet.2004.07.071
40. Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914. doi:10.1021/ja972012z
41. Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995. doi:10.1021/ar020066u
42. Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993–9003. doi:10.1021/jo061027p
43. Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030. doi:10.1016/j.tet.2004.06.071

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Novel synthesis of pseudopeptides bearing a difluoromethyl group by Ugi reaction and desulfanylation

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Full Research Paper

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Keywords:

difluoromethyl functionality; *gem*-difluoromethylene-containing acid;
pseudopeptides; reductive cleavage; Ugi reaction

Beilstein J. Org. Chem. **2011**, *7*, 1070–1074.

doi:10.3762/bjoc.7.123

Received: 07 April 2011

Accepted: 12 July 2011

Published: 08 August 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

Thirteen difluoromethyl-containing pseudopeptides were synthesized by Ugi reaction using the novel building block 2,2-difluoro-2-(phenylthio)acetic acid (**2**) as one component, followed by removal of the phenylsulfanyl protecting group in the presence of tri-n-butyltin hydride and azobisisobutyronitrile.

Introduction

Fluorinated amino acids and pseudopeptides have increasingly attracted attention in recent years [1-5]. The selective incorporation of fluorine-containing groups, such as trifluoromethyl, difluoromethyl and difluoromethylene, into peptides or peptidomimetics often drastically alters the chemical, physical, and biological properties of the parent compounds [6-9]. Nowadays, difluoromethyl-containing compounds are increasingly being applied in pharmaceuticals and agrochemicals [10-12]. It is reported that difluoromethyl functionality (CF₂H) is isosteric and isopolar to the hydroxyl group and can behave as a hydrogen donor through hydrogen bonding [13].

However, to date, most fluorine-containing peptide modifications involve the introduction of trifluoromethyl or difluoro-

methylene into molecules [14-18]. Only a few examples have been reported of the preparation and bioassay of pseudopeptides and peptidomimetics bearing difluoromethyl groups. For example, compound **I** can act as bradykinin B1 antagonist or inverse agonist and can be used in the prevention of inflammation and pain [19]. Compound **II** is an inhibitor of microsomal triglyceride transfer protein (MTP) and useful for the treatment of obesity and atherosclerosis (Figure 1) [20].

Among the protocols for the preparation of pseudopeptide derivatives, the Ugi four-component reaction offers significant advantages over conventional linear-step synthesis [21]. Various fluorinated building blocks have been used in the Ugi four-component reaction to construct a fluorinated compound

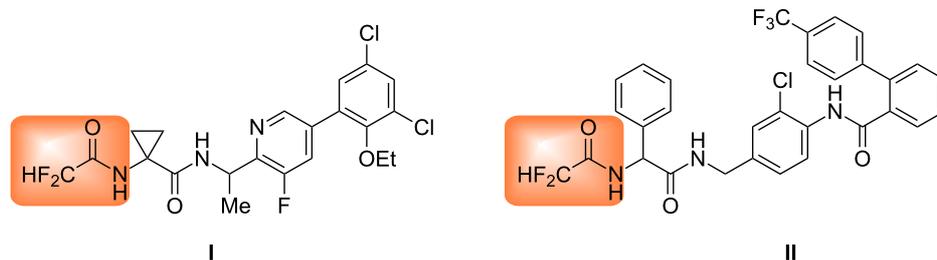


Figure 1: Two examples of bioactive pseudopeptides bearing a CF₂H group.

library [22–25]. Our group has always been interested in developing efficient methods for the preparation of difluoromethyl-containing compounds through multicomponent reactions [26–30]. Recently, we reported a novel and general strategy for the construction of a difluoromethyl compound library, and we further illustrated this strategy by application to the synthesis of CF₂H-bearing pseudopeptides and 1,2,3-triazoles through Ugi and click reaction, respectively [27,30]. In continuation of our interest in the synthesis of diverse difluoromethyl-containing pseudopeptides, we herein report a novel and efficient synthesis of difluoromethyl-containing pseudopeptides through Ugi reaction, with *gem*-difluoromethylene-containing acid as a key component, followed by reductive cleavage of the phenylsulfanyl group (Scheme 1).

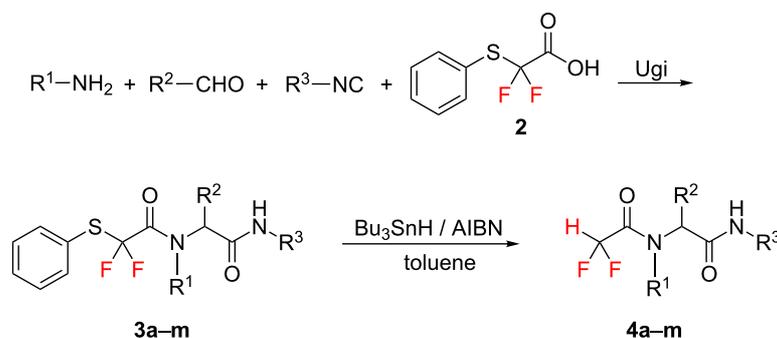
Results and Discussion

For the purpose of screening novel bioactive compounds, we recently prepared a variety of diverse difluoromethyl-containing pseudopeptides. In our initial experiments, we tried to use difluoroacetic acid as one component to undergo Ugi reaction to prepare difluoromethyl-containing pseudopeptides. Unfortunately, the anticipated difluoromethyl-containing product **4a** was not obtained (Scheme 2). Although there are a few examples of acetic acid and trifluoroacetic acid acting as substrates in an Ugi reaction [24,31], up to now, no literature was found

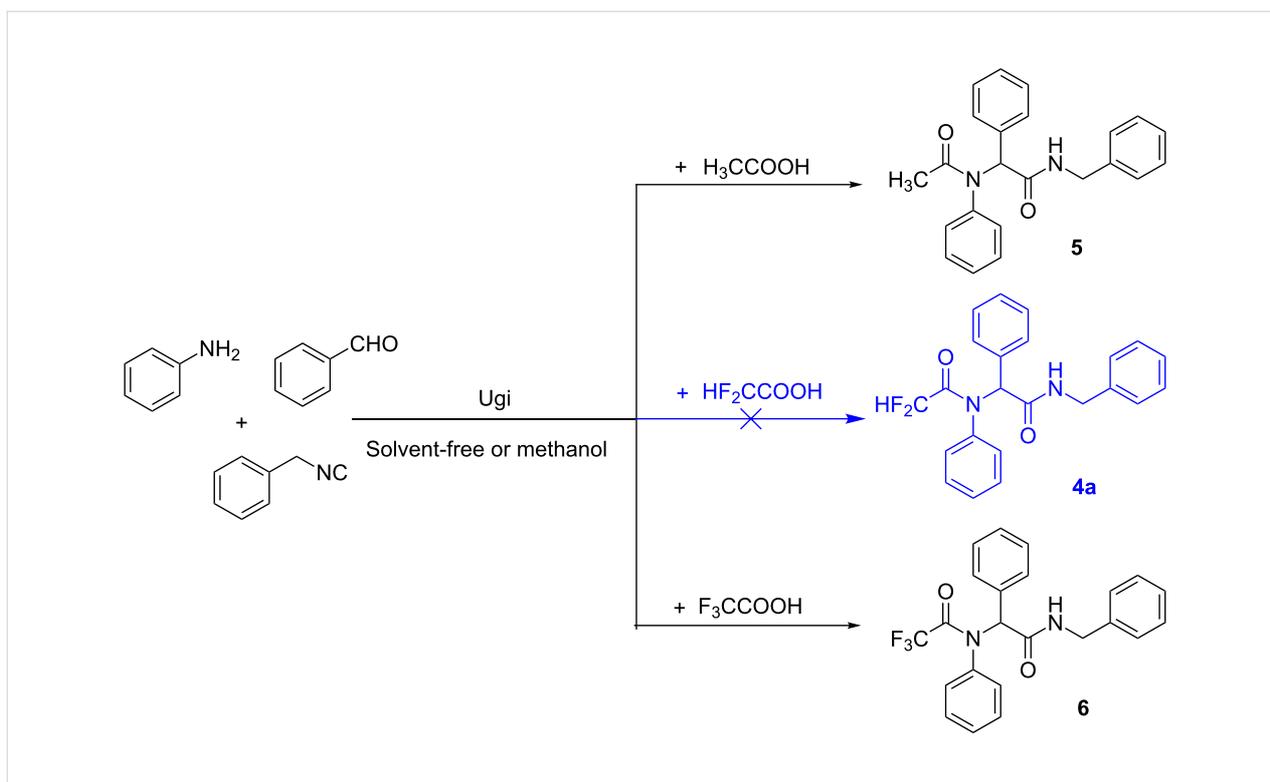
concerning the use of difluoroacetic acid as one of the components in the Ugi reaction. For a comparative study, acetic acid and trifluoroacetic acid served as the substrates for the Ugi reaction under the same reaction conditions as those used for the difluoroacetic acid, and the results indicated that the reaction proceeded efficiently regardless of reaction conditions, and the Ugi products (**5** and **6**) were obtained in good yields. The hydrogen atom next to the CF₂ group seems to influence the formation of Ugi product.

In previous studies, we developed a synthetic methodology to prepare functionalized small molecules having a CF₂H group [27]. In this work, we first synthesized a protected difluoro-containing building block, 2,2-difluoro-2-(phenylthio)acetic acid (**2**). The synthesis of compound **2** is illustrated in Scheme 3. The ethyl 2,2-difluoro-2-(phenylthio)acetate (**1**) was readily prepared by the reaction of ethyl bromodifluoroacetate and thiophenol according to the known procedure [32]. The novel difluorinated acid **2** was obtained by hydrolysis of the ester under basic condition in nearly quantitative yield.

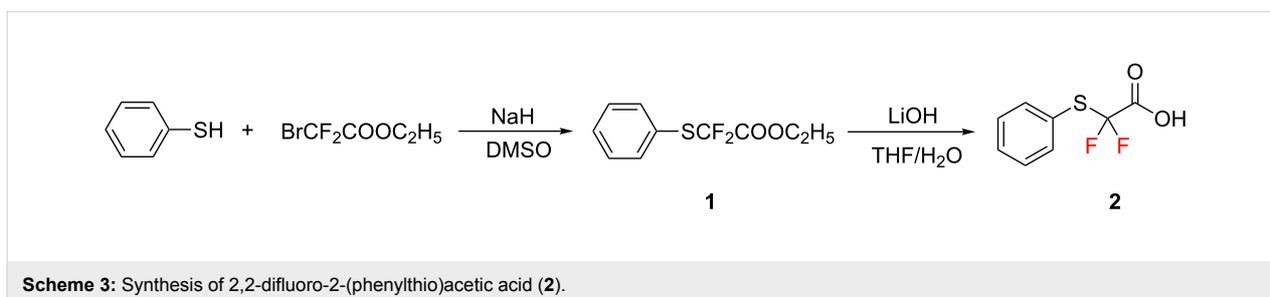
After successful synthesis of the protected functionalized CF₂ building block **2**, we tried to use it as one of the components in the preparations of the difluoromethylene-containing pseudopeptides by Ugi reaction. Indeed, the reaction of aniline,



Scheme 1: Synthesis of difluoromethyl-containing pseudopeptides (**4a–m**) by Ugi reaction and desulfanylation.



Scheme 2: The Ugi reaction of aniline, benzaldehyde, (isocyanomethyl)benzene with acetic acid, difluoroacetic acid and trifluoroacetic acid in methanol or under solvent-free conditions.



Scheme 3: Synthesis of 2,2-difluoro-2-(phenylthio)acetic acid (**2**).

benzaldehyde, (isocyanomethyl)benzene with **2** proceeded efficiently under solvent-free conditions. Finally, we removed the protecting group (PhS) with $\text{Bu}_3\text{SnH/AIBN}$ according to our previous research, and the desired difluoromethyl-containing pseudopeptide was successfully obtained [27].

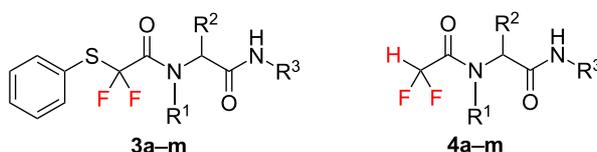
To demonstrate the scope of the method, several different substituted anilines, substituted benzaldehydes, isocyanides and this novel difluorinated building block **2** were subjected to Ugi reaction under solvent-free conditions, followed by reductive cleavage of the phenylsulfanyl group. It was found that both Ugi reaction and desulfanylation proceeded smoothly for all substrates used to give the corresponding difluoromethylene-containing and difluoromethyl-containing pseudopeptides (**3a–m** and **4a–m**) in good yields (Table 1).

Conclusion

In summary, we have developed a novel and efficient protocol for the synthesis of CF_2H -containing pseudopeptides by Ugi reaction of substituted anilines, benzaldehyde, isocyanides and the novel building block 2,2-difluoro-2-(phenylthio)acetic acid (**2**), followed by the cleavage of the phenylsulfanyl group.

Experimental General

All reagents were of analytic grade, obtained from commercial suppliers and were used without further purification. Melting points were measured in an open capillary using Büchi melting point B-540 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as

Table 1: Synthesis of difluoromethylene-containing pseudopeptides (**3a–m**) and difluoromethyl-containing pseudopeptides (**4a–m**).

Entry	R ¹	R ²	R ³	3 Yield (%) ^a	4 Yield (%) ^a
a	Ph	Ph	Bn	82	75
b	2-MePh	Ph	Bn	78	68
c	2-MePh	4-MePh	Bn	75	74
d	4-MeOPh	Ph	Bn	79	75
e	Ph	4-MeOPh	Bn	78	70
f	2-MePh	4-MeOPh	Bn	74	67
g	4-MePh	4-MeOPh	Bn	72	78
h	4-FPh	4-MeOPh	Bn	70	71
i	Ph	4-FPh	Bn	77	75
j	2-MePh	4-FPh	Bn	70	69
k	4-MeOPh	4-FPh	Bn	72	74
l	Ph	Ph	Ph	68	66
m	Ph	4-MeOPh	Ph	66	60

^aIsolated yield.

internal standard. The ¹⁹F NMR were obtained using a Bruker AM-400 spectrometer (376 MHz) and the ¹⁹F NMR were measured with external CF₃CO₂H as standard. Gas chromatography-mass spectra (GC-MS) were recorded on HP 5973 MSD with 6890 GC. High resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument and recorded on a MicroMass LCTM spectrometer. Column chromatography was carried out with Merck 60 (230–400 mesh) silica gel.

General procedure for compounds **3a–m**

To a stirred amine (1 mmol), the aldehyde (1 mmol) was added in portions for about 5 min. The mixture was stirred for 30 min at rt. Then, the reaction mixture was heated to 60 °C, and isocyanide (1 mmol) and 2,2-difluoro-2-(phenylthio)acetic acid (**2**) (1 mmol) were added. Stirring was continued at 60 °C for 1 h (TLC). The crude residue was purified by chromatography to give the desired products **3**.

General procedure for compounds **4a–m**

Bu₃SnH (0.58 g, 2 mmol) was added under argon atmosphere to a solution of **3** (1 mmol) in dry toluene (3 mL). Deoxygenation was continued for 5 min. Azobisisobutyronitrile (AIBN) (0.02 g, 0.1 mmol) was added and the solution was heated at reflux for 9 h (TLC). The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (5 mL). The solution was stirred with KF/H₂O (15 mg/0.15 mL)

for 3 h and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed successively with water (20 mL) and brine (20 mL), and dried over anhydrous Na₂SO₄. After removal of the solvent, the crude product was purified by chromatography to give the desired products **4**.

Supporting Information

Supporting Information File 1

Experimental procedures and compound characterization.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-123-S1.pdf>]

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (Grant No. 21072057), the National Basic Research Program of China (973 Program, 2010CB126101), the Shanghai Foundation of Science and Technology (09391911800) and the Shanghai Leading Academic Discipline Project (B507).

References

1. Qiu, X.; Meng, W.; Qing, F. *Tetrahedron* **2004**, *60*, 6711–6745. doi:10.1016/j.tet.2004.05.051
2. Jäckel, C.; Kocsch, B. *Eur. J. Org. Chem.* **2005**, 4483–4503. doi:10.1002/ejoc.200500205

3. Meng, H.; Kumar, K. *J. Am. Chem. Soc.* **2007**, *129*, 15615–15622. doi:10.1021/ja075373f
4. Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151–1157. doi:10.1039/b701559c
5. Mlostoń, G.; Objalska, E.; Heimgartner, H. *J. Fluorine Chem.* **2010**, *131*, 829–843. doi:10.1016/j.jfluchem.2010.05.014
6. Zanda, M. *New J. Chem.* **2004**, *28*, 1401–1411. doi:10.1039/B405955G
7. Giménez, D.; Andreu, C.; del Olmo, M.; Varea, T.; Diaz, D.; Asensio, G. *Bioorg. Med. Chem.* **2006**, *14*, 6971–6978. doi:10.1016/j.bmc.2006.06.027
8. Olimpieri, F.; Tambaro, S.; Fustero, S.; Lazzari, P.; Sanchez-Roselló, M.; Pani, L.; Volonterio, A.; Zanda, M. *Bioorg. Med. Chem.* **2009**, *19*, 4715–4719. doi:10.1016/j.bmcl.2009.06.064
9. Kitamoto, T.; Marubayashi, S.; Yamazaki, T. *Tetrahedron* **2008**, *64*, 1888–1894. doi:10.1016/j.tet.2007.11.085
10. Goure, W. F.; Leschinsky, K. L.; Wratten, S. J.; Chupp, J. P. *J. Agric. Food Chem.* **1991**, *39*, 981–986. doi:10.1021/jf00005a036
11. Ojima, I.; Lin, S.; Slater, J. C.; Wang, T.; Pera, P.; Bernacki, R. J.; Ferlini, C.; Scambia, G. *Bioorg. Med. Chem.* **2000**, *8*, 1619–1628. doi:10.1016/S0968-0896(00)00093-6
12. Ferreira, S. B.; Costa, M. S.; Boechat, N.; Bezerra, R. J. S.; Genestra, M. S.; Canto-Cavaleiro, M. M.; Kover, W. B.; Ferreira, V. F. *Eur. J. Med. Chem.* **2007**, *42*, 1388–1395. doi:10.1016/j.ejmech.2007.02.020
13. Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626–1631. doi:10.1021/jo00111a021
14. Formicola, L.; Maréchal, X.; Basse, N.; Bouvier-Durand, M.; Bonnet-Delpon, D.; Milcent, T.; Reboud-Ravaux, M.; Onger, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 83–86. doi:10.1016/j.bmcl.2008.11.012
15. Fustero, S.; Chiva, G.; Piera, J.; Sanz-Cervera, J. F.; Volonterio, A.; Zanda, M.; Ramirez de Arellano, C. *J. Org. Chem.* **2009**, *74*, 3122–3132. doi:10.1021/jo9001867
16. Peng, W.; Zhao, J.; He, P.; Zhu, S. *Synlett* **2006**, 296–300. doi:10.1055/s-2006-926225
17. Li, G.; van der Donk, W. A. *Org. Lett.* **2007**, *9*, 41–44. doi:10.1021/ol062401a
18. Bigotti, S.; Meille, S. V.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2008**, *129*, 767–774. doi:10.1016/j.jfluchem.2008.06.018
19. Bock, M. G.; Feng, D.; Kuduk, S. Aminocyclopropanecarboxamide derivatives as bradykinin antagonists. Patent WO/2005/085198, Sept 15, 2005.
20. Bertinato, P.; Maddux, T. M. Microsomal triglyceride transfer protein inhibitors. Patent WO/2004/056775, July 8, 2004.
21. Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. doi:10.1021/cr0505728
22. Shibata, N.; Das, B. K.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4234–4236. doi:10.1039/b007455l
23. Gouge, V.; Jubault, P.; Quirion, J.-C. *Tetrahedron Lett.* **2004**, *45*, 773–776. doi:10.1016/j.tetlet.2003.11.019
24. Gulevich, A. V.; Shevchenko, N. E.; Balenkova, E. S.; Röscenthaler, G.-V.; Nenajdenko, V. G. *Tetrahedron* **2008**, *64*, 11706–11712. doi:10.1016/j.tet.2008.10.004
25. Wu, J.; Cao, S. *Curr. Org. Chem.* **2009**, *13*, 1791–1804. doi:10.2174/138527209789630460
26. Liu, N.; Cao, S.; Shen, L.; Wu, J.; Yu, J.; Zhang, J.; Li, H.; Qian, X. *Tetrahedron Lett.* **2009**, *50*, 1982–1985. doi:10.1016/j.tetlet.2009.02.056
27. Wu, J.; Cao, S.; Liu, N.; Shen, L.; Yu, J.; Zhang, J.; Li, H.; Qian, X. *Org. Biomol. Chem.* **2010**, *8*, 2386–2391. doi:10.1039/c000835d
28. Li, H.; Yu, J.; Cao, S.; Shen, L.; Wu, M.; Cheng, J.; Qian, X. *Sci. China, Ser. B: Chem.* **2010**, *53*, 1509–1513. doi:10.1007/s11426-010-4005-0
29. Wu, M.; Yu, J.; Zhao, W.; Wu, J.; Cao, S. *J. Fluorine Chem.* **2011**, *132*, 155–159. doi:10.1016/j.jfluchem.2010.12.010
30. Zhang, J.; Wu, J.; Shen, L.; Jin, G.; Cao, S. *Adv. Synth. Catal.* **2011**, *353*, 580–584. doi:10.1002/adsc.201000791
31. Bouma, M.; Masson, G.; Zhu, J. *J. Org. Chem.* **2010**, *75*, 2748–2751. doi:10.1021/jo100302y
32. Eto, H.; Kaneko, Y.; Takeda, S.; Tokizawa, M.; Sato, S.; Yoshida, K.; Namiki, S.; Ogawa, M.; Maebashi, K.; Ishida, K.; Matsumoto, M.; Asaoka, T. *Chem. Pharm. Bull.* **2001**, *49*, 173–182. doi:10.1248/cpb.49.173

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Multicomponent synthesis of artificial nucleases and their RNase and DNase activity

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Keywords:

DNA; isocyanide; multicomponent reaction; organocatalysis; peptidomimetic; RNA

Beilstein J. Org. Chem. **2011**, *7*, 1135–1140.

doi:10.3762/bjoc.7.131

Received: 03 May 2011

Accepted: 14 June 2011

Published: 19 August 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

The synthesis of new, artificial ribonucleases containing two amino acid residues connected by an aliphatic linker has been developed. Target molecules were synthesized via a catalytic three-component Ugi reaction from aliphatic diisocyanides. Preliminary investigations proved unspecific nuclease activity of the new compounds towards single-stranded RNA and double-stranded circular DNA.

Introduction

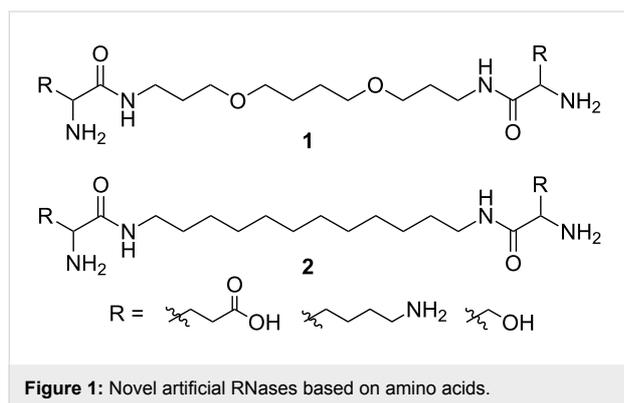
RNA cleavage can serve as a molecular tool for biological research [1], as well as for development of anticancer drugs [2,3] and new therapeutics against RNA-containing viruses. Recently, a number of synthetic RNA-cleaving molecules (artificial ribonucleases) had been developed and tested in vitro [4-11]. Among numerous artificial ribonucleases, peptidomime-

tics showed evident advantages due to their lower cytotoxicity and elevated potential penetration into living eukaryotic cells. Moreover, a few dipeptides [12] were shown to induce interferon production, thus providing antiviral defence. Therefore, the development of new peptidomimetics with ribonuclease activity is an important task in organic and biomolecular chem-

istry. In this paper we present the rational design, multicomponent synthesis, and RT-qPCR quantitation of nuclease activity of novel amino acids derivatives.

Results and Discussion

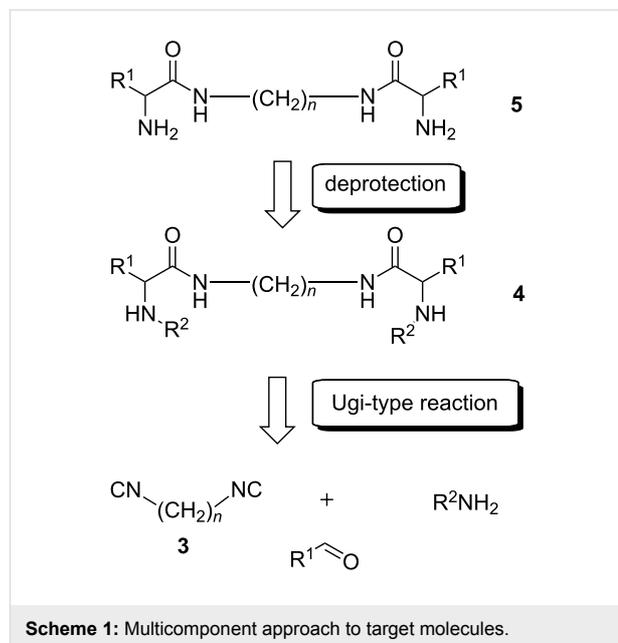
Recently, a number of artificial peptide ribonucleases modeling known catalytic centers of natural RNases A and T1 have been described [13-15]. RNA cleavage was shown to be more efficient in the presence of aliphatic hydrophobic linkers [16]. However, the potential role of the alkyl chain of the catalyst remains unclear. Interaction of hydrophobic residues in peptides was suggested to result in formation of RNase mimetics in solution thus enhancing their ribonuclease activity. To prove this suggestion, symmetric aliphatic diamides **1** and **2** containing natural amino acid residues have been synthesized (Figure 1). The compounds showed high ribonuclease activity with model oligoribonucleotides and an HIV-1 recombinant RNA fragment 96 nucleotides long [17].



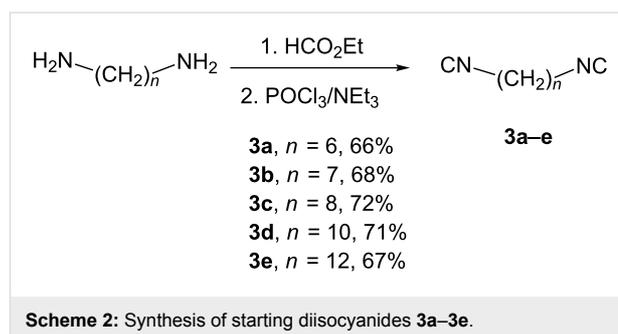
Previously, compounds **1** and **2** have been synthesized from the corresponding diamines by condensation with protected natural amino acids and subsequent deprotection [18]. This approach is significantly limited by using available natural amino acids (R is a natural amino acid residue). Consequently, the development of new simple, atom-economic methods for the synthesis of this class of potential biologically active compounds is of great importance in bioorganic and medicinal chemistry. The development of multicomponent approaches is especially important because multicomponent reactions (MCR) could be adapted to a high throughput synthesis of libraries of compounds.

It is known that isocyanide-based MCR are very efficient for synthesis of peptides and peptide molecules [19-24]. We proposed that the desired compounds **5**, containing two amide bonds and variable substituents, can be synthesized by the Ugi reaction with subsequent removal of diamine residue (Scheme 1). Original substrates for the synthesis could be ali-

phatic diisocyanides **3**, amines (with an easily removable protective group) and aldehydes. We used an organocatalytic three-component modification of the Ugi reaction, recently developed by List et al. [25]. The reaction results in diamines **4**, thus avoiding the acid residue removal stage.

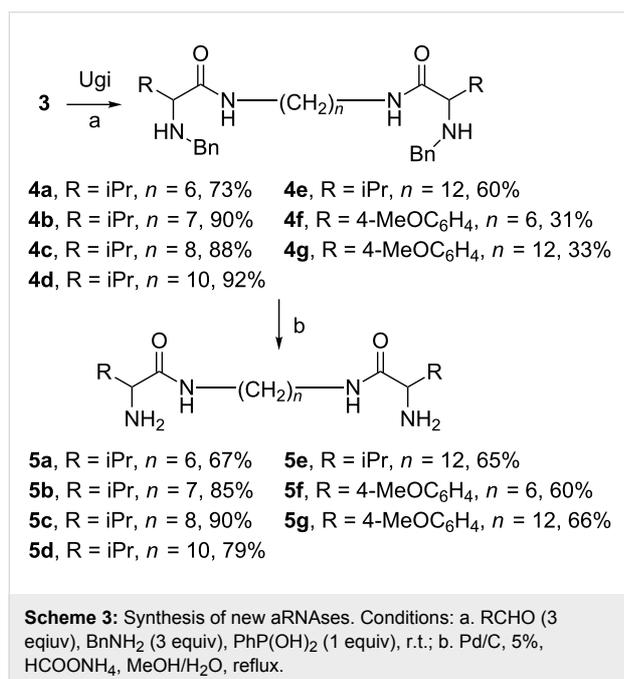


The starting diisocyanides **3** were obtained in good overall yields from commercially available diamines containing 6, 7, 8, 10 or 12 carbon atoms by the standard formylation–dehydration protocol (Scheme 2).



We found that these diisocyanides **3** participate successfully in the catalytic three-component reaction via a modified List procedure [25]. Diamides **4** with benzyl protective groups were synthesized in moderate to good yields under mild conditions. There is no obvious dependence of yield on the length of the carbon chain in **3**; aliphatic aldehydes gave better results in comparison to aromatic aldehydes (Scheme 3). Obviously, the suggested approach is an efficient and short method to form the skeleton of the target diamides. The benzyl groups can be easily

removed from compounds **4** by the standard hydrogenolysis procedure. For example, using Pd/C as catalyst we obtained the target peptidomimetics **5** in up to 90% yield. Thus, we synthesized a number of racemic peptidomimetics **4** and **5**, containing aliphatic or aromatic groups as well as various aliphatic linkers. With these diamides in hand we began the investigation of their biological activity.



Currently, real-time PCR is the better method for the quantitation of the target nucleic acids because of its high specificity and sensitivity of up to a few genome equivalents in a complex mixture [26]. In the present work, ribonuclease activity of the new synthesized compounds was studied in vitro by cleavage of the total cellular and the tick-borne encephalitis virus (TBEV) full-length genomic RNA isolated from infected mouse brain, with subsequent detection by RT-qPCR (TBEV is a human pathogenic member of the *Flaviviridae* family of RNA-containing viruses of positive polarity).

Complete cleavage of 2 μ g of cellular RNA including 10⁵ genome equivalents of the TBEV full-length RNA was observed after incubation of the total RNA from the virus-infected mouse brain with 2.5 mM aqueous solutions of peptidomimetics **5a–g** for 2 hours at 37 °C. Denaturing electrophoresis in SDS-agarose gel revealed complete cleavage of the total RNA (Supporting Information File 1, Figure S1) and RT-real time PCR showed complete destruction of the TBEV RNA (Figure 2).

Compounds **5e** and **5g**, the most hydrophobic among synthesized substances, might potentially penetrate through cellular or viral membranes and therefore the dependence of RNA cleavage on the concentration of the peptidomimetics was studied in detail. The concentration of compounds **5e** and **5g**, optimal for RNA cleavage, was determined by varying the

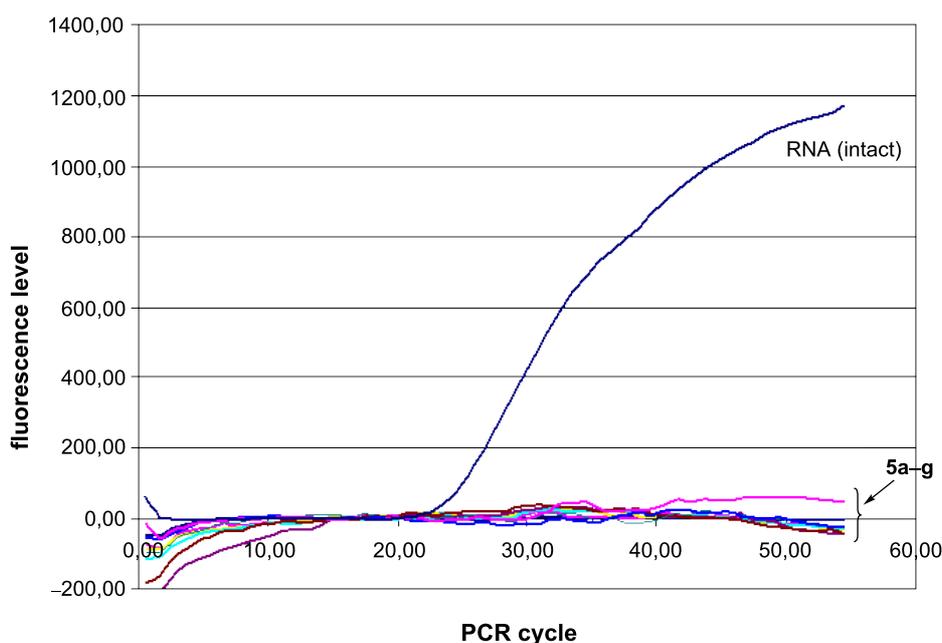


Figure 2: Results of RT-qPCR of the TBEV RNA cleavage products in presence of 2.5 mM peptidomimetics **5a–g** at 37 °C for 2 hours in H₂O.

concentration from 2.5×10^{-3} to 2.5×10^{-7} M (Supporting Information File 1, Figure S2 A and B). Dependence of optimal RNA cleavage on the concentration of peptidomimetics was not evident: Complete RNA cleavage of 2 μ g RNA was observed at a concentration of 2.5 mM for both **5e** with an aliphatic substituent and **5g** with an aromatic one.

Ribonuclease activity of the compounds **5c–e** and **5g** at 2.5 mM concentration was assayed in cultural medium RPMI 1640 and compared cleavage in H₂O. All artificial RNases cleaved RNA more efficiently in water than in RPMI 1640 (Figure 3 and Figure 4). Results of RT-real time PCR (Figure 3) and electrophoresis RT-qPCR products in 2% TBE-agarose gel (Figure 4) showed varying degrees of destruction of the TBEV RNA, respectively.

To analyze DNase activity of the novel compounds, both double-stranded circular recombinant plasmid DNA with cloned full-length TBEV copy of genome and single-stranded cDNA after reverse transcription of the TBEV RNA from the infected mouse brain with random N₆ primer was used. No destruction of single-stranded cDNA was observed after incubation with 2.5 mM solutions of compounds **5e** or **5g** for 2 hours at 37 °C (Supporting Information File 1, Figure S3). However, these compounds could partly cleave double-stranded plasmid DNA (Supporting Information File 1, Figure S4).



Figure 4: Results of electrophoresis in 2% TBE-agarose gel with ethidium bromide of RT-qPCR products from Figure 3. (Cleavage of total RNA from 10% brain suspensions from ICR mice infected with TBEV). Lanes: 1 - negative control; 2 and 3 - compound **5e** incubated with RNA in RPMI 1640 and in H₂O, respectively; 4 and 5 - compound **5g** incubated with RNA in RPMI 1640 and in H₂O, respectively; 6 and 7 - compound **5c** incubated with RNA in RPMI 1640 and in H₂O, respectively; 8 and 9 - compound **5d** incubated with RNA in RPMI 1640 and in H₂O, respectively.

Generally, all synthesized compounds were shown to be able to cleave completely single-stranded RNA but not single-stranded cDNA or hybrid of RNA with cDNA after reverse transcription irrespective of the structures of their substituents and the length of polymethylene linkers. Double-stranded circular plasmid DNA was partially destroyed possibly because of single-stranded DNA breaks. The mechanism has been previously shown for several artificial metal-free [27] and metal-dependent nucleases [28]. A further study of the TBEV RNA cleavage, both in extracellular virions and within infected cells as well as specific cleavage of only viral RNA, is required. Further investigations of developed artificial RNases are in progress.

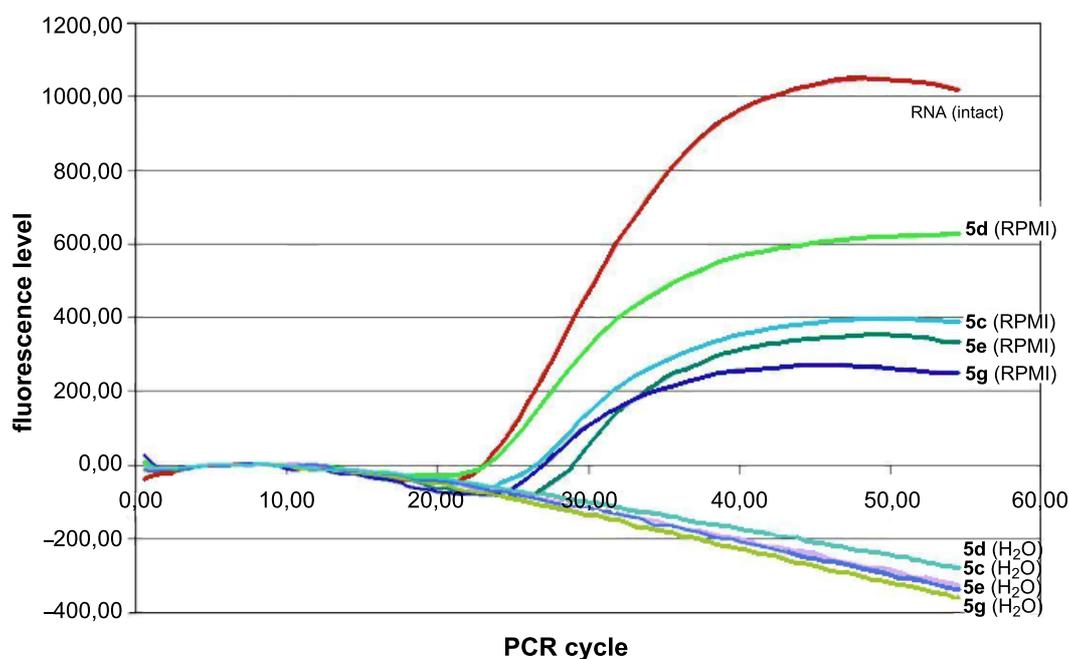


Figure 3: Results of RT-qPCR of the TBEV RNA cleavage products in the presence of 2.5 mM peptidomimetics after incubation in H₂O and in cultural medium RPMI 1640.

Conclusion

New artificial nucleases based on diamides containing two amino acid residues connected by aliphatic linkers were synthesized by a catalytic three-component Ugi-type reaction and subsequent deprotection. To quantitative cleavage of any nucleic acids, including single-stranded RNA and cDNA as well as double-stranded circular plasmid DNA, high-throughput RT-qPCR was developed and used. All synthesized compounds were shown to be able to cleave completely single-stranded RNA but not single-stranded cDNA or hybrid of RNA with cDNA after reverse transcription irrespective of the structure of their substituents and the length of the polymethylene linker.

Experimental

General procedure for the synthesis of diisocyanides **3**

A solution of the corresponding diamine (0.1 mol) in ethyl formate (100 mL) was heated under reflux for 5 h. The reaction mixture was concentrated in vacuo. The resulting formamide (without additional purification) was suspended in anhydrous dichloromethane (200 mL) and triethylamine (51 g, 0.5 mol) added. The mixture was cooled to 0 °C and POCl₃ (0.21 mol, 32 g) added dropwise at such a rate that the reaction temperature remained below 0 °C. The mixture was stirred for 2 h. The reaction mixture was poured into ice–water (500 mL) containing K₂CO₃ (100 g) maintaining the temperature below 25 °C. The resulting emulsion was stirred for 1 h at rt. The organic layer was separated, the aqueous layer extracted with CH₂Cl₂ (2 × 50 mL), and the combined organic layers were dried (K₂CO₃), purified by flash chromatography and concentrated in vacuo. The diisocyanide was obtained as a dark oil.

1,6-Diisocyanohexane (3a): Yield 66%, dark oil, *R*_f 0.8 (hexane/EtOAc 2:1); ¹H NMR (400 MHz, CDCl₃) δ 1.39–1.47 (m, 4H, (CH₂CH₂CH₂NC)₂), 1.55–1.73 (m, 4H, (CH₂CH₂CH₂NC)₂), 3.30–3.40 (m, 4H, (CH₂CH₂CH₂NC)₂); ¹³C NMR (100 MHz, CDCl₃) δ 155.6 (t, *J* = 5.9 Hz, NC), 41.1 (t, *J* = 6.6 Hz, (CH₂CH₂CH₂NC)₂), 28.5, 25.2; IR (cm⁻¹) 2150 (NC); Anal. calcd for C₈H₁₂N₂: C, 70.55; H, 8.88; found: C, 70.34; H, 8.62.

General procedure for the synthesis of **4a–g**

The corresponding isocyanide **3** (3 mmol) and phenyl phosphinic acid (3 mmol, 441 mg) were added to a mixture of the aldehyde (9 mmol) and benzylamine (9 mmol, 963 mg) in CH₂Cl₂ or MeOH (30 mL). The mixture was stirred for 48 h at rt, the solvent removed in vacuo and the residue purified by column chromatography (hexane/ethyl acetate 1:1). The product (colorless oil or white solid) can be converted into the corresponding hydrochloride by treatment with gaseous HCl in MeOH.

Compound 4a: The reaction was carried out in CH₂Cl₂, yield 73%; colorless oil; *R*_f 0.4 (hexane/EtOAc 1:1); ¹H NMR (400 MHz, CDCl₃) δ 0.86 (d, *J* = 7.1 Hz, 6H, 2 × CH₃), 0.94 (d, *J* = 7.1 Hz, 6H, 2 × CH₃), 1.29–1.36 (m, 4H, (CH₂CH₂CH₂NHCO)₂), 1.44–1.52 (m, 4H, (CH₂CH₂CH₂NHCO)₂), 1.6 (br s, 2H, 2 × NH), 2.06–2.15 (m, 2H, 2 × CH(CH₃)₂), 2.95 (d, *J* = 4.3 Hz, 2H, 2 × CH), 3.17–3.30 (m, 4H, (CH₂CH₂CH₂NHCO)₂), 3.68 (AB-system, *J* = 13.1 Hz, 4H, 2 × CH₂Ph), 7.20–7.35 (m, 12H, Ph, 2 × NH); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 139.6, 128.6, 128.1, 127.3, 67.9, 53.5, 38.6, 31.2, 29.7, 26.5, 19.6, 17.7; IR (cm⁻¹) 1640 (CONH), 3300 (br, CONH); ESI-MS (*m/z*): [M + H]⁺ calcd for C₃₀H₄₆N₄O₂, 495.3621; found, 495.3698.

Cleavage of the benzyl group

A solution of HCOONH₄ (1 g in 5 mL H₂O) was added to a solution of the corresponding amide **4** (1 mmol) in 10 mL of MeOH. The catalyst, Pd/C, (100 mg, 5%) was added and the mixture heated under reflux for 5 h. The mixture was concentrated and treated with aqueous K₂CO₃. The product was extracted with CH₂Cl₂ (3 × 30 mL), the organic layer dried (K₂CO₃) and concentrated in vacuo. The residue was purified by column chromatography (CH₂Cl₂/MeOH 10:1). The resulting product (colorless oil or white solid) can be converted into corresponding hydrochloride by treatment with gaseous HCl in MeOH.

Compound 5a: Yield 67%; colorless oil; *R*_f 0.6 (CH₃CN/EtOH/NH₃ 80:12:8); ¹H NMR (400 MHz, CDCl₃) δ 0.81 (d, *J* = 7.1 Hz, 6H, 2 × CH₃), 0.97 (d, *J* = 7.1 Hz, 6H, 2 × CH₃), 1.30–1.40 (m, 4H, (CH₂CH₂CH₂NHCO)₂), 1.44–1.52 (m, 4H, (CH₂CH₂CH₂NHCO)₂), 2.26–2.36 (m, 2H, 2 × CH(CH₃)₂), 3.17–3.30 (m, 6H, 2 × CH, (CH₂CH₂CH₂NHCO)₂), 7.26–7.33 (m, 2H, 2 × NH); ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 60.2, 38.6, 31.2, 29.7, 26.5, 19.6, 17.7; IR (cm⁻¹) 1638 (CONH), 3290 (br, NH, NH₂); ESI-MS (*m/z*): [M + H]⁺ calcd for C₁₆H₃₄N₄O₂, 314.2682; found, 314.2670.

Supporting Information

Supporting Information File 1

General information, procedures, spectral data of all compounds, results of bioassay, and copies of selected NMR spectra.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-131-S1.pdf>]

Acknowledgements

The study was partly supported by SB RAS-83, 88 and RFBR-09-04-01483.

References

- Zenkova, M. A., Ed. *Artificial Nucleases; Nucleic Acids and Molecular Biology*, Vol. 13; Springer-Verlag: Berlin Heidelberg, 2004.
- Makarov, A. A.; Ilinskaya, O. N. *FEBS Lett.* **2003**, *540*, 15–20. doi:10.1016/S0014-5793(03)00225-4
- Leland, P. A.; Raines, R. T. *Chem. Biol.* **2001**, *8*, 405–413.
- Silnikov, V. N.; Vlassov, V. V. *Russ. Chem. Rev.* **2001**, *70*, 491–508.
- Niittymäki, T.; Lönnberg, H. *Org. Biomol. Chem.* **2006**, *4*, 15–25. doi:10.1039/b509022a
- Lu, Z. L.; Liu, C. T.; Neverov, A. A.; Brown, R. S. *J. Am. Chem. Soc.* **2007**, *129*, 11642–11652. doi:10.1021/ja073780l
- Koroleva, L. S.; Kuz'min, V. E.; Muratov, E. N.; Artemenko, A. G.; Silnikov, V. N. *Russ. J. Bioorg. Chem.* **2008**, *34*, 442–452.
- Niittymäki, T.; Virta, P.; Ketomäki, K.; Lönnberg, H. *Bioconjugate Chem.* **2007**, *18*, 1583–1592. doi:10.1021/bc070071o
- Michaelis, K.; Kalesse, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2243–2245. doi:10.1002/(SICI)1521-3773(19990802)38:15<2243::AID-ANIE2243>3.0.CO;2-V
- Scheffer, U.; Strick, A.; Ludwig, V.; Peter, S.; Kalden, E.; Göbel, M. W. *J. Am. Chem. Soc.* **2005**, *127*, 2211–2217. doi:10.1021/ja0443934
- Giegé, R.; Felden, B.; Zenkova, M. A.; Sil'nikov, V. N.; Vlassov, V. V. *Methods Enzymol.* **2000**, *318*, 147–165. doi:10.1016/S0076-6879(00)18050-4
- Nosik, D. N.; Lavrukina, L. A.; Kondrashina, N. G.; Garaev, T. M.; Shibnev, V. A. *Problems of Virology* **2010**, *3*, 41–43.
- Zhdan, N. S.; Kuznetsova, I. L.; Vlassov, A. V.; Sil'nikov, V. N.; Zenkova, M. A.; Vlassov, V. V. *Russ. J. Bioorg. Chem.* **1999**, *25*, 639–647.
- Kuznetsova, I. L.; Zhdan, N. S.; Zenkova, M. A.; Vlassov, V. V.; Sil'nikov, V. N. *Russ. Chem. Bull.* **2004**, *53*, 455–462. doi:10.1023/B:RUCB.0000030824.26304.cb
- Koroleva, L. S.; Donina, A. A.; Tamkovich, N. V.; Kovalev, N. A.; Zenkova, M. A.; Sil'nikov, V. N. *Russ. Chem. Bull.* **2005**, *54*, 2682–2691. doi:10.1007/s11172-006-0176-4
- Konevets, D. A.; Mironova, N. L.; Beck, I. E.; Zenkova, M. A.; Shishkin, G. V.; Vlassov, V. V.; Silnikov, V. N. *Russ. J. Bioorg. Chem.* **2002**, *28*, 331–341. doi:10.1023/A:1019504227151
- Koroleva, L. S.; Svisheva, N. S.; Rustamova, L. M.; Gribkova, N. V.; Silnikov, V. N. *Amino Acids* **2009**, *37*, S64–S65.
- Koroleva, L. S.; Svisheva, N. S.; Burakova, E. A.; Gribkova, N. V.; Schmeleva, N. P.; Rustamova, L. M.; Sabynin, V. M.; Sil'nikov, V. N. *Pharm. Chem. J.* **2010**, *44*, 679–682. doi:10.1007/s11094-011-0541-y
- Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235–5331. doi:10.1021/cr900411f
- Gulevich, A. V.; Shevchenko, N. E.; Balenkova, E. S.; Röschenhaler, G.-V.; Nenajdenko, V. G. *Synlett* **2009**, 403–406. doi:10.1055/s-0028-1087529
- Zhdanko, A. G.; Gulevich, A. V.; Nenajdenko, V. G. *Tetrahedron* **2009**, *65*, 4692–4702. doi:10.1016/j.tet.2009.04.030
- Gulevich, A. V.; Shpilevaya, I. V.; Nenajdenko, V. G. *Eur. J. Org. Chem.* **2009**, 3801–3808. doi:10.1002/ejoc.200900330
- Zhdanko, A. G.; Nenajdenko, V. G. *J. Org. Chem.* **2009**, *74*, 884–887. doi:10.1021/jo802420c
- Nenajdenko, V. G.; Gulevich, A. V.; Sokolova, N. V.; Mironov, A. V.; Balenkova, E. S. *Eur. J. Org. Chem.* **2010**, 1445–1449. doi:10.1002/ejoc.200901326
- Pan, S. C.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3622–3625. doi:10.1002/anie.200800494
- Bustin, S. A. *J. Mol. Endocrinol.* **2000**, *25*, 169–193. doi:10.1677/jme.0.0250169
- Li, Y.; Zhao, Y.; Hatfield, S.; Wan, R.; Zhu, Q.; Li, X.; McMills, M.; Ma, Y.; Li, J.; Brown, K. L.; He, C.; Liu, F.; Chen, X. *Bioorg. Med. Chem.* **2000**, *8*, 2675–2680. doi:10.1016/S0968-0896(00)00208-X
- Branum, M. E.; Tipton, A. K.; Zhu, S.; Que, L., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 1898–1904. doi:10.1021/ja0010103

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One-pot four-component synthesis of pyrimidyl and pyrazolyl substituted azulenes by glyoxylation–decarbonylative alkynylation–cyclocondensation sequences

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Keywords:

azulenes; catalysis; decarbonylation; multicomponent reactions;
ynones

Beilstein J. Org. Chem. **2011**, *7*, 1173–1181.

doi:10.3762/bjoc.7.136

Received: 01 June 2011

Accepted: 29 July 2011

Published: 26 August 2011

This article is part of the Thematic Series "Multicomponent reactions".

Associate Editor: I. Marek

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Abstract

A novel one-pot four-component synthesis of pyrimidyl- and pyrazolylazulenes through the use of glyoxylation–decarbonylative alkynylation–cyclocondensation sequences starting from azulene or guaiazulene as substrates, gives rise to the formation of the target compounds in moderate to good yields.

Introduction

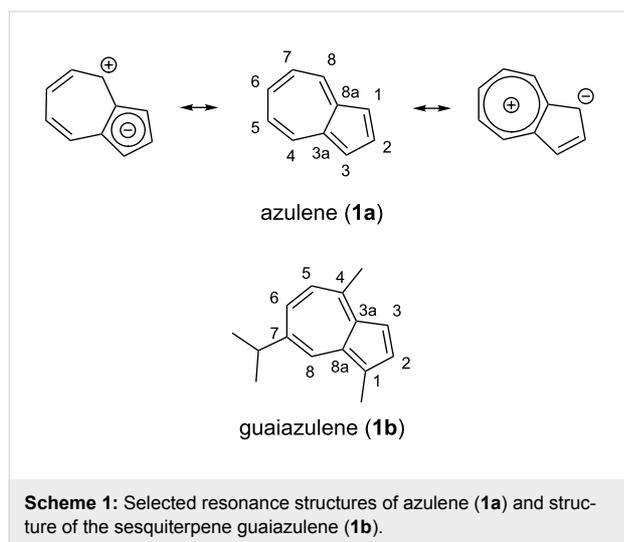
Diversity-oriented synthesis has become an important field in organic chemistry, initiated by the increasing demand for new scaffolds for pharmaceuticals and biologically active compounds over the past decades [1-3]. Herein, multicomponent reactions adopt a central position since each component can be varied within a wide range of functionalities and substituents [4-8]. Furthermore, these one-pot processes are highly advantageous because they combine shortened reaction times and resource efficiency with diminished waste production in com-

parison to traditional multistep syntheses. Thus, they can be considered to be economically and ecologically efficient [9,10].

In particular, multicomponent syntheses of heterocycles initiated by transition metal catalysis received increasing attention in the past decade [11]. As a one-pot synthetic methodology, this novel concept combines the unique reactivity patterns of transition metal catalysis with fundamental organic reactivity, in a sequential or consecutive fashion. Over the years, we have

contributed to this concept through Pd/Cu-catalyzed accesses to enones and ynones and the in situ transformation of these intermediates into many classes of heterocycles [12–15]. These novel MCRs nicely correspond with diversity-oriented strategies towards functional organic chromophores [1,2].

The striking blue color of azulene (**1a**) (from the Spanish word “azul” = blue) has aroused scientific attention for a long time [16,17]. This prominent appearance results from the electronic transition between the S_0 and S_1 state [18], as a consequence of low energy frontier molecular orbital transitions [19]. The bicyclic structure of this nonbenzoid hydrocarbon results from a five–seven ring annulation with a planar, cyclic conjugation of 10 π -electrons. The dipole moment of **1a** at $\mu = 1.08$ D [20] is astoundingly large in comparison to that of naphthalene at $\mu = 0$ D and can be rationalized by a significant contribution of cyclopentadienyl anion/tropylium cation resonance structures (Scheme 1) [19].



Since the elucidation of the structure and the first synthesis of the azulene skeleton by Pfau and Plattner [21,22], its reactivity has been intensively studied [23–26]. The aromatic system is susceptible to nucleophilic addition in the 4-, 6- and 8-positions [23], whereas electrophilic aromatic substitution, such as

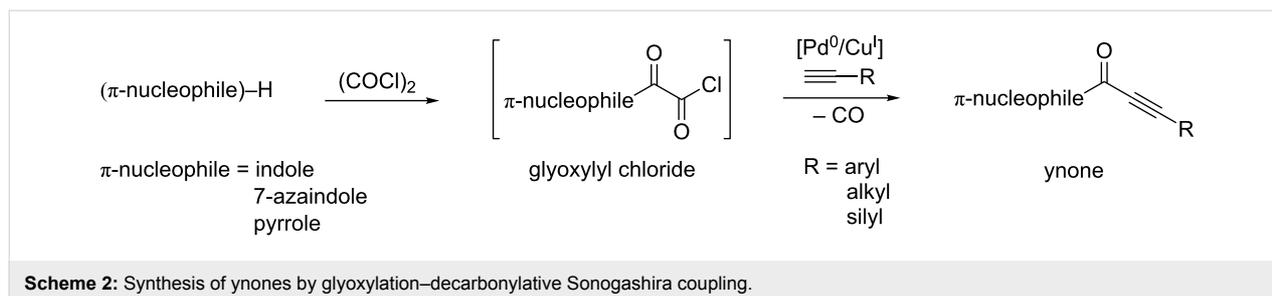
Friedel–Crafts-type reactions, generally occurs in the 1-position [24]. Interestingly, the azulene motif is also found in terpenoids [27,28]. Guaiazulene (**1b**) (Scheme 1), a commonly known derivative of azulene (**1a**), is a naturally occurring sesquiterpene [29]. Guaiazulene (**1b**) has found entry in a wide range of cosmetic formulations [30]. In addition, numerous azulene derivatives display appealing properties for material [31–33] and pharmaceutical sciences [34–38]. Furthermore, the use of the azulene moiety as part of a protecting group chromophore in carbohydrate chemistry has recently been reported [39].

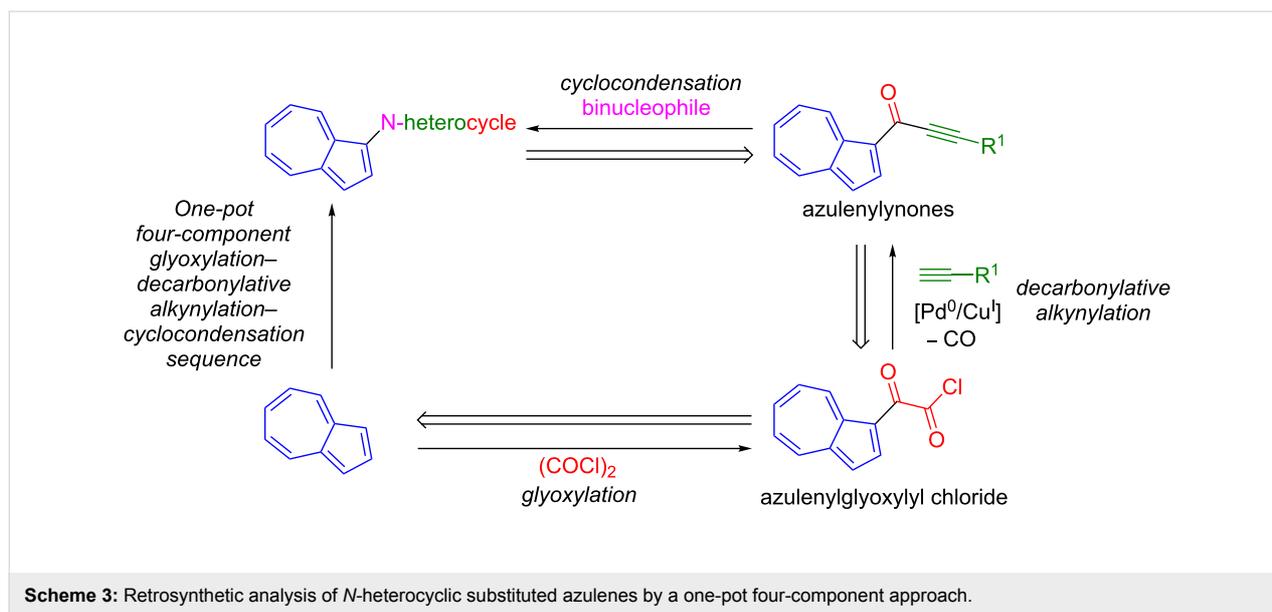
N-Heteroaryl-substituted azulenes can be accessed by stoichiometric [40,41] as well as Pd-catalyzed cross-coupling processes [42–44]. However, these methods have only delivered a narrow range of derivatives. Prior to application in Pd-catalyzed processes, azulenes must be functionalized, either by halogenation or borylation, and some of these derivatives were found to be quite unstable [45,46]. To the best of our knowledge, no diversity-oriented multicomponent syntheses of azulenyl heterocycles have been reported so far. Here, we report the development of one-pot four-component syntheses toward pyrimidyl- and pyrazolylazulenes.

Results and Discussion

Recently, we reported a three-component synthesis leading to the formation of ynones by a conceptually novel glyoxylation–decarbonylative Sonogashira coupling sequence (Scheme 2) [47]. The Lewis acid free glyoxylation of electron rich *N*-heterocycles, such as indoles and pyrroles, leads to the formation of glyoxylyl chlorides, which can be reacted without isolation by decarbonylative Sonogashira coupling to form the desired ynones. So far, only one example of the synthesis of azulenyl-ynones has been described [48].

Our retrosynthetic analysis (Scheme 3) suggests that a wide range of *N*-heterocycle-substituted azulenes should be accessible through Michael addition–cyclocondensation of azulenyl-ynones with binucleophiles. Azulenyl-ynones in turn could be simply disconnected by our glyoxylation–decarbonylative alkylation transform [47] back to azulenes.

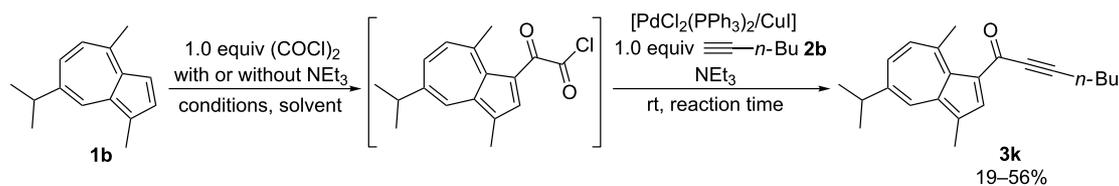




Previously, glyoxylation of azulene (**1a**), with oxalyl chloride in 1-position was reported to be essentially complete within 5 min [39]. Oxalyl bromide could be equally used as a glyoxyating agent [49,50]. Likewise, the glyoxylation of **1b** has been reported to proceed in 3-position with both reagents, yet with lower reactivity, and its conversion was found to be incomplete even after 2 h. In addition, the formation of side products [51] and decarbonylation [52] was observed, presumably caused by the steric hindrance of the methyl group in 4-position.

Encouraged by our smooth glyoxylation–alkynylation sequences with a variety of unfunctionalized π -nucleophiles, such as pyrazoles, thiophenes, furans, and even the hydrocarbon azulene (**1a**) [53], we decided to perform optimization studies of the glyoxylation–decarbonylative alkynylation with guai azulene (**1b**), a commercially available and inexpensive azulene derivative, and 1-hexyne (**2b**) as model substrates (Table 1) (for experimental details, see Supporting Information File 1).

Table 1: Optimization studies for the synthesis of ynone **3k**.^a



Entry	Glyoxylation step			Sonogashira coupling step				Yield 3k [%] ^b
	NEt ₃ [equiv]	T [°C]	t [h]	PdCl ₂ (PPh ₃) ₂ [mol %]	CuI [mol %]	NEt ₃ [equiv]	t [h]	
1	1.0	0 °C to rt	4	1	1	1.0	1	40
2	-	0 °C to rt	4	1	1	2.0	1	43
3	1.0	0 °C to rt	24	1	1	1.0	1	36
4	1.0	0 °C to rt	2	1	1	1.0	1	25
5	1.0	0 °C to rt	4	1	1	1.0	2	41
6 ^c	-	rt to 50 °C	4	1	1	2.0	1	19
7	-	0 °C to rt	4	2	2	2.0	1	56
8 ^c	-	rt	4	2	2	2.0	1	55

^aThe reactions were performed on a 2.00 mmol scale in 10 mL of THF as a solvent (*c* (**1b**) = 0.2 M); ^bisolated yield; ^c1,4-Dioxane was used as a solvent (*c* (**1b**) = 0.2 M).

Initially, the optimized conditions for the glyoxylation–decarbonylative alkylation of indoles were applied [47], except for the addition of one equivalent of triethylamine in the glyoxylation step for scavenging the generated hydrogen chloride (Table 1, entry 1). However, the use of the amine base in the first step was unsatisfactory (Table 1, entry 2). Prolonged reaction times in the first step did not affect the yield. According to monitoring by TLC, glyoxylation of guaiazulene (**1b**) was incomplete even after 24 h reaction time (Table 1, entry 3). Shorter reaction times in the first step caused a substantial decrease of the yield (Table 1, entry 4), whereas longer reaction times in the Sonogashira coupling had no effect on the yield (Table 1, entry 5). Raising the reaction temperature of the glyoxylation step to 50 °C considerably diminished the yield (Table 1, entry 6). However, doubling the catalyst loading furnished significantly higher yields (Table 1, entry 7). 1,4-Dioxane was equally well employed as a solvent (Table 1, entry 8). From this optimization study, the conditions of entry 7 (Table 1) were considered to be optimal and were applied in the three-component synthesis of the azulenylynyones **3** (Scheme 4,

Table 2) (for experimental details, see Supporting Information File 1). Their structures were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis.

Azulene (**1a**) and guaiazulene (**1b**) were both applied as substrates in the reaction sequence, giving rise to azulenylyl- and guaiazulenylynyones **3**. The azulenylyl derivatives **3a** and **3b** were obtained in higher yields compared to the guaiazulenylynyones **3c–n**. A variety of substituted arylacetylenes were utilized in the reaction sequence. Electron neutral (Table 2, entries 1 and 3), electron withdrawing (Table 2, entries 5–7), and electron donating (Table 2, entries 4 and 8) substituents were equally well tolerated. In addition, heteroaryl-substituted acetylenes (Table 2, entries 9 and 10) as well as simple aliphatic acetylenes (Table 2, entries 2, 11, and 12) were successfully employed. Finally, propargylaldehyde diethylacetal (Table 2, entry 13) and TIPS-protected acetylene (Table 2, entry 14) also participated in the sequence, although relatively low yields were achieved.

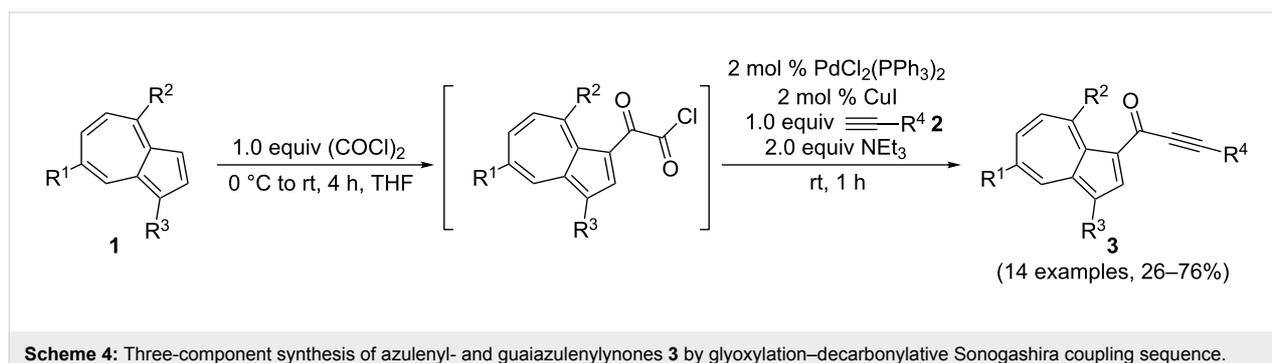


Table 2: Three-component synthesis of azulenylyl- and guaiazulenylynyones **3**.^a

Entry	Azulene 1	Alkyne 2	Azulenylynyone 3	[%] ^b
1	1a (R ¹ = R ² = R ³ = H)	2a (R ⁴ = Ph)		65 ^c
2	1a	2b (R ⁴ = <i>n</i> -Bu)		66 ^c
3	1b (R ¹ = <i>i</i> Pr, R ² = R ³ = Me)	2a		55

Table 2: Three-component synthesis of azulenylyl- and guaiazulenylylones **3**.^a (continued)

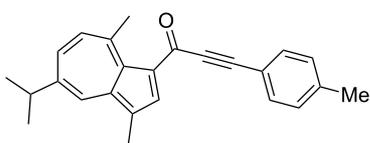
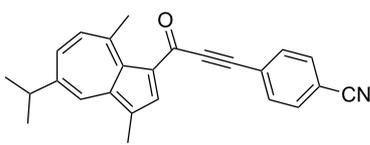
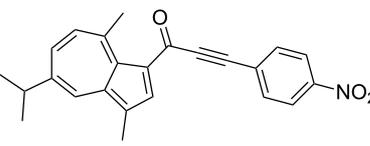
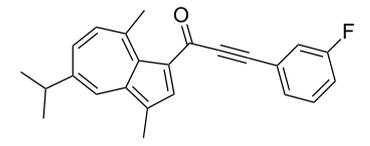
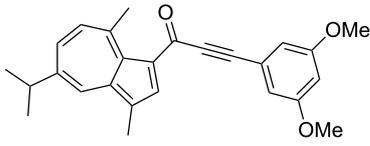
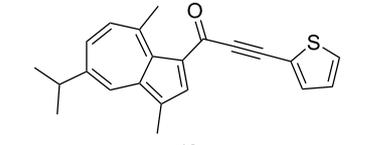
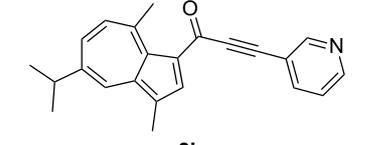
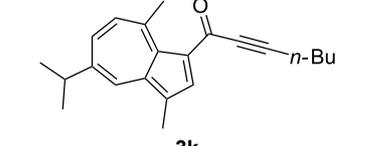
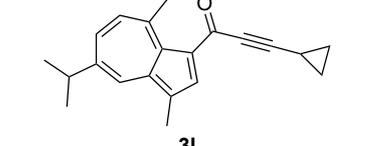
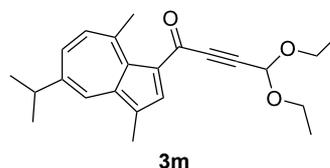
4	1b	2c ($R^4 = p\text{-tolyl}$)	 3d	57
5	1b	2d ($R^4 = p\text{-CNC}_6\text{H}_4$)	 3e	60
6	1b	2e ($R^4 = p\text{-NO}_2\text{C}_6\text{H}_4$)	 3f	76
7	1b	2f ($R^4 = m\text{-FC}_6\text{H}_4$)	 3g	51
8	1b	2g ($R^4 = 3,5\text{-(MeO)}_2\text{C}_6\text{H}_3$)	 3h	47
9	1b	2h ($R^4 = 2\text{-C}_4\text{H}_3\text{S}$)	 3i	55
10	1b	2i ($R^4 = 3\text{-pyridyl}$)	 3j	31
11	1b	2b	 3k	56
12	1b	2j ($R^4 = \text{cyclopropyl}$)	 3l	42

Table 2: Three-component synthesis of azulenyl- and guaiazulenyllynones **3**.^a (continued)

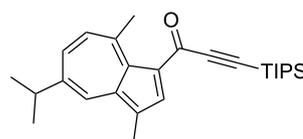
13

1b**2k** ($R^4 = \text{CH(OEt)}_2$)

30

3m

14

1b**2l** ($R^4 = \text{TIPS}$)

26

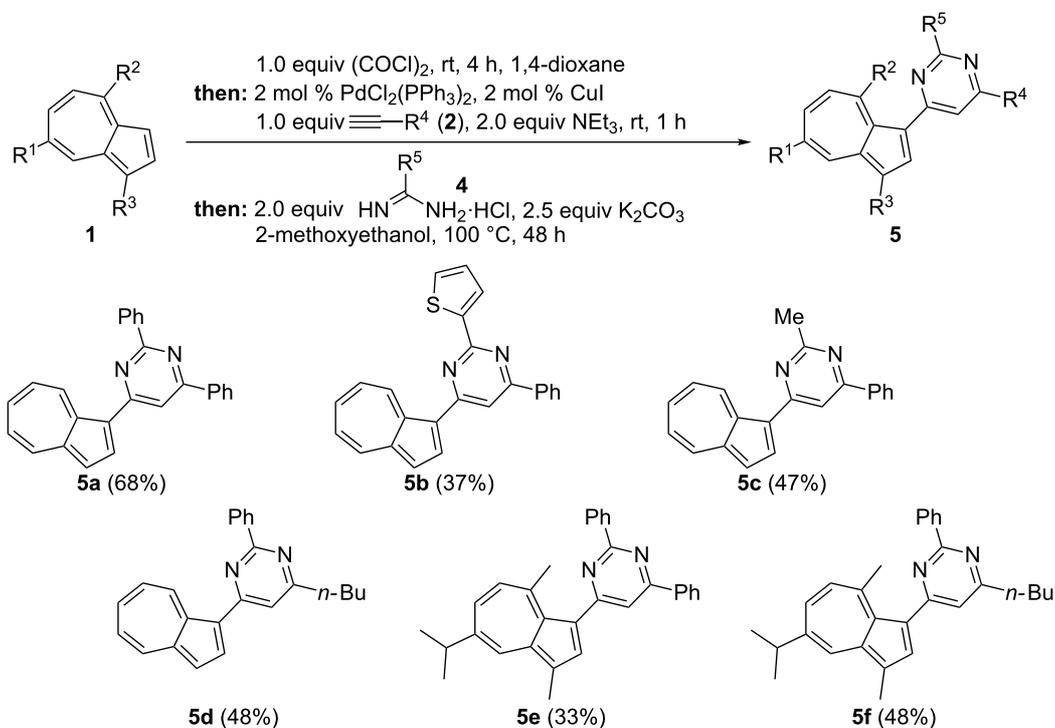
3n

^aThe reactions were performed on a 2.00 mmol scale in 10 mL of THF as a solvent ($c(\mathbf{1}) = 0.2 \text{ M}$); ^bIsolated and purified compounds; ^cThe reactions were performed on a 1.00 mmol scale in 5 mL THF as a solvent ($c(\mathbf{1}) = 0.2 \text{ M}$).

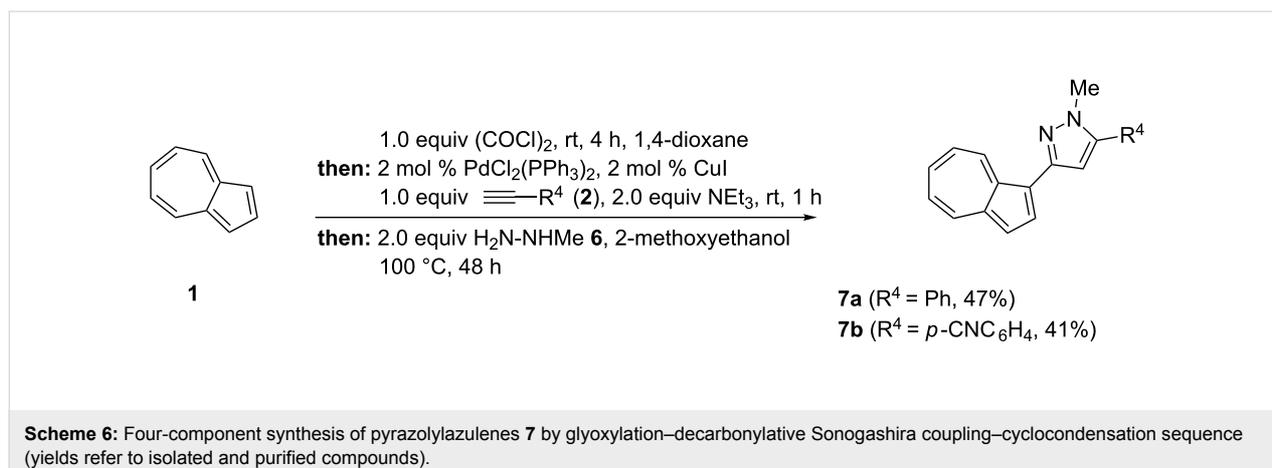
With this versatile three-component synthesis of azulenyl-ynones in hand, the stage was set to expand the sequence to a four-component access to pyrimidyl- and pyrazolyl-substituted azulenes. Hence, the conditions for the terminating Michael addition–cyclocondensation step, adopted from a recent work [54], were only slightly adjusted as a consequence of the lower electrophilicity of azulenyllynones in comparison to aryl- and heteroaryl-substituted ynones that we have previously synthesized. Therefore, upon the subsequent reaction of the azulenes **1**

with oxalyl chloride, followed by Pd/Cu-catalyzed decarbonylative alkylation with terminal alkynes **2**, and finally by cyclocondensation of the ynone intermediates with substituted amidine hydrochlorides **4**, pyrimidylazulenes **5** were obtained in moderate to good yields in a one-pot fashion (Scheme 5) (for experimental details, see Supporting Information File 1).

The diversity-oriented nature of this four-component approach to pyrimidylazulenes **5** is underlined by flexible variation of the



Scheme 5: Four-component synthesis of pyrimidylazulenes **5** by glyoxylation–decarbonylative Sonogashira coupling–cyclocondensation sequence (yields refer to isolated and purified compounds).



azulenyl, the alkynyl, and the amidinyl substrates. In particular, the amidine component **4** leads to the formation of aryl (compounds **5a**, **5d–5f**), heteroaryl (compound **5b**) or alkyl (compound **5c**) pyrimidylazulene derivatives.

Likewise, pyrazolylazulenes were obtained in the course of a consecutive glyoxylation–decarbonylative Sonogashira coupling, followed by a cyclocondensation with methylhydrazine (**6**) to furnish two *N*-methylpyrazoles **7** in moderate yields (Scheme 6) (for experimental details, see Supporting Information File 1).

Attempts to employ phenylhydrazine, *N*-Boc-hydrazine, and hydrazine hydrate under standard conditions were met with failure. Based upon previous syntheses of *N*-methylpyrazoles from ynones and methylhydrazine [55,56] and the appearance of a single set of resonances in the proton and carbon NMR spectra, it is obvious that only a single regioisomer was formed. Although the synthesis of similarly substituted pyrazolylazulenes has already been described [57], our one-pot four-component approach utilizes readily available starting materials as well as a simple catalyst system. In addition, it avoids tedious multiple workup and purification operations.

Conclusion

In conclusion, we have developed a one-pot four-component process for the synthesis of novel pyrimidyl- and pyrazolylazulenes. A wide range of substituents can be introduced by this modular approach to *N*-heterocyclic azulene derivatives. The key step of this diversity-oriented synthesis is the generation of azulenylynones by the glyoxylation–decarbonylative alkynylation sequence with azulene or guaiazulene as substrates. Undoubtedly, this novel four-component approach to heterocyclic derivatives of azulene is well suited for the development of functional chromophores with extended π -conjugation.

Supporting Information

Supporting Information File 1

Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of compounds **3**, **5**, and **7**.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-136-S1.pdf>]

Acknowledgements

The authors cordially thank Merck KGaA, Darmstadt, and the Fonds der Chemischen Industrie for their generous support.

References

- Müller, T. J. J.; D'Souza, D. M. *Pure Appl. Chem.* **2008**, *80*, 609–620. doi:10.1351/pac200880030609
- Müller, T. J. J. In *Functional Organic Materials. Synthesis, Strategies, and Applications*; Müller, T. J. J.; Bunz, U. H. F., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 179–223.
- Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58. doi:10.1002/anie.200300626
- Sunderhaus, J. D.; Martin, S. F. *Chem.–Eur. J.* **2009**, *15*, 1300–1308. doi:10.1002/chem.200802140
- Isambert, N.; Lavilla, R. *Chem.–Eur. J.* **2008**, *14*, 8444–8454. doi:10.1002/chem.200800473
- Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499. doi:10.1055/s-2003-40507
- Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. doi:10.1021/cr800296p
- Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1085–1109. doi:10.1016/j.tetasy.2010.04.045
- Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. doi:10.1021/cr950027e
- Coquerel, Y.; Boddart, T.; Presset, M.; Mailhol, D.; Rodriguez, J. Multiple Bond-Forming Transformations: The Key Concept toward Eco-Compatible Synthetic Organic Chemistry. In *Ideas in Chemistry and Molecular Sciences: Advances in Synthetic Chemistry*; Pignataro, B., Ed.; Wiley-VCH: Weinheim, Germany, 2010; pp 187–202. doi:10.1002/9783527630554.ch9

11. D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108. doi:10.1039/B608235C
12. Müller, T. J. J. Palladium-Copper Catalyzed Alkyne Activation as an Entry to Multicomponent Syntheses of Heterocycles. In *Synthesis of Heterocycles via Multicomponent Reactions II*; Orru, R. V. A.; Ruijter, E., Eds.; Topics in Heterocyclic Chemistry, Vol. 25; Springer: Berlin/Heidelberg, Germany, 2010; pp 25–94. doi:10.1007/7081_2010_43
13. Willy, B.; Müller, T. J. J. *Curr. Org. Chem.* **2009**, *13*, 1777–1790. doi:10.2174/138527209789630479
14. Willy, B.; Müller, T. J. J. *ARKIVOC* **2008**, *2008* (i), 195–208.
15. Müller, T. J. J. Multi-component syntheses of heterocycles by virtue of palladium catalyzed generation of alkynones and chalcones. In *Targets in Heterocyclic Systems*; Attanasi, O.; Spinelli, D., Eds.; Italian Society of Chemistry: Rome, Italy, 2006; Vol. 10, pp 54–65.
16. Hansen, H. J. *Chimia* **1996**, *50*, 489–496.
17. Hansen, H. J. *Chimia* **1997**, *51*, 147–159.
18. Liu, R. S. H. *J. Chem. Educ.* **2002**, *79*, 183–185. doi:10.1021/ed079p183
19. Zeller, K.-P. *Houben-Weyl*; 1985; Vol. 5/2c, pp 127–133. And references cited therein.
20. Anderson, A. G., Jr.; Steckler, B. M. *J. Am. Chem. Soc.* **1959**, *81*, 4941–4946. doi:10.1021/ja01527a046
21. Pfau, A. S.; Plattner, P. A. *Helv. Chim. Acta* **1936**, *19*, 858–879. doi:10.1002/hlca.193601901117
22. Plattner, P. A.; Pfau, A. S. *Helv. Chim. Acta* **1937**, *20*, 224–232. doi:10.1002/hlca.19370200133
23. Hafner, K.; Bernhard, C.; Müller, R. *Justus Liebig's Ann. Chem.* **1961**, *650*, 35–41. doi:10.1002/jlac.19616500104
24. Anderson, A. G., Jr.; Nelson, J. A. *J. Am. Chem. Soc.* **1950**, *72*, 3824–3825. doi:10.1021/ja01164a528
25. Hafner, K.; Moritz, K.-L. *Justus Liebig's Ann. Chem.* **1962**, *656*, 40–53. doi:10.1002/jlac.19626560108
26. Kędziorek, M.; Mayer, P.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 1202–1206. doi:10.1002/ejoc.200801099
27. Fraga, B. M. *Nat. Prod. Rep.* **2008**, *25*, 1180–1209. doi:10.1039/B806216C
28. Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223–269. doi:10.1039/NP9951200223
29. Seo, Y.; Rho, J.-R.; Geum, N.; Yoon, J. B.; Shin, J. *J. Nat. Prod.* **1996**, *59*, 985–986. doi:10.1021/np960485y
30. Andersen, F. A. *Int. J. Toxicol.* **1999**, *18* (Suppl. 3), 27–32. doi:10.1177/109158189901800304
31. Barman, S.; Furukawa, H.; Blacque, O.; Venkatesan, K.; Yaghi, O. M.; Berke, H. *Chem. Commun.* **2010**, *46*, 7981–7983. doi:10.1039/c0cc02589e
32. Wang, F.; Lai, Y.-H. *Macromolecules* **2003**, *36*, 536–538. doi:10.1021/ma025662i
33. Zhang, X.-H.; Li, C.; Wang, W.-B.; Cheng, X.-X.; Wang, X.-S.; Zhang, B.-W. *J. Mater. Chem.* **2007**, *17*, 642–649. doi:10.1039/B613703B
34. Ramadan, M.; Goeters, S.; Watzer, B.; Krause, E.; Lohmann, K.; Bauer, R.; Hempel, B.; Imming, P. *J. Nat. Prod.* **2006**, *69*, 1041–1045. doi:10.1021/np0601556
35. Jakovlev, V.; Isaac, O.; Flaskamp, E. *Planta Med.* **1983**, *49*, 67–73. doi:10.1055/s-2007-969818
36. Chen, C.-H.; Lee, O.; Yao, C.-N.; Chuang, M.-Y.; Chang, Y.-L.; Chang, M.-H.; Wen, Y.-F.; Yang, W.-H.; Ko, C.-H.; Chou, N.-T.; Lin, M.-W.; Lai, C.-P.; Sun, C.-Y.; Wang, L.-M.; Chen, Y.-C.; Hseu, T.-H.; Chang, C.-N.; Hsu, H.-C.; Lin, H.-C.; Chang, Y.-L.; Shih, Y.-C.; Chou, S.-H.; Hsu, Y.-L.; Tseng, H.-W.; Liu, C.-P.; Tu, C.-M.; Hu, T.-L.; Tsai, Y.-J.; Chen, T.-S.; Lin, C.-L.; Chiou, S.-J.; Liu, C.-C.; Hwang, C.-S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6129–6132. doi:10.1016/j.bmcl.2010.08.025
37. Safayhi, H.; Sabieraj, J.; Sailer, E.-R.; Ammon, H. P. T. *Planta Med.* **1994**, *60*, 410–413. doi:10.1055/s-2006-959520
38. Fiori, J.; Teti, G.; Gotti, R.; Mazzotti, G.; Falconi, M. *Toxicol. in Vitro* **2011**, *25*, 64–72. doi:10.1016/j.tiv.2010.09.008
39. Timmer, M. S. M.; Stocker, B. L.; Northcote, P. T.; Burkett, B. A. *Tetrahedron Lett.* **2009**, *50*, 7199–7204. doi:10.1016/j.tetlet.2009.10.043
40. Shoji, T.; Yokoyama, R.; Ito, S.; Watanabe, M.; Toyota, K.; Yasunami, M.; Morita, N. *Tetrahedron Lett.* **2007**, *48*, 1099–1103. doi:10.1016/j.tetlet.2006.12.083
41. Shoji, T.; Okada, K.; Ito, S.; Toyota, K.; Morita, N. *Tetrahedron Lett.* **2010**, *51*, 5127–5130. doi:10.1016/j.tetlet.2010.07.090
42. Kurotobi, K.; Tabata, H.; Miyauchi, M.; Murafuji, T.; Sugihara, Y. *Synthesis* **2002**, 1013–1016. doi:10.1055/s-2002-31947
43. Wakabayashi, S.; Kato, Y.; Mochizuki, K.; Suzuki, R.; Matsumoto, M.; Sugihara, Y.; Shimizu, M. *J. Org. Chem.* **2007**, *72*, 744–749. doi:10.1021/jo061684h
44. Wakabayashi, S.; Uriu, R.; Asakura, T.; Akamatsu, C.; Sugihara, Y. *Heterocycles* **2008**, *75*, 383–390. doi:10.3987/COM-07-11229
45. Ito, S.; Kubo, T.; Morita, N.; Matsui, Y.; Watanabe, T.; Ohta, A.; Fujimori, K.; Murafuji, T.; Sugihara, Y.; Tajiri, A. *Tetrahedron Lett.* **2004**, *45*, 2891–2894. doi:10.1016/j.tetlet.2004.02.059
46. Higashi, J.; Shoji, T.; Ito, S.; Toyota, K.; Yasunami, M.; Morita, N. *Eur. J. Org. Chem.* **2008**, 5823–5831. doi:10.1002/ejoc.200800733
47. Merkul, E.; Oeser, T.; Müller, T. J. J. *Chem.–Eur. J.* **2009**, *15*, 5006–5011. doi:10.1002/chem.200900119
48. Hafner, K.; Bangert, K.-F. *Justus Liebig's Ann. Chem.* **1961**, *650*, 98–115. doi:10.1002/jlac.19616500109
49. Treibs, W.; Orttmann, H. *Naturwissenschaften* **1958**, *45*, 85–86. doi:10.1007/BF00632795
50. Ito, S.; Okujima, T.; Kikuchi, S.; Shoji, T.; Morita, N.; Asao, T.; Ikoma, T.; Tero-Kubota, S.; Kawakami, J.; Tajiri, A. *J. Org. Chem.* **2008**, *73*, 2256–2263. doi:10.1021/jo702309b
51. Reid, D. H.; Stafford, W. H.; Stafford, W. L. *J. Chem. Soc.* **1958**, 1118–1127. doi:10.1039/JR9580001118
52. Treibs, W. *Chem. Ber.* **1959**, *92*, 2152–2163. doi:10.1002/cber.19590920930
53. Merkul, E.; Dohe, J.; Gers, C.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2966–2969. doi:10.1002/anie.201007194
54. Boersch, C.; Merkul, E.; Müller, T. J. J. *Angew. Chemie, Int. Ed.* **2011**, in press.
55. Willy, B.; Müller, T. J. J. *Org. Lett.* **2011**, *13*, 2082–2085. doi:10.1021/ol2004947
56. Willy, B.; Müller, T. J. J. *Eur. J. Org. Chem.* **2008**, 4157–4168. doi:10.1002/ejoc.200800444
57. Wang, D.-L.; Deng, J.-J.; Xu, J.; Imafuku, K. *Heterocycles* **2007**, *71*, 2237–2242. doi:10.3987/COM-07-11101

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The definitive version of this article is the electronic one which can be found at:
[doi:10.3762/bjoc.7.136](https://doi.org/10.3762/bjoc.7.136)

Synthesis of diverse dihydropyrimidine-related scaffolds by fluorous benzaldehyde-based Biginelli reaction and post-condensation modifications

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Letter

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Keywords:
Biginelli reaction; dihydropyrimidine; diversity-oriented synthesis;
fluorous; Suzuki coupling

Beilstein J. Org. Chem. **2011**, *7*, 1294–1298.
doi:10.3762/bjoc.7.150

Received: 10 June 2011
Accepted: 23 August 2011
Published: 16 September 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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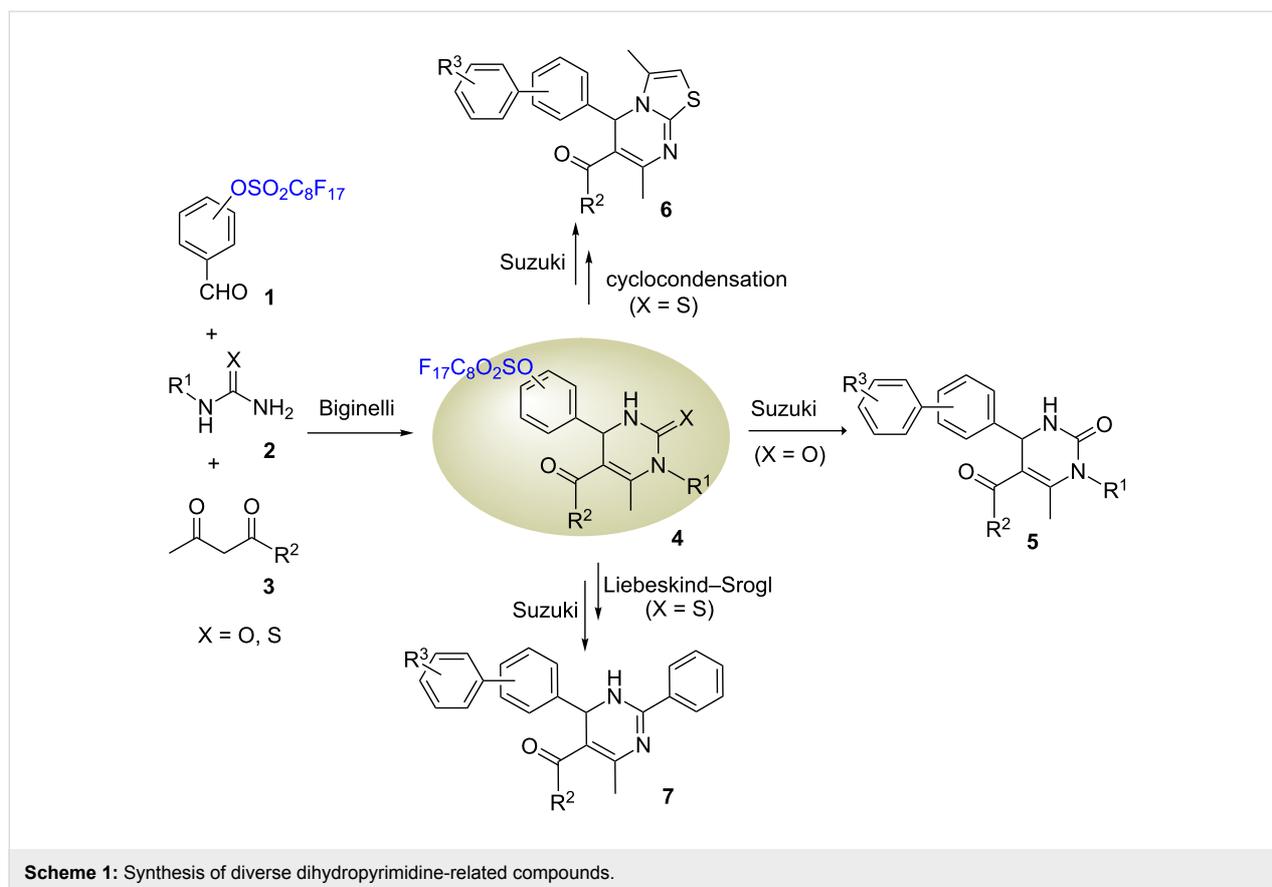
Abstract

Dihydropyrimidinones and dihydropyrimidinethiones generated from the Biginelli reactions of perfluorooctanesulfonyl-attached benzaldehydes are used as common intermediates for post-condensation modifications such as cycloaddition, Liebeskind–Srogl reaction and Suzuki coupling to form biaryl-substituted dihydropyrimidinone, dihydropyrimidine, and thiazolopyrimidine compounds. The high efficiency of the diversity-oriented synthesis is achieved by conducting a multicomponent reaction for improved atom economy, under microwave heating for fast reaction, and with fluorous solid-phase extractions (F-SPE) for ease of purification.

Introduction

Dihydropyrimidinone and dihydropyrimidine derivatives have broad biologically activities. Many synthetic samples have been studied as antibacterial, antiviral, antihypertensive, and anticancer agents [1], and the natural products containing these heterocyclic moieties have been studied as new leads for AIDS therapies [2]. The Biginelli reaction of a β -keto ester, an aldehyde, and urea is considered as one of the most efficient ways to synthesize dihydropyrimidinones [3]. This acid-catalyzed reaction can be conducted under conventional or microwave

heating [4,5]. Reported in this paper is a diversity-oriented synthesis of biaryl-substituted dihydropyrimidinone **5**, thiazolopyrimidine **6**, and dihydropyrimidine **7** compounds (Scheme 1). The perfluorooctanesulfonyl-attached benzaldehydes **1** were used as a key component for the Biginelli reactions [6]. The Biginelli products **4** were used as a common intermediate for post-condensation reactions including cycloaddition, Liebeskind–Srogl reaction and Suzuki coupling to form three different heterocyclic skeletons. The high efficiency of the



diversity-oriented synthesis was achieved by conducting fast, microwave-heated reactions and simple fluororous solid-phase extractions (F-SPE) for purification [7]. The perfluorooctanesulfonyl group served as a phase tag for F-SPE and also as a convertible linker for the Suzuki coupling to introduce biaryl functionality to the heterocyclic skeletons [8-12].

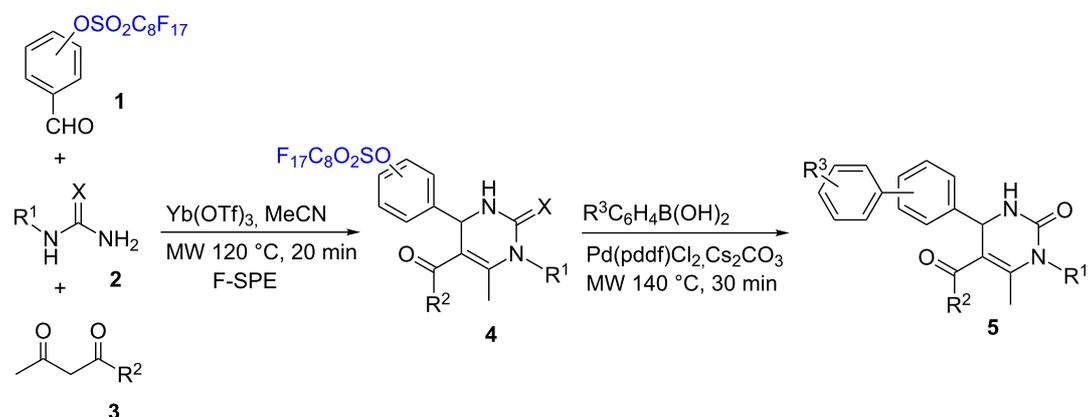
Result and Discussion

Fluorous benzaldehydes **1** were prepared by the reaction of phenols with perfluorooctanesulfonyl fluoride, by following the reported procedure [13]. Compounds **1** were used as a limiting agent to react with urea/thiourea **2** and acetylacetone **3** for the Biginelli reactions. The reactions were promoted by $\text{Yb}(\text{OTf})_3$ as a catalyst [14,15], acetonitrile as a solvent, and under microwave irradiation at 120 °C for 20 min. This optimized condition was developed after other solvents, including water, EtOH and toluene, and different microwave reaction temperatures (100–130 °C) and times (10–20 min) were explored. The Biginelli products were separated from the reaction mixtures by F-SPE eluted with fluorophobic 80:20 MeOH/H₂O and then fluorophilic 100% MeOH or acetone [7]. The fluororous Biginelli products were collected from the MeOH fraction to give dihydropyrimidinones **4a–d** and dihydropyrimidinethiones **4e,f** in 85–95% yields (Table 1). The Biginelli products **4a–e** were

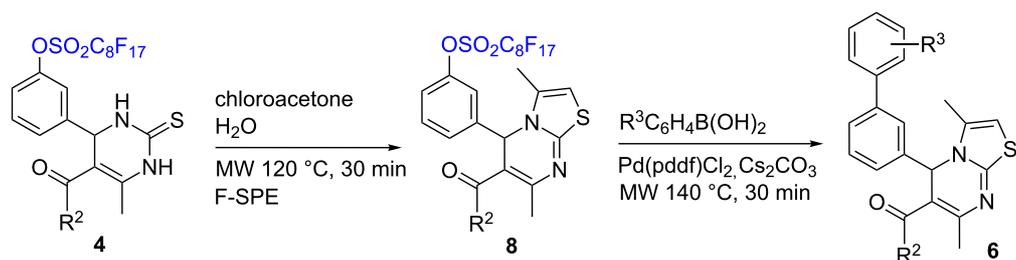
used for Suzuki coupling reactions to remove the fluororous linker and introduce the biaryl functional group. The coupling reactions were promoted by microwave heating at 140 °C for 30 min with $\text{Pd}(\text{pddf})\text{Cl}_2$ as a catalyst, Cs_2CO_3 as a base, and 4:4:1 acetone/toluene/H₂O as a solvent [13]. Dihydropyrimidinones **4a–d** gave the expected products **5a–h** in 51–68% yield after F-SPE and flash chromatography purification. However, no reactions occurred with the dihydropyrimidinethiones **4e,f** under these reaction conditions.

Since dihydropyrimidinethiones **4e,f** failed to give Suzuki coupling products, our next effort was to convert them to thiazolopyrimidine through cyclocondensation with chloroacetone [16,17]. The reaction was performed in water under microwave heating at 120 °C for 30 min to afford thiazolopyrimidines **8a** and **8b** in 89% and 85% yields, respectively, after F-SPE. Suzuki reactions of **8a** and **8b** with four boronic acids yielded 5-biaryl-5*H*-thiazolo[3,2-*a*]pyrimidines **6a–h** in 55–64% yields after F-SPE and flash chromatography purifications (Table 2).

Dihydropyrimidinethione **4f** was used for the Liebeskind–Srogl coupling reaction with a phenylboronic acid to convert to 2-aryl-1,6-dihydropyrimidine **9** [18–20]. The reaction was performed following a literature procedure [21] and was

Table 1: Biginelli reactions followed by Suzuki reactions of dihydropyrimidinones and dihydropyrimidinethiones.

R ¹	R ²	X	F-Sulfonyl position	4 (yield)	R ³	5 (yield)
CH ₃	CH ₃	O	<i>meta</i>	4a (91%)	<i>p</i> -OCH ₃	5a (67%)
					H	5b (56%)
CH ₃	OCH ₃	O	<i>meta</i>	4b (95%)	<i>p</i> -OCH ₃	5c (57%)
					H	5d (51%)
CH ₃	CH ₃	O	<i>para</i>	4c (90%)	<i>p</i> -OCH ₃	5e (68%)
					H	5f (62%)
CH ₃	OCH ₃	O	<i>para</i>	4d (88%)	<i>p</i> -OCH ₃	5g (58%)
					H	5h (60%)
H	CH ₃	S	<i>meta</i>	4e (89%)	H	-
H	OCH ₃	S	<i>meta</i>	4f (85%)	H	-

Table 2: Synthesis of biaryl-substituted thiazolopyrimidines.

4	R ²	8	R ³	6 (yield)
4e	CH ₃	8a (89%)	H	6a (61%)
			<i>p</i> -OCH ₃	6b (64%)
			<i>m</i> -Cl	6c (56%)
			<i>p</i> -CH ₃	6d (62%)
4f	OCH ₃	8b (85%)	H	6e (58%)
			<i>p</i> -OCH ₃	6f (55%)
			<i>m</i> -Cl	6g (63%)
			<i>p</i> -CH ₃	6h (55%)

catalyzed by $\text{Pd}(\text{PPh}_3)_4$ and copper(I) thiophene-2-carboxylate (CuTC) under microwave heating at 100 °C for 25 min to afford aryl-substituted dihydropyrimidine **9** in 76% yield. This compound was then subjected to Suzuki coupling reactions with four boronic acids to yield 2-aryl-6-biaryl substituted dihydropyrimidines **7a–d** after F-SPE and flash chromatography purifications (Table 3).

Conclusion

We have developed a new application of perfluorooctanesulfonyl-attached benzaldehydes for the diversity-oriented synthesis of heterocyclic scaffolds. The intermediates obtained from the Biginelli reaction were used for post-condensation modifications to afford biaryl-substituted dihydropyrimidinone, dihydropyrimidine, and thiazolopyrimidine compounds. A set of reaction and separation techniques such as multicomponent reactions, microwave heating, and F-SPE was employed to increase the synthetic efficiency. The fluorosulfonyl group not only served as a phase tag for F-SPE separation, but also as a cleavable linker for the Suzuki coupling reactions.

Experimental

Typical Biginelli reaction procedure: Synthesis of 5-acetyl-4-(4-(perfluorooctylsulfonyloxy)phenyl)-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (4c)

A solution of *p*-perfluorooctanesulfonyl benzaldehyde **1** (1.2 g, 2.0 mmol), methylurea **2** (0.18 g, 2.4 mmol), methyl acetoacetate **3** (0.35 g, 3.0 mmol) and $\text{Yb}(\text{OTf})_3$ (124 mg, 0.2 mmol) in 2 mL of acetonitrile was heated in a Biotage Initiator microwave synthesizer at 120 °C for 20 min. The resulting mixture was purified by F-SPE eluted with 40 mL of 80:20 MeOH/

H_2O and then 40 mL of acetone. The acetone fraction was concentrated to give **4c** (1.3 g) in 90% yield.

Typical Suzuki reaction procedure: Synthesis of 5-acetyl-4-(4'-methoxy-[1,1'-biphenyl]-3-yl)-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (5a)

A solution of **4a** (75 mg, 0.1 mmol), 4-methoxyphenylboronic acid (23 mg, 0.15 mmol), Cs_2CO_3 (81 mg, 0.25 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (16 mg, 0.02 mmol) in 3 mL of 4:1:4 acetone/ H_2O /toluene was heated in a Biotage Initiator microwave synthesizer at 140 °C for 30 min. The resulting mixture was purified by flash chromatography to give **5a** (24 mg) in 67% yield.

Typical procedure for cyclocondensation of 4e,f. Synthesis of methyl 3,7-dimethyl-5-(3-(perfluorooctylsulfonyloxy)phenyl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (8b)

A solution of 3,4-dihydropyrimidinethione **4f** (0.76 g, 1 mmol), chloroacetone (185 mg, 1.5 mmol) in 2 mL water was heated in Biotage Initiator microwave synthesizer at 120 °C for 30 min. The resulting mixture was purified by F-SPE eluted with 30 mL of 80:20 MeOH/ H_2O and then 30 mL of acetone. The acetone fraction was concentrated to give **8b** (0.67 g) in 85% yield.

Typical Liebeskind–Srogl reaction procedure. Synthesis of methyl 4-methyl-6-(3-(perfluorooctylsulfonyloxy)phenyl)-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (9)

A solution of 3,4-dihydropyrimidinethione **4f** (152 mg, 0.20 mmol), phenylboronic acid (82 mg, 0.3 mmol), CuTC (95 mg, 0.6 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (3 mol %) in 2 mL THF was heated in Biotage Initiator microwave synthesizer at 100 °C for 25

Table 3: Synthesis of 2-aryl-6-biaryl-substituted dihydropyrimidines.

R^3	7 (yield)
H	7a (45%)
<i>p</i> - OCH_3	7b (48%)
<i>m</i> -Cl	7c (31%)
<i>p</i> - CH_3	7d (48%)

min. The mixture was purified by F-SPE eluted with 30 mL of 80:20 MeOH/H₂O and then 30 mL of acetone. The acetone fraction was concentrated to give **9** (0.85 g) in 76% yield.

20. Prokopcová, H.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 4440–4448. doi:10.1021/jo070408f

21. Prokopcová, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 2276–2286. doi:10.1002/anie.200802842

Supporting Information

Supporting Information File 1

LC-MS, ¹H NMR and ¹³C NMR data and spectra for compounds **4c**, **5a**, **6b**, **7b**, **8b**, **9**.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-150-S1.pdf>]

Acknowledgments

This work was supported by the Healey grant from University of Massachusetts Boston. We would like to thank Dave York for his participation in some initial experiments of this project.

References

- Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888. doi:10.1021/ar000048h
- Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052. doi:10.1016/S0223-5234(00)01189-2
- Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360–416.
- Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1–116. doi:10.1002/0471264180.or063.01
- Kappe, C. O. The Biginelli Reaction. In *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 95–120.
- Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917–2924.
- Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837–11865. doi:10.1016/j.tet.2006.08.051
- Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582–9584. doi:10.1021/jo9612990
- Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583–5587. doi:10.1021/jo970362y
- Kadam, A.; Zhang, Z.; Zhang, W. *Curr. Org. Synth.* **2011**, *8*, 295–309. doi:10.2174/157017911794697259
- Zhang, W. *Chem. Rev.* **2009**, *109*, 749–795. doi:10.1021/cr800412s
- Zhang, W. *Comb. Chem. High Throughput Screening* **2007**, *10*, 219–229.
- Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473–1476. doi:10.1021/ol0496428
- Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discovery* **2006**, *5*, 51–63. doi:10.1038/nrd1926
- Dallinger, D.; Kappe, C. O. *Nat. Protoc.* **2007**, *2*, 1713–1721. doi:10.1038/nprot.2007.224
- Wang, X.-C.; Quan, Z.-J.; Zhang, Z.; Liu, Y.-J.; Ji, P.-Y. *Lett. Org. Chem.* **2007**, *4*, 370–373. doi:10.2174/157017807781212139
- Quan, Z.-J.; Zhang, Z.; Wang, J.-K.; Wang, X.-C.; Liu, Y.-J.; Ji, P.-Y. *Heteroat. Chem.* **2008**, *19*, 149–152. doi:10.1002/hc.20386
- Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260–11261. doi:10.1021/ja005613q
- Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734–15735. doi:10.1021/ja074931n

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A straightforward approach towards combined α -amino and α -hydroxy acids based on Passerini reactions

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Full Research Paper

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Keywords:
amino acids; chelated enolates; epoxides; Passerini reactions; Ugi
reactions

Beilstein J. Org. Chem. **2011**, *7*, 1299–1303.
doi:10.3762/bjoc.7.151

Received: 14 May 2011
Accepted: 23 August 2011
Published: 19 September 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

Complex amino acids with an α -acyloxycarbonyl functionality in the side chain are easily available through epoxide opening by chelated enolates and subsequent oxidation/Passerini reaction. This protocol works with both, aldehyde and ketone intermediates, as long as the ketones are activated by electron-withdrawing groups. In principle Ugi reactions are also possible, allowing the generation of diamino acid derivatives.

Introduction

Multicomponent reactions (MCR) are a very popular and powerful tool in modern organic synthesis [1-4]. Besides a wide range of heterocycle syntheses [5] and catalytic cross coupling reactions [6], the isonitrile-based MCRs (IMCR) especially have developed exceptionally well during the last few decades [7,8]. Based on the pioneering work of Passerini, who observed the first three-component coupling of carbonyls with carboxylic acids and isonitriles in 1921 [9], the so-called Passerini reaction became a powerful tool for the synthesis of acylated α -hydroxyacid amides [10]. Later on, in 1961, Ugi and Steinbrückner reported the extension of this protocol by incorporating also a primary amine as a fourth component [11].

Therefore, the Ugi reaction is even more flexible than the Passerini approach, but both reactions together have made the IMCR highly popular in combinatorial chemistry [7,8].

Our group has been involved in amino acid and peptide synthesis for nearly two decades [12,13], and multicomponent reactions are known to play a dominant role [14,15]. In particular, the Ugi reaction has so far been used for the construction of exotic peptides [16-19] and cyclopeptides [20,21]. Herein we describe a straightforward protocol towards combined α -amino and α -hydroxy acids through Passerini reactions. Suitable amino acid precursors with an oxygen functionality in the side

chain can be obtained by chelated enolate Claisen rearrangement [22,23] or transition metal-catalyzed allylic alkylation of chelated enolates [24] and subsequent oxidative cleavage of the γ - δ -unsaturated amino acids obtained.

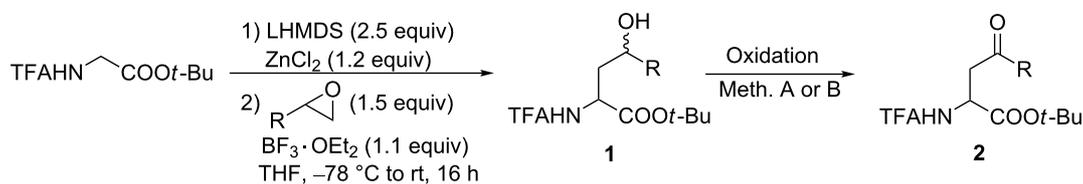
Results and Discussion

An alternative approach is based on regioselective ring opening of epoxides, followed by oxidation of the hydroxy amino acid formed. While aryl-substituted epoxides react preferentially at the benzylic position giving rise to the terminal primary alcohols [25], the corresponding alkyl-substituted epoxides provide secondary alcohols **1** by nucleophilic attack of the enolate at the

sterically least-hindered position [26]. These alcohols can easily be oxidized by Swern-oxidation [27] or with Dess–Martin-periodinane (DMP) [28], giving rise to the required γ -oxo-amino acids **2** (Table 1). In principle both protocols are suitable for oxidation, but in general the yields obtained were better with DMP (82–93%), while under Swern conditions the yields were in the range of $75 \pm 3\%$.

With these γ -oxo- α -amino acids **2** in hand, we investigated the Passerini reactions under neat conditions with acetic acid as the (liquid) acidic component and isocyano acetates as the reactive component (Table 2). Interestingly, no reaction was observed

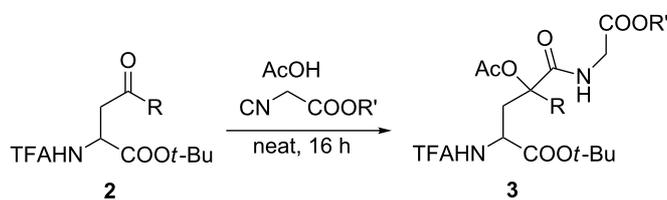
Table 1: Synthesis of γ -oxo-amino acids.



Entry	1	R	Yield (%)	2	Yield (%)	
					Meth. A ^a	Meth. B ^b
1	1a [26]	CH ₃	92	2a	78	91
2	1b [26]	CH ₂ Cl	82	2b	75	90
3	1c [26]	CH ₂ OC ₆ H ₅	86	2c	76	93
4	1d	CH ₂ O-(<i>p</i> -Cl-C ₆ H ₄)	88	2d	72	82
5	1e	CH ₂ O-(<i>o</i> -NO ₂ -C ₆ H ₄)	84	2e	75	87
6	1f	CH ₂ O-(<i>p</i> -NO ₂ -C ₆ H ₄)	83	2f	74	84

^aMethod A: Swern oxidation; ^bMethod B: DMP oxidation.

Table 2: Passerini reactions of γ -oxo-amino acids.



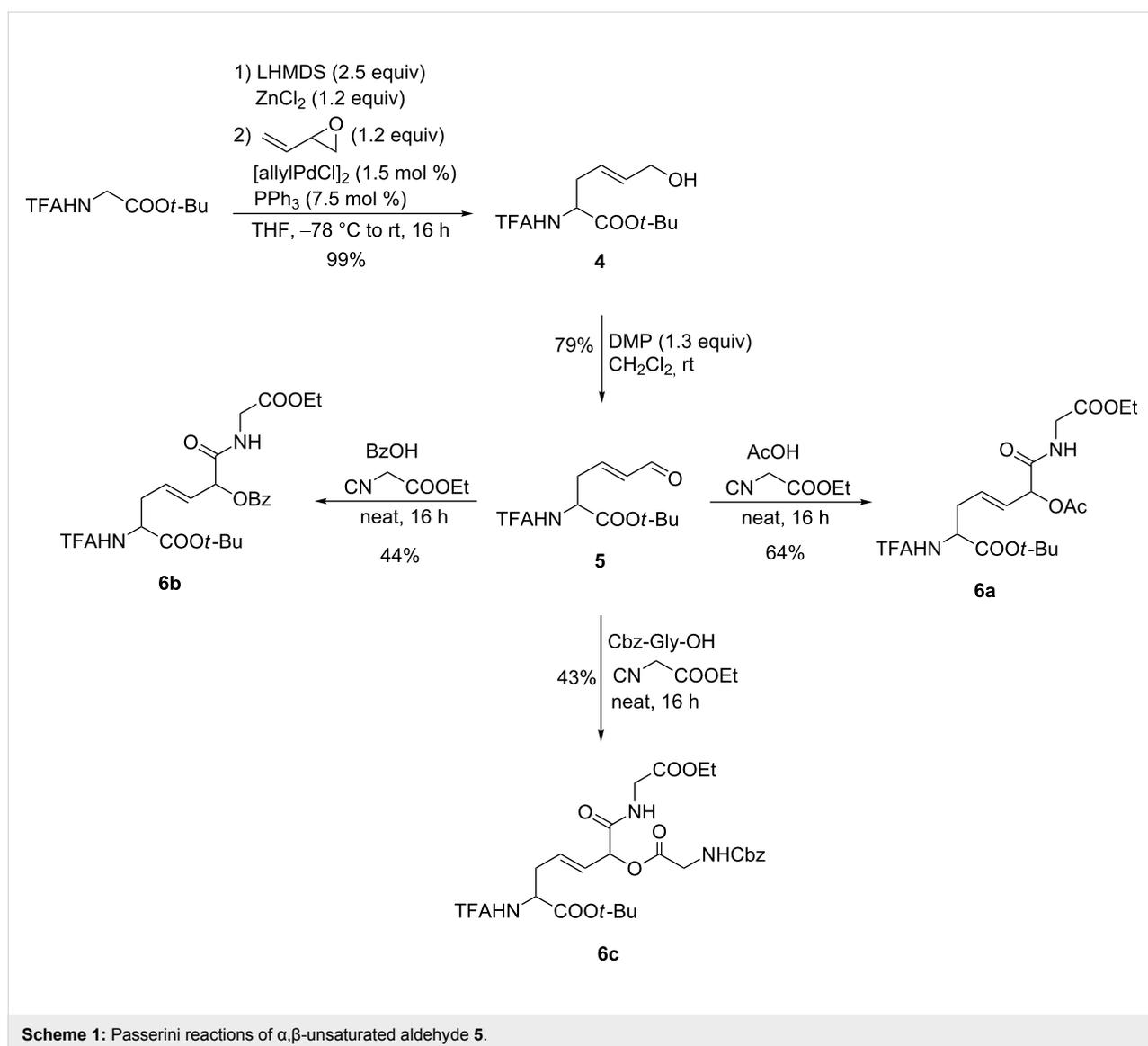
Entry	2	R	R'	3	Yield (%)
1	2a	CH ₃	Me	3a	–
2	2b	CH ₂ Cl	Me	3b	65
3	2c	CH ₂ OC ₆ H ₅	Me	3c	57
4	2d	CH ₂ O-(<i>p</i> -Cl-C ₆ H ₄)	Me	3d	69
5	2e	CH ₂ O-(<i>o</i> -NO ₂ -C ₆ H ₄)	Me	3e	62
6	2f	CH ₂ O-(<i>p</i> -NO ₂ -C ₆ H ₄)	Et	3f	69
7	2d	CH ₂ O-(<i>p</i> -Cl-C ₆ H ₄)	Et	3g	68

with the methyl-substituted oxo acid **2a** (entry 1); only the starting material was recovered. For this reason, we switched to activated ketones bearing an electron-withdrawing group at the α -position. With the chlorinated ketone **2b** the yield was 65% (entry 2), and similar results were obtained with a range of aryloxy-substituted derivatives **2c–2f** (entries 3–7). The new stereogenic center was formed without significant selectivity.

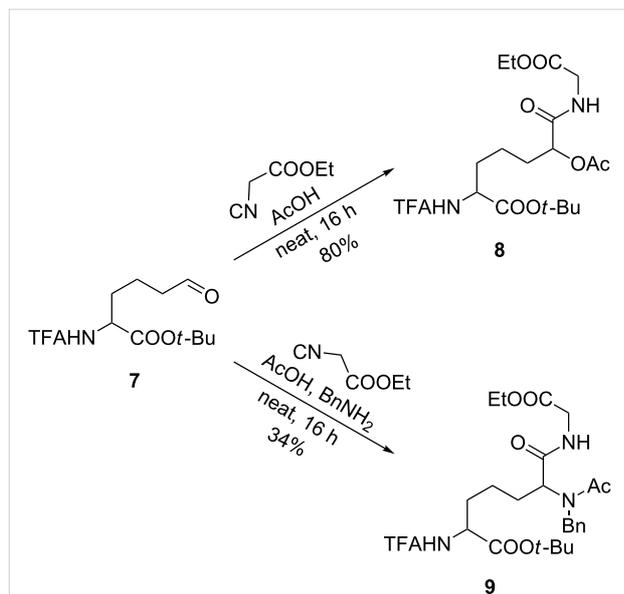
To increase the synthetic potential of this protocol we also applied the Pd-catalyzed opening of a vinyl epoxide with our chelated enolate (Scheme 1) [29]. In this case an amino acid **4** with an allyl alcohol side chain was formed which could be oxidized to the α,β -unsaturated aldehyde **5**. Although these types of aldehydes are critical candidates in Passerini and Ugi reactions [30], we were interested to see if we could also obtain unsaturated Passerini adducts by this procedure. Our first

attempts in CH_3OH and CH_2Cl_2 were unsuccessful. While no reaction was observed in CH_2Cl_2 , in CH_3OH the only product (besides starting material) was the unsaturated acetal resulting from a nucleophilic attack of the solvent on the aldehyde group. Therefore, we decided to run the reaction also under neat conditions as reported for the γ -oxo-amino acids. With acetic acid as the acidic component the yield of **6a** was comparable to the previous examples. In principle, other acids such as benzoic acid or Cbz-protected glycine can be used as well. The lower yield obtained in these cases probably results from stirring problems under these solvent-free conditions.

To circumvent the problems caused by the α,β -unsaturated aldehyde, we hydrogenated **4** before oxidation to obtain the saturated aldehyde **7**. And indeed, under our optimized reaction conditions the addition product **8** could be obtained in 80%



yield (Scheme 2). In principle, Ugi reactions are also possible, as illustrated with the formation of **9**, although the yield was significantly lower in this case and the products are formed as a 1:1 diastereomeric mixture.



Scheme 2: Passerini and Ugi reaction of saturated aldehyde **7**.

Conclusion

In conclusion, we showed that the ring opening of epoxides, either directly or Pd-catalyzed, with chelated enolates combined with Passerini reactions is a suitable tool for the synthesis of highly functionalized α -hydroxy and α -amino acid derivatives. These new compounds are interesting building blocks for peptide-derived drugs. Attempts to improve the yields and to evaluate the scope and limitations are currently underway.

Supporting Information

Supporting Information features detailed experimental procedures, NMR as well as analytical data of all compounds.

Supporting Information File 1

Experimental section.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-151-S1.pdf>]

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft. A. F. Zahoor thanks the DAAD and HEC (Pakistan) for a PhD fellowship.

References

- Ramón, D. J.; Yus, M. *Angew. Chem.* **2005**, *117*, 1628–1661. doi:10.1002/ange.200460548
Angew. Chem., Int. Ed. **2005**, *44*, 1602–1634. doi:10.1002/anie.200460548
- Zhu, J.; Bienaymé, H., Eds. *Multicomponent reactions*; Wiley: Weinheim, Germany, 2005.
- Dolle, R. E.; Le Bourdonnec, B.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M. *J. Comb. Chem.* **2006**, *8*, 597–635. doi:10.1021/cc060095m
- Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. doi:10.1021/cr800296p
- Isambert, N.; Lavilla, R. *Chem.–Eur. J.* **2008**, *14*, 8444–8454. doi:10.1002/chem.200800473
- Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169–6193. doi:10.1021/cr100108k
- Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. doi:10.1021/cr0505728
- El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153–2171. doi:10.1016/j.tet.2008.12.002
- Passerini, M. *Gazz. Chim. Ital.* **1921**, *51-2*, 126–129.
- Banfi, L.; Riva, R. The Passerini Reaction. *Organic Reactions*; Wiley: New Jersey, 2005; Vol. 65, pp 1–140. doi:10.1002/0471264180.or065.01
- Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734–742. doi:10.1002/cber.19610940323
- Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, *11*, 1523–1535. doi:10.1055/s-2000-7904
- Deska, J.; Kazmaier, U. *Curr. Org. Chem.* **2008**, *12*, 355–385. doi:10.2174/138527208783743697
- Schmidt, C.; Kazmaier, U. *Org. Biomol. Chem.* **2008**, *6*, 4643–4648. doi:10.1039/b811382c
- Kazmaier, U.; Schmidt, C. *Synlett* **2009**, 1136–1140. doi:10.1055/s-0028-1088150
- Kazmaier, U.; Hebach, C. *Synlett* **2003**, 1591–1594. doi:10.1055/s-2003-40987
- Pick, R.; Bauer, M.; Kazmaier, U.; Hebach, C. *Synlett* **2005**, *5*, 757–760. doi:10.1055/s-2005-863722
- Kazmaier, U.; Ackermann, S. *Org. Biomol. Chem.* **2005**, *3*, 3184–3187. doi:10.1039/b507028g
- Kazmaier, U.; Persch, A. *Org. Biomol. Chem.* **2010**, *8*, 5442–5447. doi:10.1039/c00b00453g
- Hebach, C.; Kazmaier, U. *J. Chem. Soc., Chem. Commun.* **2003**, 596–597. doi:10.1039/b210952b
- Kazmaier, U.; Hebach, C.; Watzke, A.; Maier, S.; Mues, H.; Huch, V. *Org. Biomol. Chem.* **2005**, *3*, 136–145. doi:10.1039/b411228h
- Kazmaier, U.; Maier, S. *Tetrahedron* **1996**, *52*, 941–954. doi:10.1016/0040-4020(95)00946-9
- Krebs, A.; Kazmaier, U. *Tetrahedron Lett.* **1996**, *37*, 7945–7946. doi:10.1016/0040-4039(96)01764-9
- Kazmaier, U. *Curr. Org. Chem.* **2003**, *7*, 317–328. doi:10.2174/1385272033372888
- Zahoor, A. F.; Kazmaier, U. *Synthesis* **2011**, *7*, 1059–1066. doi:10.1055/s-0030-1258460
- Kazmaier, U.; Zahoor, A. F. *ARKIVOC* **2011**, *IV*, 6–16.
- Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482. doi:10.1021/jo00406a041
- Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. doi:10.1021/jo00170a070
- Thies, S.; Kazmaier, U. *Synlett* **2010**, *1*, 137–141. doi:10.1055/s-0029-1218536

30. Baker, R. H.; Schlesinger, A. H. *J. Am. Chem. Soc.* **1945**, *67*, 1499–1500. doi:10.1021/ja01225a027

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[doi:10.3762/bjoc.7.151](https://doi.org/10.3762/bjoc.7.151)

Ugi post-condensation copper-triggered oxidative cascade towards pyrazoles

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Letter

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Keywords:

aerobic oxidation; copper(II); [3 + 2] cycloaddition; hydrazone;
isocyanide; pyrazolidinone

Beilstein J. Org. Chem. **2011**, *7*, 1310–1314.

doi:10.3762/bjoc.7.153

Received: 20 June 2011

Accepted: 26 August 2011

Published: 21 September 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

Pyrazolidinones were prepared in a two-step sequence starting from α -hydrazonocarboxylic acids. After a four-component Ugi coupling, the resulting hydrazone was engaged in a copper triggered [3 + 2] cycloaddition/aerobic oxidation cascade.

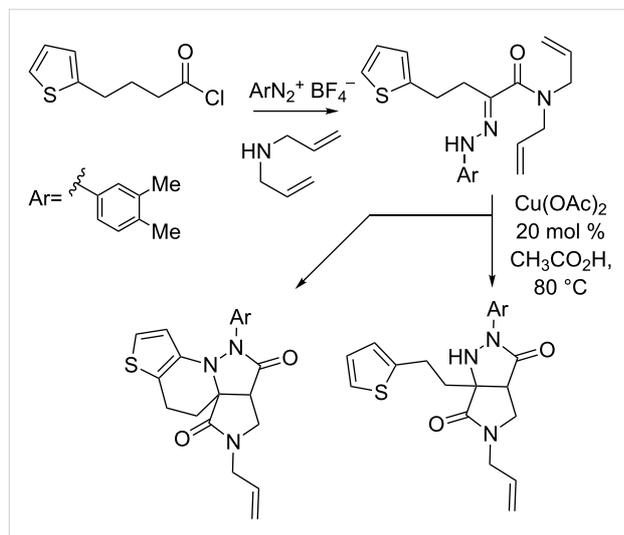
Introduction

In the last twenty years, the Ugi reaction coupled with its various post-condensations towards heterocyclic libraries has established the success of isocyanide-based multicomponent reactions [1-7]. Chemists in both academia and industry have taken advantage of the functional group tolerance of the Ugi coupling to apply to these adducts the various cyclizations offered by the chemists toolkit. We became involved in the Ugi-post-condensation field through our initial interest in radical processes. We found that, compared with classical cycloadditions, cyclocondensations and organometallic couplings, there was no existing description of radical processes on such

adducts. Thus, we decided to undertake various studies using xanthate transfer [8-10], Mn(III) or copper(II) triggered oxidative couplings [11,12].

We recently reported a new synthesis of fused pyrazolidinone under oxidative conditions from simple hydrazone derivatives (Scheme 1) [13]. The cascade features a [3 + 2] cycloaddition coupled with an aerobic oxidation of the resulting pyrazolidine. A further oxidative coupling may be observed according to the substitution pattern of the starting acyl chloride. Considering our interest in IMCR, we envisioned that a similar cascade

could be performed on a properly functionalized Ugi adduct allowing us to reach a new 4-component access to pyrazole derivatives. The present letter summarizes our efforts in this direction.

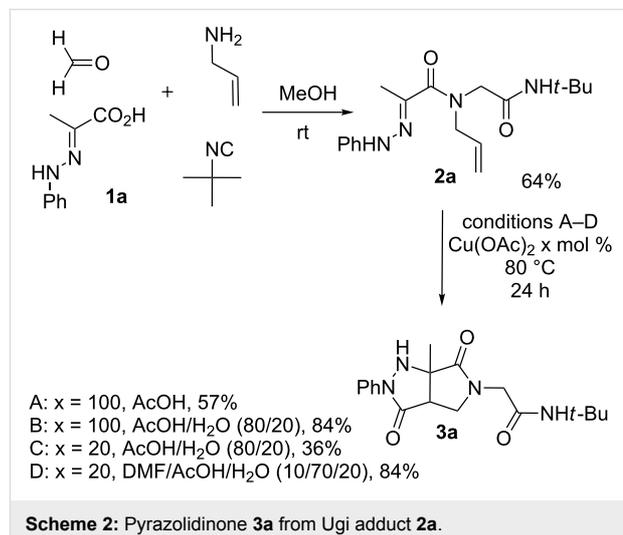


Results and Discussion

Among the possible Ugi pathways to introduce an alkene moiety that is prone to undergo an intramolecular [3 + 2] cycloaddition with a hydrazone, we selected the Ugi coupling between α -hydrazonocarboxylic acids and allylamine as the most straightforward path. There are several reports on the use of hydrazones in Ugi reactions [14–23], however, to the best of our knowledge, there is no report involving α -hydrazonocarboxylic acids.

Hydrazone **1a** was prepared through condensation of pyruvic acid with phenylhydrazine. Adding **1a** to aqueous formaldehyde, allylamine and *tert*-butylisocyanide in MeOH under standard Ugi conditions, led to the formation of the amide **2a** in 64% isolated yield. The compatibility of the hydrazone with this coupling is certainly due to the higher electrophilicity of the intermediate iminium. The latter traps the isocyanide before any interaction with the hydrazone. The first attempted oxidative cyclization of **2a** was made with one equivalent of copper acetate in acetic acid as solvent and gave the expected pyrazolidinone **3a** in a 57% isolated yield (Scheme 2, condition A). Based on our previous study, the yield was improved to reach 84% with a mixture of acetic acid and water (80/20). A combination of DMF, acetic acid and water allowed us to optimize this reaction working with a reduced 20 mol % of copper (84% isolated yield, Scheme 2, condition D). The reaction was performed at 80 °C, overnight, and under

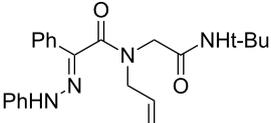
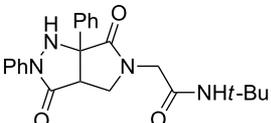
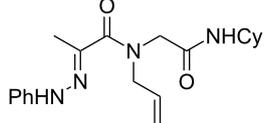
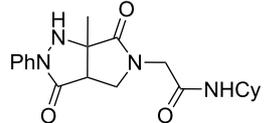
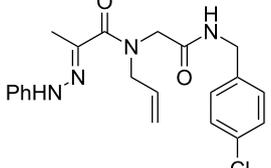
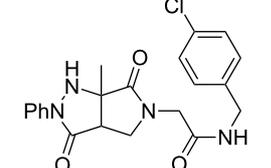
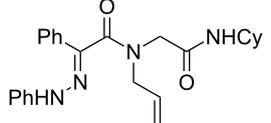
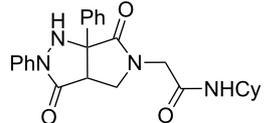
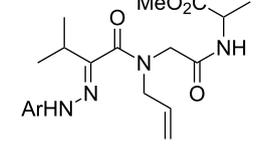
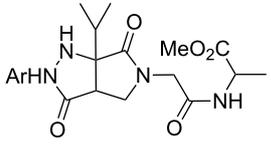
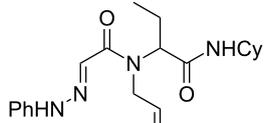
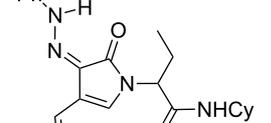
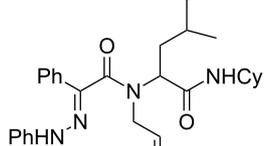
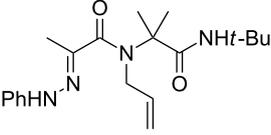
argon. We believe that under these conditions a slow uptake of oxygen helps to control the selective oxidation process. Reactions performed under air were faster but led to intractable mixtures.

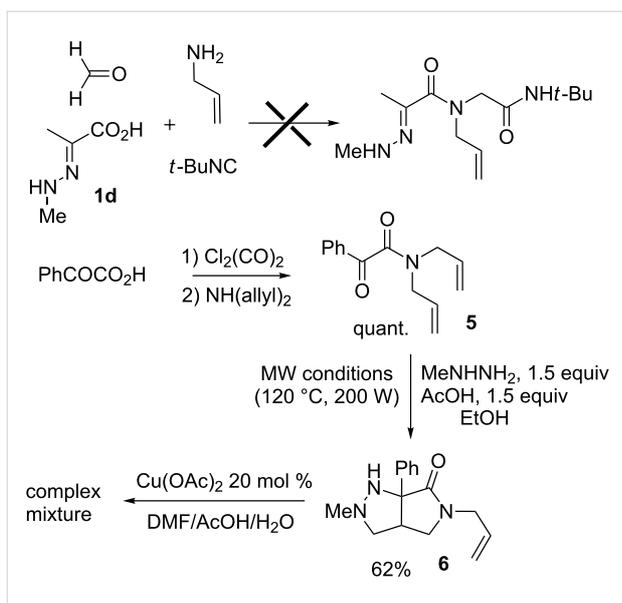


Analogous hydrazones prepared from pyruvic acid and benzoylformic acid with hydrazine derivatives were tested in this Ugi/oxidative cyclization sequence under these optimized conditions. Results are reported in Table 1. Surprisingly, the reaction appears to be only efficient with Ugi adducts prepared with formaldehyde as the carbonyl component (Table 1, entries 1–5). With other aldehydes and ketones, even if the Ugi reaction was performed easily, the following cyclization failed to give the expected pyrazolidinones and resulted in complex mixture formation. Intermediate Ugi adduct **3g** (Table 1, entry 6) only resulted in a small amount of ring-opened product **4g**. The reaction is also limited to *N*-aryl hydrazones due to the lower efficiency of the Ugi reaction with *N*-alkyl hydrazones: An attempt of Ugi coupling with hydrazone **1d**, formaldehyde, allylamine and *tert*-butylisocyanide failed to give any isolable adduct (Scheme 3). This may be explained by an enhanced nucleophilicity of the *N*-monoalkyl hydrazone leading to a competition between the hydrazone and the amine component in the Ugi steps.

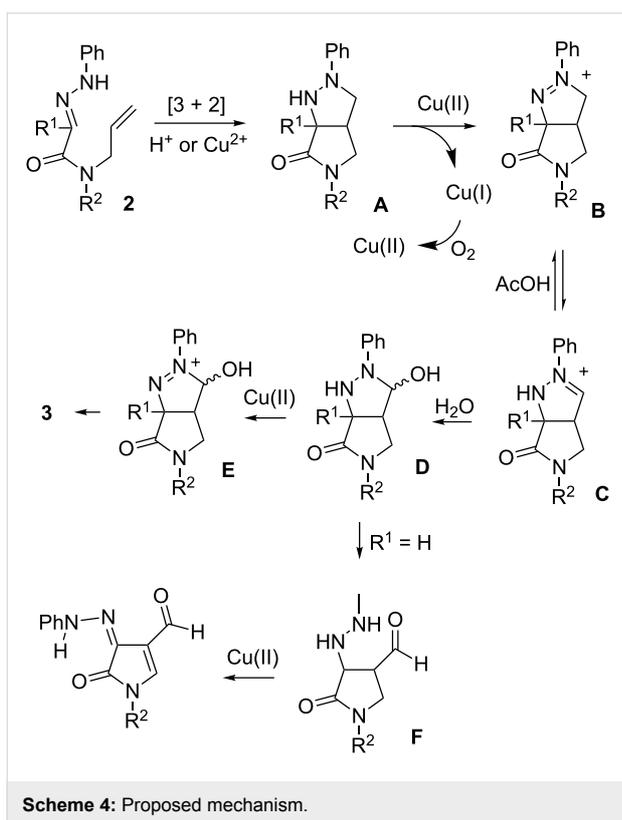
In order to gain further insight into the reactivity of *N*-alkyl derivatives, we decided to synthesize an initial hydrazone by a more conventional route. Benzoylformic acid was converted into its *N*-diallyl amide derivative. The latter failed to produce a hydrazone with methylhydrazine under standard conditions (EtOH, toluene, rt to reflux, with or without added acetic acid). However, we were able to trigger the addition under microwave conditions (in EtOH with 1.5 equiv of AcOH). The expected hydrazone was still not synthesized, however, the cycloadduct **6**

Table 1: Cycloaddition/oxidation cascade from Ugi hydrazone adducts.

Entry	Ugi Product	Cycloadduct
1	 <p>2b, 79%</p>	 <p>3b, 68%</p>
2	 <p>2c, 78%</p>	 <p>3c, 76%</p>
3	 <p>2d, 71%</p>	 <p>3d, 90%</p>
4	 <p>2e, 94%</p>	 <p>3e, 72%</p>
5	 <p>Ar = 4-Cl-C₆H₄ 2f, 37%</p>	 <p>Ar = 4-Cl-C₆H₄ 3f, 49%</p>
6	 <p>2g, 58%</p>	 <p>4g, 12%</p>
7	 <p>2h, 52%</p>	–
8	 <p>2i, 50%</p>	–



Scheme 3: Attempted reactions of N-methyl hydrazones.



Scheme 4: Proposed mechanism.

was obtained, probably through a [3 + 2] cycloaddition triggered by acetic acid. The attempted oxidation of **6** with copper acetate in DMF/AcOH/H₂O gave only complex mixtures.

The oxidation sequence may be explained by the mechanism depicted in Scheme 4. The process starts with a [3 + 2] cyclo-

addition triggered either by copper acetate or acetic acid [24–29]. The resulting pyrazoline **A** may be oxidized by copper(II) salts forming intermediate **D** after addition of water [30,31]. Two alternative paths may then be observed from **D**: Ring-opening leading to azo or hydrazono derivatives such as **4g**, further oxidation without ring-opening giving the fused pyrazolidinone **3**.

Conclusion

In conclusion, we have disclosed a new Ugi coupling with α -hydrazonocarboxylic acids. These Ugi adducts have been used in an Ugi post-condensation involving a [3 + 2] cycloaddition followed by an oxidative cascade. Among potential Ugi post-condensations, radical and oxidative processes represent a very promising route towards the formation of complex scaffolds. We are currently exploring the reactivity of the *N*-aryl Ugi–Smiles adducts using similar strategies.

Experimental

Typical procedure for the first step: (*E*)-*N*-allyl-*N*-(2-(*tert*-butylamino)-2-oxoethyl)-2-(2-phenylhydrazono)propanamide (2a**):** To a solution of formaldehyde (210 μ L, 2.8 mmol) in methanol (1 M) were added successively allylamine (210 μ L, 2.8 mmol), 2-(2-phenylhydrazono)propanoic acid (500 mg, 2.8 mmol), and *tert*-butylisocyanide (230 mg, 2.8 mmol). The resulting mixture was stirred at 40 °C until completion of the reaction (TLC). The solvent was removed under reduced pressure. The product was isolated by flash chromatography on silica gel (PE/Et₂O) with a yield of 64%. ¹H NMR (CDCl₃, 400 MHz) δ 7.52 (br s, 1H), 7.29 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.16 (br s, 1H), 5.96–5.88 (m, 1H), 5.28–5.23 (m, 2H), 4.34–4.00 (m, 4H), 2.14 (s, 3H), 1.35 (s, 9H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 168.7, 168.6, 143.9, 136.9, 132.8, 129.8, 122.0, 119.0, 114.0, 53.9, 51.7, 51.3, 29.1, 12.6.

Typical procedure for the oxidative cyclization: *N*-*tert*-butyl-2-(6a-methyl-3,6-dioxo-2-phenylhexahydropyrrolo-[3,4-*c*]pyrazol-5(1*H*)-yl)acetamide (3a**):** To a solution of hydrazone **2a** (100 mg, 0.3 mmol) in a 10/70/20 DMF/CH₃COOH/H₂O mixture (0.06 M) was added Cu(OAc)₂ (20 mol %). The resulting mixture was heated at 80 °C under argon. The pH was adjusted to 6 with an aqueous sodium hydrogencarbonate solution, and the aqueous phase was extracted with AcOEt. Then the organic layers were washed ten times with water, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The product was isolated by flash chromatography on silica gel (PE/Et₂O with 1% of TEA) with a yield of 84%. ¹H NMR (CDCl₃, 400 MHz) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.37 (dd, *J* = 8.3, 7.3 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 5.52 (br s, 1H, NH), 4.89 (br s, 1H), 3.93 (d, *J* = 16.2 Hz,

1H), 3.85 (dd, $J = 10.3, 6.3$ Hz, 1H), 3.80 (d, $J = 16.2$ Hz, 1H), 3.76 (d, $J = 10.3$ Hz, 1H), 3.22 (d, $J = 6.3$ Hz, 1H), 1.63 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 174.6, 169.8, 166.3, 138.1, 129.2, 125.8, 119.5, 63.7, 52.0, 48.0, 47.6, 29.0, 18.9.

Supporting Information

Supporting Information File 1

Experimental procedures with characterization data for all new compounds.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-153-S1.pdf>]

Acknowledgements

We thank the ENSTA for financial support and C.R. thanks the École Polytechnique for fellowship.

References

- Zhu, J.; Bienaymé, H., Eds. *Multicomponent reactions*; Wiley-VCH: Weinheim, Germany, 2005.
- Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131. doi:10.1021/ar9502083
- Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. doi:10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U
- Bienaymé, H.; Hulme, C.; Odon, G.; Schmitt, P. *Chem.–Eur. J.* **2000**, *6*, 3321–3329. doi:10.1002/1521-3765(20000915)6:18<3321::AID-CHEM3321>3.0.CO;2-A
- Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53–66. doi:10.3390/80100053
- Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. doi:10.1021/cr0505728
- El Kaïm, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153–2171. doi:10.1016/j.tet.2008.12.002
- El Kaïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259–8261. doi:10.1016/j.tetlet.2006.09.123
- Gámez-Montaño, R.; Ibarra-Rivera, T.; El Kaïm, L.; Miranda, L. D. *Synthesis* **2010**, 1285–1290. doi:10.1055/s-0029-1218700
- El Kaïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E.; Cano-Herrera, M. A.; Perez-Labrada, K. *Chem. Commun.* **2010**, *46*, 2489–2491. doi:10.1039/b924207d
- El Kaïm, L.; Grimaud, L.; Vieu, E. *Org. Lett.* **2007**, *9*, 4171–4173. doi:10.1021/ol701678d
- El Kaïm, L.; Grimaud, L.; Legoff, X.; Azarte, M. M.; Miranda, L. D. *Chem. Commun.* **2011**, *47*, 8145–8147. doi:10.1039/c1cc12236c
- Dos Santos, A.; El Kaïm, L.; Grimaud, L.; Ronssey, C. *Eur. J. Org. Chem.* **2011**, *17*, 3117–3121. doi:10.1002/ejoc.201100261
- Ugi, I.; Bodesheim, F. *Chem. Ber.* **1961**, *94*, 2797–2801. doi:10.1002/cber.19610941031
- Ugi, I.; Bodesheim, F. *Justus Liebigs Ann. Chem.* **1963**, *666*, 61–64. doi:10.1002/jlac.19636660108
- Zinner, G.; Kliegel, W. *Arch. Pharm.* **1966**, *299*, 746–756. doi:10.1002/ardp.19662990903
- Zinner, G.; Bock, W. *Arch. Pharm.* **1971**, *304*, 933–943. doi:10.1002/ardp.19713041212
- Failli, A.; Nelson, V.; Immer, H.; Götz, M. *Can. J. Chem.* **1973**, *51*, 2769–2775. doi:10.1139/v73-414
- Marcaccini, S.; Pepino, R.; Polo, C.; Pozo, M. C. *Synthesis* **2001**, 85–88. doi:10.1055/s-2001-9745
- Marcos, C. F.; Marcaccini, S.; Pepino, R.; Polo, C.; Torroba, T. *Synthesis* **2003**, 691–694. doi:10.1055/s-2003-38071
- Sañudo, M.; Marcaccini, S.; Basurto, S.; Torroba, T. *J. Org. Chem.* **2006**, *71*, 4578–4584. doi:10.1021/jo060434y
- Krasavin, M.; Bushkova, E.; Parchinsky, V.; Shumsky, A. *Synthesis* **2010**, 933–942. doi:10.1055/s-0029-1219274
- Krasavin, M.; Parchinsky, V.; Shumsky, A.; Konstantinov, I.; Vantskul, A. *Tetrahedron Lett.* **2010**, *51*, 1367–1370. doi:10.1016/j.tetlet.2009.12.141
- Le Fevre, G.; Sinbandhit, S.; Hamelin, J. *Tetrahedron* **1979**, *35*, 1821–1824. doi:10.1016/0040-4020(79)80005-8
- Fouchet, B.; Joucla, M.; Hamelin, J. *Tetrahedron Lett.* **1981**, *22*, 1333–1336. doi:10.1016/S0040-4039(01)90310-7
- Shimizu, T.; Hayashi, Y.; Miki, M.; Teramura, K. *J. Org. Chem.* **1987**, *52*, 2277–2285. doi:10.1021/jo00387a031
- Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 11279–11282. doi:10.1021/ja049498l
- Frank, E.; Kardos, Z.; Wölfling, J.; Schneider, G. *Synlett* **2007**, 1311–1313. doi:10.1055/s-2007-977452
- Gergely, J.; Morgan, J. B.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 9144–9152. doi:10.1021/jo061537j
- Ciesielski, M.; Pufky, D.; Döring, M. *Tetrahedron* **2005**, *61*, 5942–5947. doi:10.1016/j.tet.2005.01.111
For an oxidation of hydrazones induced by copper(II) salts.
- Kabalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, *5*, 4129–4131. doi:10.1021/ol035544v
For an oxidation of hydrazines induced by copper(II) salts.

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Amines as key building blocks in Pd-assisted multicomponent processes

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Review

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Keywords:

amines; multicomponent reactions; palladium

Beilstein J. Org. Chem. **2011**, *7*, 1387–1406.

doi:10.3762/bjoc.7.163

Received: 20 May 2011

Accepted: 14 September 2011

Published: 10 October 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

In the last few years, palladium-mediated three-component synthesis has emerged as an important synthetic methodology to gain access to nitrogen-containing structures. The latest developments in this area are discussed in this review.

Introduction

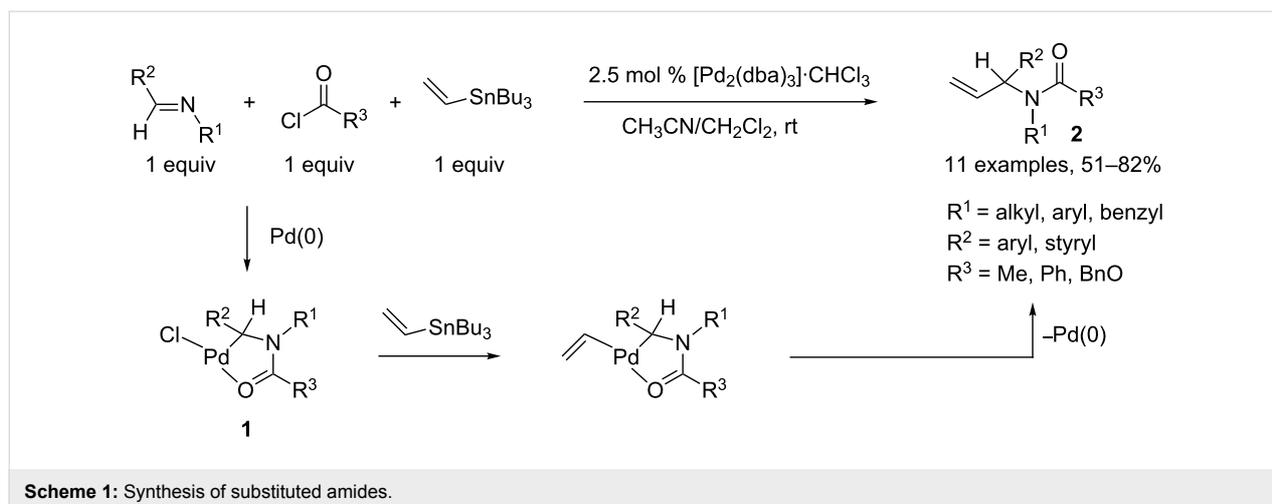
Nitrogen-containing structures are present in numerous bioactive natural and synthetic products. The development of new methodologies to prepare these useful frameworks has attracted great attention from organic chemists. Among these developments, multicomponent strategies offer significant advantages over stepwise procedures since several bonds are formed in a one-pot operation, minimizing the formation of waste and competitive reactions [1]. In line with this, remarkable new strategies have been developed based on palladium-mediated coupling process. The purpose of this review is to discuss recent achievements in the design of palladium-catalyzed multicomponent preparation of nitrogen-containing structures and this article is divided into sections relating to the introduction of the amine functionality.

Review

Imines as electrophilic partners

The imine function plays an important role in the development of multicomponent approaches to polyfunctionalized nitrogen acyclic or cyclic compounds due to the ease of their in situ preparation. Many strategies have been developed based on this concept, the imines being either directly used as starting building blocks or generated in situ as part of the multicomponent process.

Arndtsen and coworkers elaborated a three-component process allowing the synthesis of α -substituted amides. This methodology relied on the oxidative addition of an *N*-acyliminium species, generated in situ from an imine and an acid chloride, to

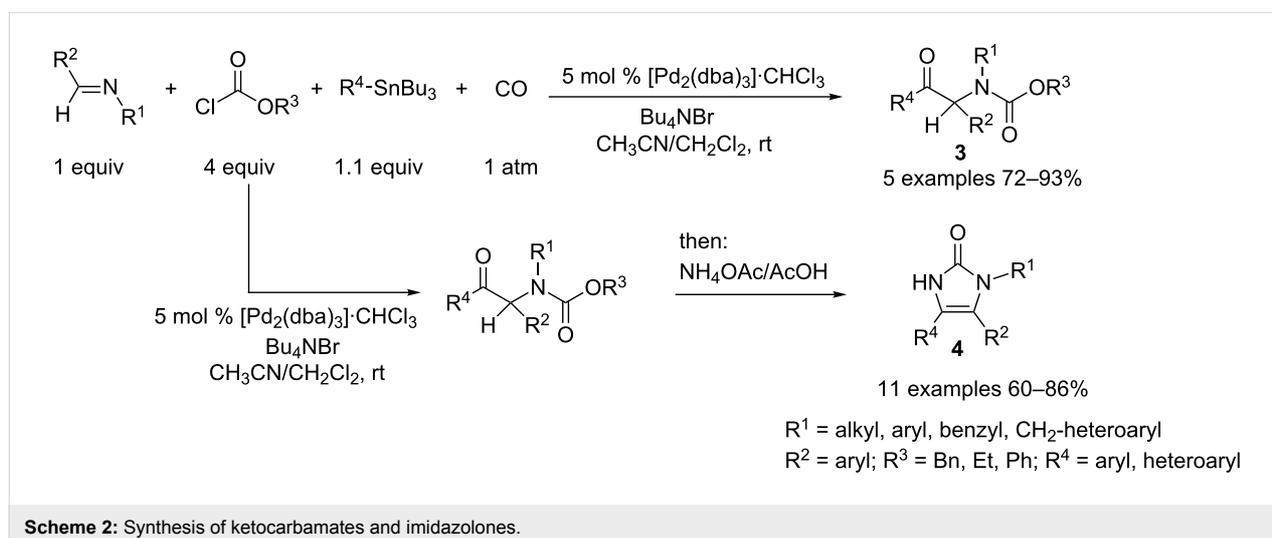


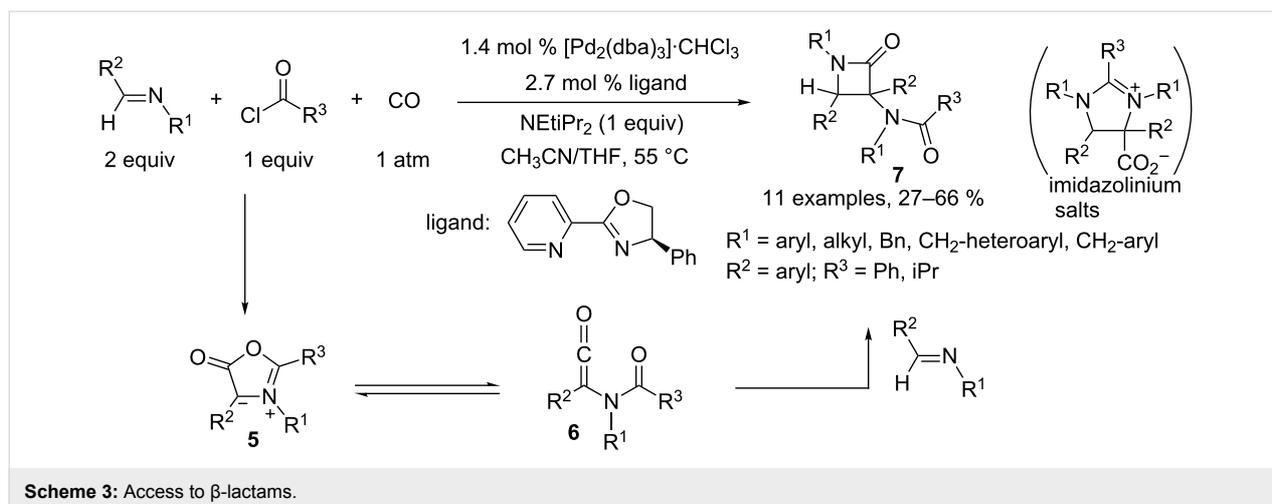
a Pd(0) complex, furnishing a stable chelated palladium adduct **1**, which was isolated and fully characterized. When vinyltributyltin was added as a third component in the reaction medium, a transmetalation step occurred, followed by a reductive elimination step, furnishing amides **2** in good to excellent yields [2]. This reaction tolerated various functional groups on the imine moiety, such as ether, thioether and ester groups, although enolizable alkylimines were not suitable under these conditions (Scheme 1).

Replacement of the acid chloride with a chloroformate under 1 atmosphere of carbon monoxide as a fourth component led to ketocarbamates **3** in a single operation through a carbonylative coupling [3]. Various chloroformates and imines can participate in this reaction, stannanes being limited to aryl, benzyl or ethyl ones. When vinylstannane was used, the transmetalation step was more rapid than the CO insertion, giving instead substituted carbamates. After removal of the solvents in vacuo,

the addition of acetic acid and 15 equivalents of ammonium acetate to the crude mixture resulted in a postcyclization leading to imidazolones **4**, with spontaneous elimination of the initial chloroformate substituent (Scheme 2).

Arndtsen also demonstrated that 3-amido-substituted β -lactams **7** can be obtained, based on a similar strategy, through the assembly of four components, namely, imines, acid chloride and carbon monoxide. The process is thought to begin with formation of a münchnone **5**, resulting from oxidative addition of an acyliminium species to Pd(0), followed by CO insertion and β -hydride elimination. This münchnone is in equilibrium with its ketene isomeric form **6**, and a formal [2 + 2] cycloaddition with a second equivalent of imine generates the lactam (Scheme 3). The authors pointed out that the trapping of HCl by a sterically hindered base (NETiPr₂) is the key point in this methodology to enable access to this heterocycle and to avoid formation of imidazolium salts [4].



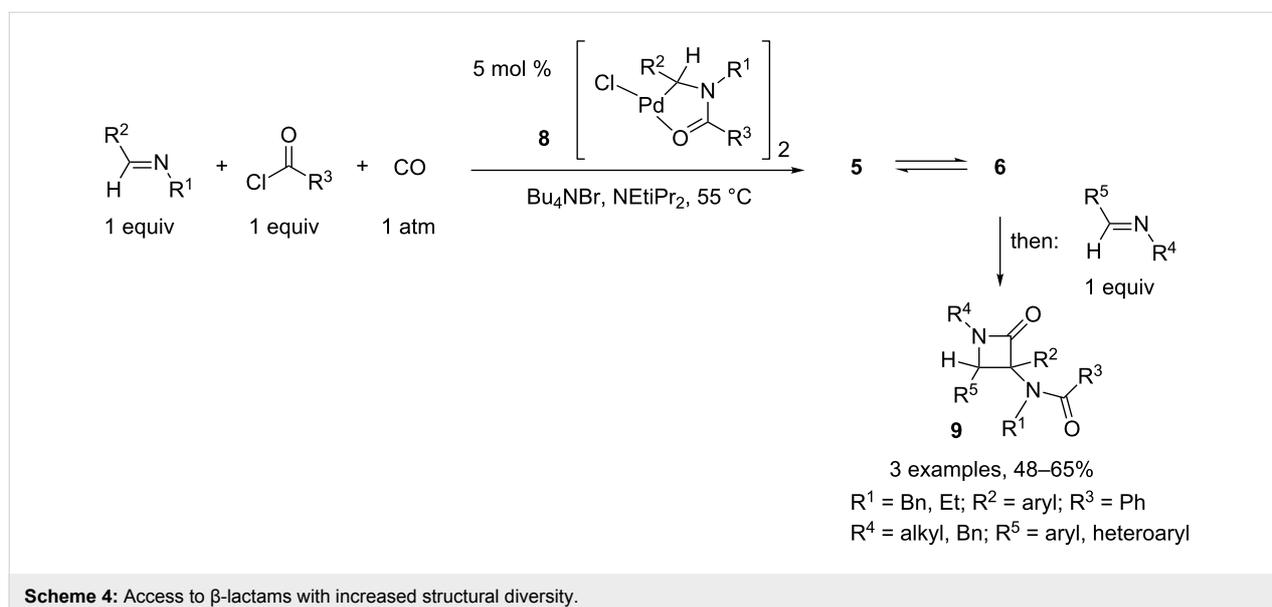


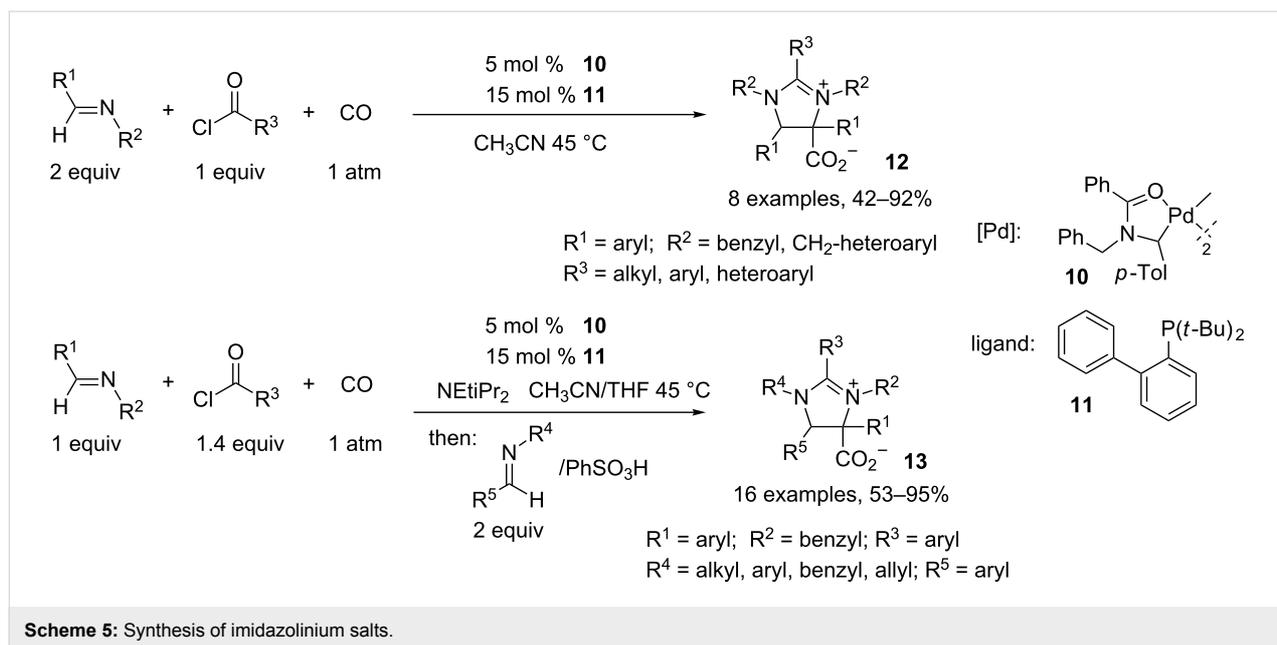
To increase the structural diversity of the final lactam, a modified process was developed that allows introduction of two distinct imines in this reaction. This coupling process was catalyzed by palladacycle **8** and led to the mesoionic compound **5** under these conditions. Subsequent addition of a second, different imine produced β -lactams **9** in good yields, after heating at 55 °C for 24 h (Scheme 4) [4].

As mentioned above, imidazolium salts **12** can be obtained by a dipolar cycloaddition of münchnone intermediates with imines. Arndtsen and coworkers developed a new highly active palladium catalyst to improve previous results in this area. Moreover, this strategy allows the selective incorporation of two different imines leading to polysubstituted imidazoliums **13**. After a large screening of palladium precatalysts and ligands, the palladacycle **10** in combination with the di-*tert*-

butyl-2-biphenylphosphine (**11**) furnished the best results in terms of reaction time and yield. A large variety of imines and acid chlorides can be used in this reaction, with only enolizable imines and those bearing bulky nitrogen substituents being incompatible. In order to have four independent tunable substrates, the authors added a base (NEt₃Pr₂) to the reaction medium that favors formation of the münchnone intermediate. The second imine was added after 16 h of heating at 45 °C, together with PhSO₃H, which catalyzed the dipolar cycloaddition and avoided formation of a β -lactam as shown before (Scheme 5) [5].

The palladium-catalyzed trans-addition-alkylative cyclization (anti-Wacker cyclization) of *o*-ethynylbenzaldehyde with organoboron reagents in the presence of secondary amines was accomplished by Tsukamoto and coworkers [6]. This novel

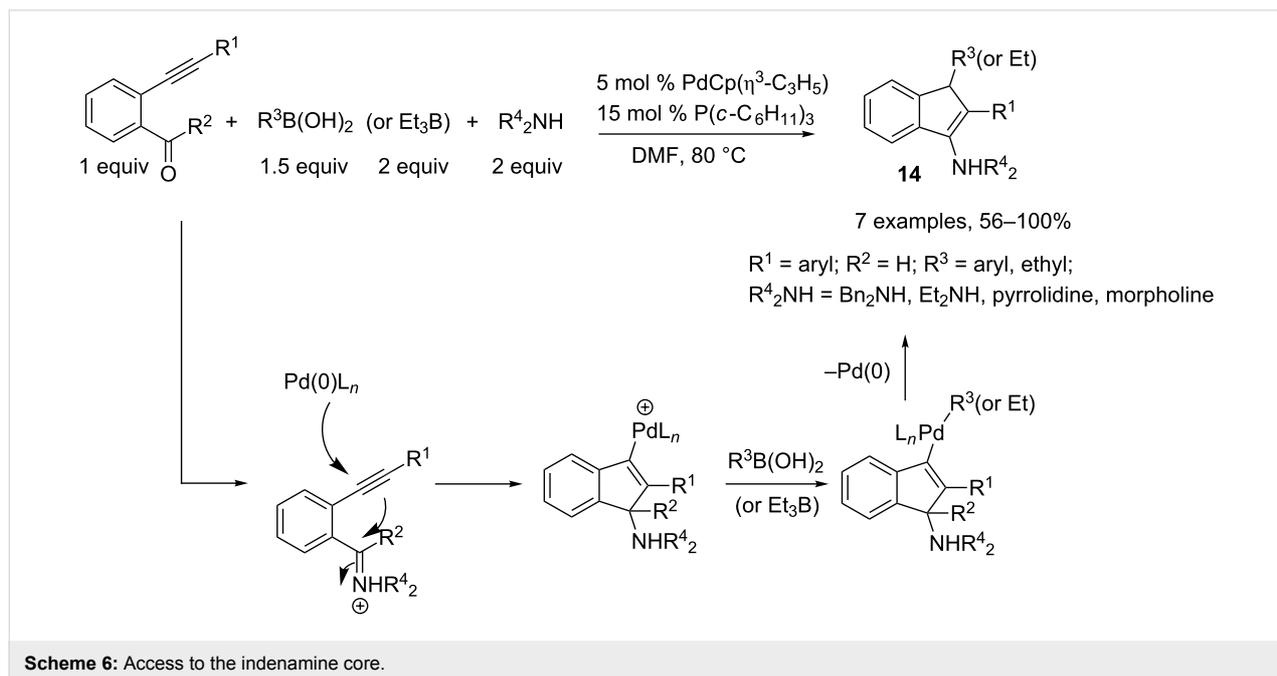




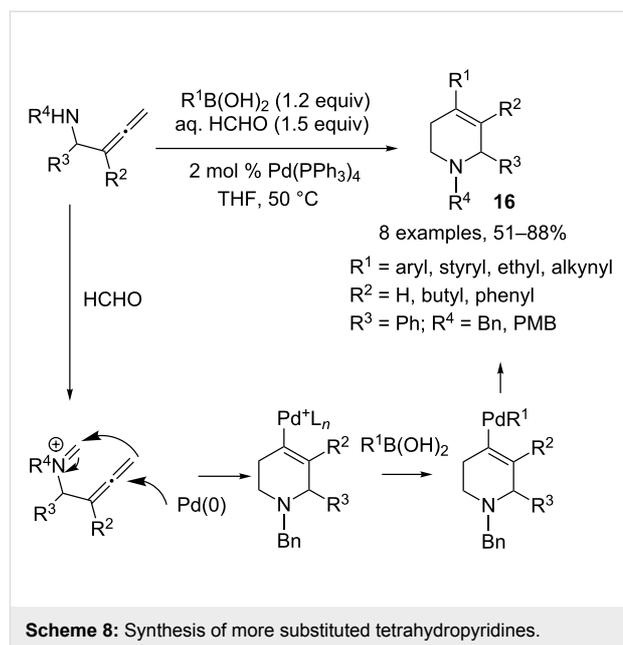
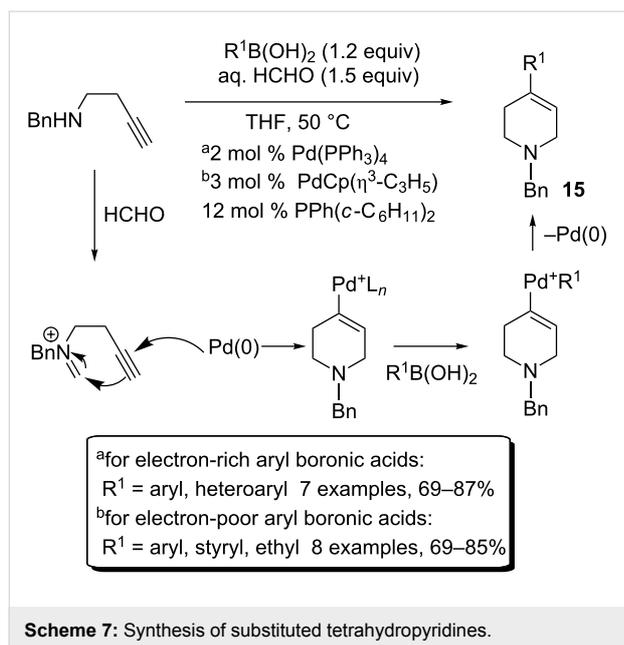
Scheme 5: Synthesis of imidazolium salts.

strategy, dedicated to the synthesis of indenamines **14**, involves addition of an electron-rich palladium/phosphine complex to a triple bond, followed by nucleophilic addition to an iminium ion generated in situ by addition of a secondary amine to an aldehyde. Transmetalation of the resulting species with a boronic acid or triethylborane, followed by a reductive elimination, afforded the indenamine core in good to excellent yields. However, this Pd-catalyzed cyclization was only effective for aldehydes since ketones did not participate in the process (Scheme 6).

Tsukamoto extended this methodology further to the cyclization of alkynyl- and allenyliminiums in order to access 1,4-disubstituted-1,2,3,6-tetrahydropyridines **15** or **16** following the same strategy [7]. For alkynyliminiums, two different catalytic systems were developed according to the nature of the aryl- or heteroarylboronic acids used. For neutral or electron-rich acids, $\text{Pd}(\text{PPh}_3)_4$ as catalyst gave excellent results, whereas it was necessary to use $\text{PdCp}(\eta^3\text{-C}_3\text{H}_5)$ in the presence of $\text{PPh}(c\text{-C}_6\text{H}_{11})_2$ as a ligand for those bearing electron-withdrawing groups (Scheme 7).



Scheme 6: Access to the indenamine core.

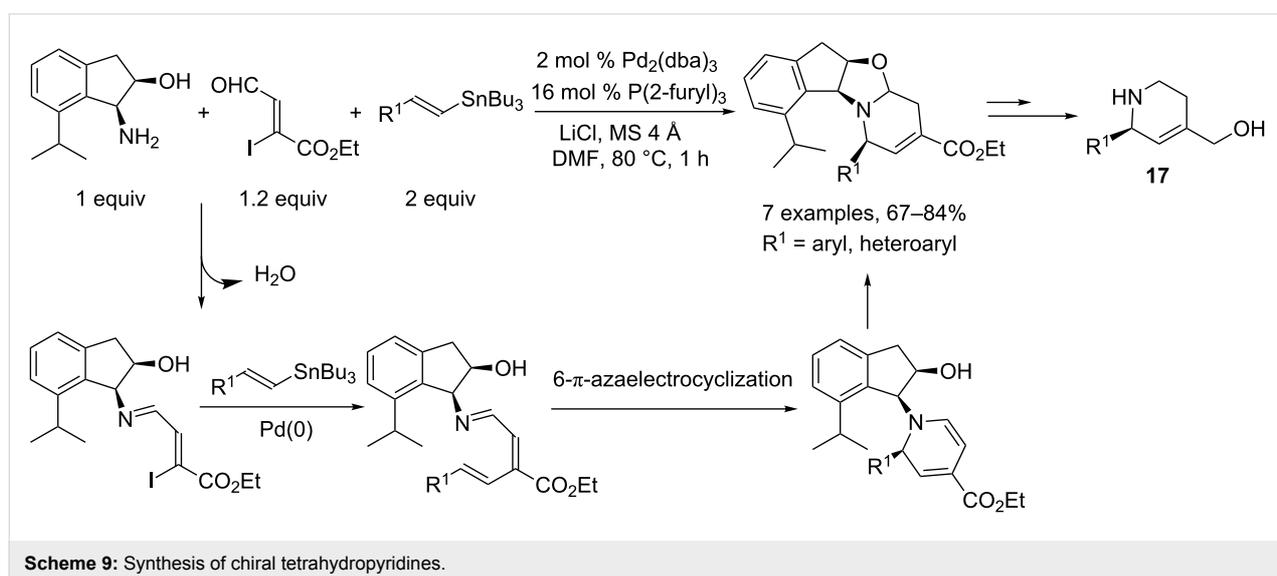


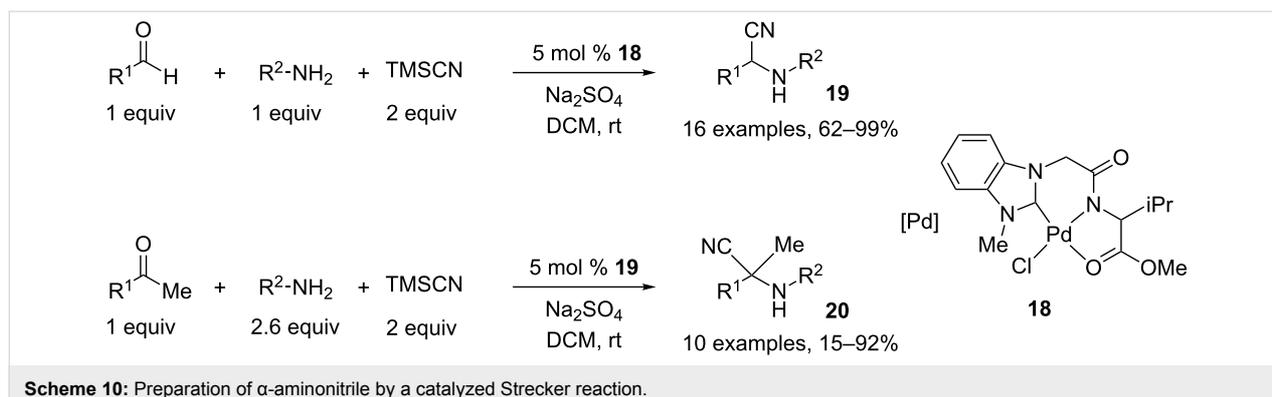
The proposed mechanism involves addition of Pd(0) onto the triple bond, followed by nucleophilic attack on the iminium generated in situ. The resulting vinylpalladium species reacts with the boron or alkynyl compound as previously shown. Allenylamines are also compatible with this anti-Wacker process, leading to more substituted tetrahydropyridines **16** in good to excellent yields (Scheme 8).

Another strategy allowing access to pyridine derivatives was developed by Katsumura and coworkers. They showed that chiral 2,4-disubstituted 1,2,5,6-tetrahydropyridines **17** can be obtained through a one pot imine synthesis, Stille coupling, 6 π -azaelectrocyclization and aminoacetal formation. The chiral

auxiliary can be removed by further treatment with DIBAL-H and Pb(OAc)₄ (Scheme 9) [8].

The Strecker reaction, employing aldehydes or ketones and a cyanide source, is a very useful route for the preparation of α -aminonitriles **19** or **20**. A general and efficient three-component method was reported by Jung and coworkers who used a new catalytic system based on a NHC–amidate palladium(II) complex **18**. This complex acts as a Lewis acid to favor addition of cyanide to the imine generated in situ. This methodology employs smooth conditions and works with aldehydes as well as ketones, giving good to excellent yields (Scheme 10) [9].



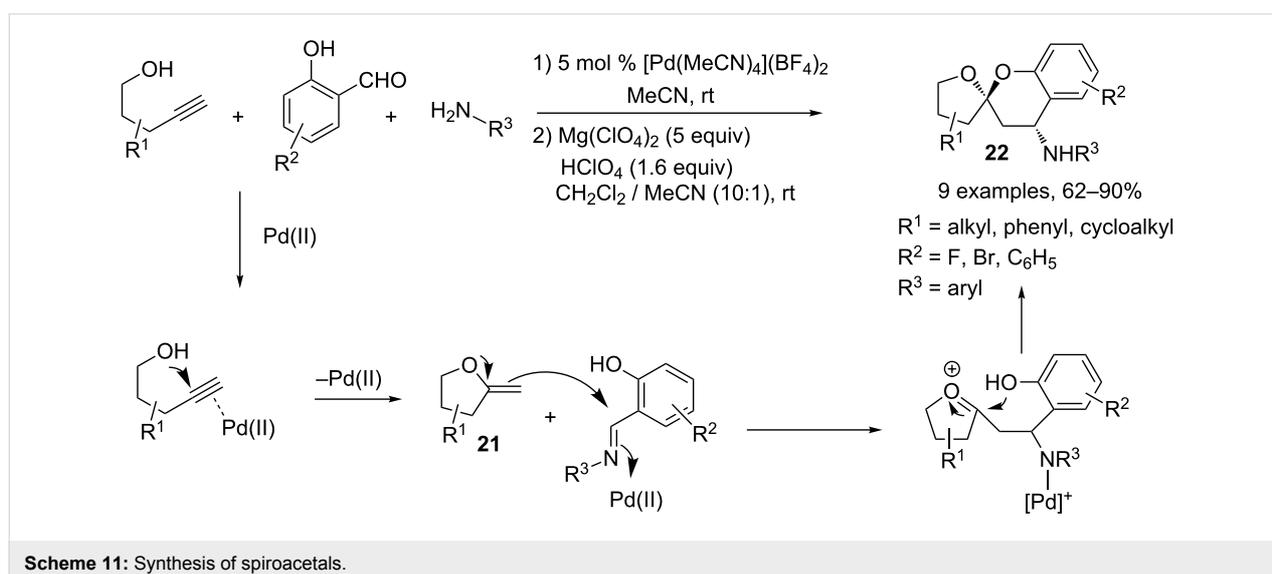


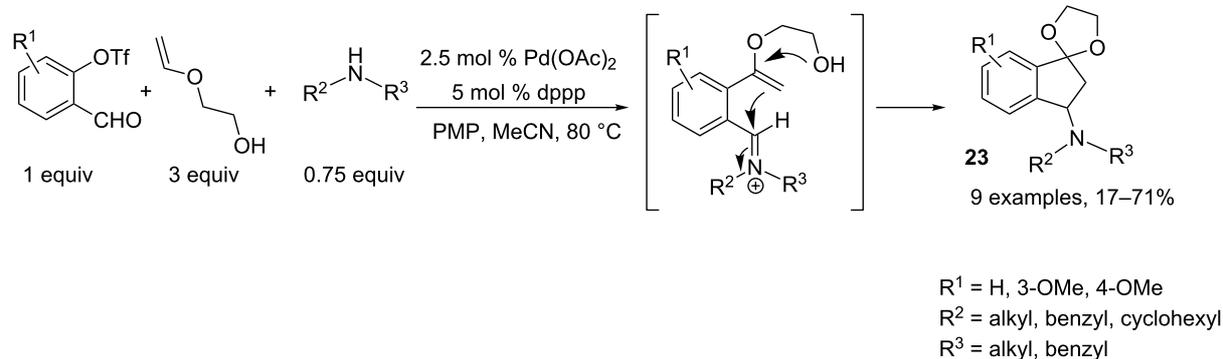
Barluenga and coworkers reported a synthesis of spiroacetals **22**, through a Pd(II)-catalyzed three-component cascade reaction, starting from an alkynol, an aldehyde and a primary amine. The authors suggested that the first step of the reaction was the attack of the hydroxyl group onto the triple bond activated by a Pd(II) cationic complex, followed by a protodemetalation, which afforded the methylenefuran **21**. This reacts with the imine activated by the Pd(II) species through a Mannich-type process. Finally, addition of the phenol to the oxonium can lead to spiroacetal **22**. One major drawback of this MCR is the formation of an equimolar amount of two diastereomers, which can be circumvented by further treatment of the crude mixture with 5 equivalents of MgClO_4 and 1.6 equivalents of HClO_4 in $\text{CH}_2\text{Cl}_2/\text{MeCN}$ at room temperature. Under these acidic conditions, one diastereomer was cleanly and completely transformed into the other one (Scheme 11) [10].

Hallberg and coworkers developed a one-pot strategy towards the synthesis of masked 3-aminoindan-1-ones **23**. This process was initiated by Heck addition of an aryl triflate to a vinyl ether,

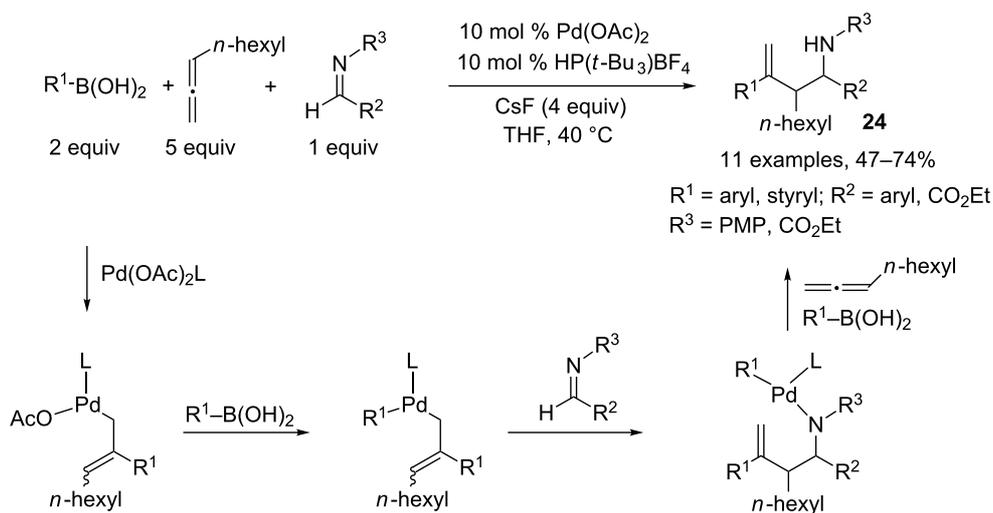
leading to an α -arylation product, followed by iminium formation in the presence of a secondary amine and subsequent tandem cyclization. The authors showed the importance of the ratio of the diverse reactants, notably that the amount of amine should remain low to avoid formation of aminal derivatives that would block the ring closure (Scheme 12) [11].

Homoallylic amines and α -aminoesters **24** were prepared by Malinakova and coworkers, by a palladium(II)-catalyzed coupling of boronic acids, 1,2-nonadiene, and aliphatic, aromatic or heteroaromatic imines [12]. The authors postulated a transmetalation step between the Pd(II) complex and a boronic acid activated by CsF, followed by insertion of the resulting σ -arylpalladium(II) into the allenic moiety leading to a π -allyl intermediate. This can undergo a nucleophilic allyl transfer to the imine, generating an amino-Pd(II) complex, which can subsequently add to another allenic unit. After a new transmetalation step with the boronic acid, the active catalytic species can be released and entered into a new catalytic cycle (Scheme 13).





Scheme 12: Synthesis of masked 3-aminoindan-1-ones.

Scheme 13: Synthesis of homoallylic amines and α -aminoesters.

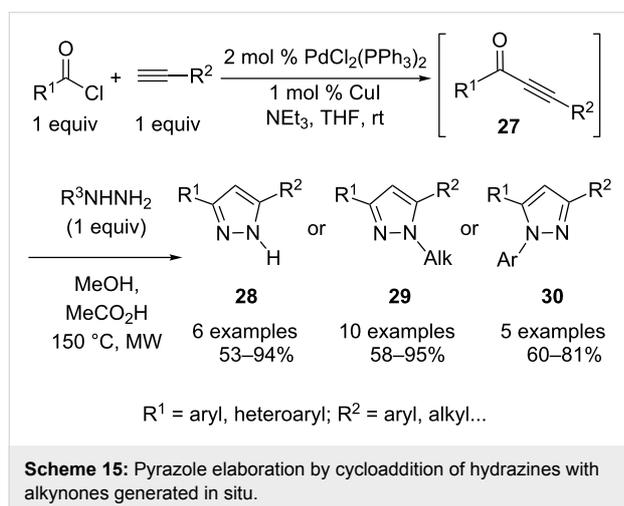
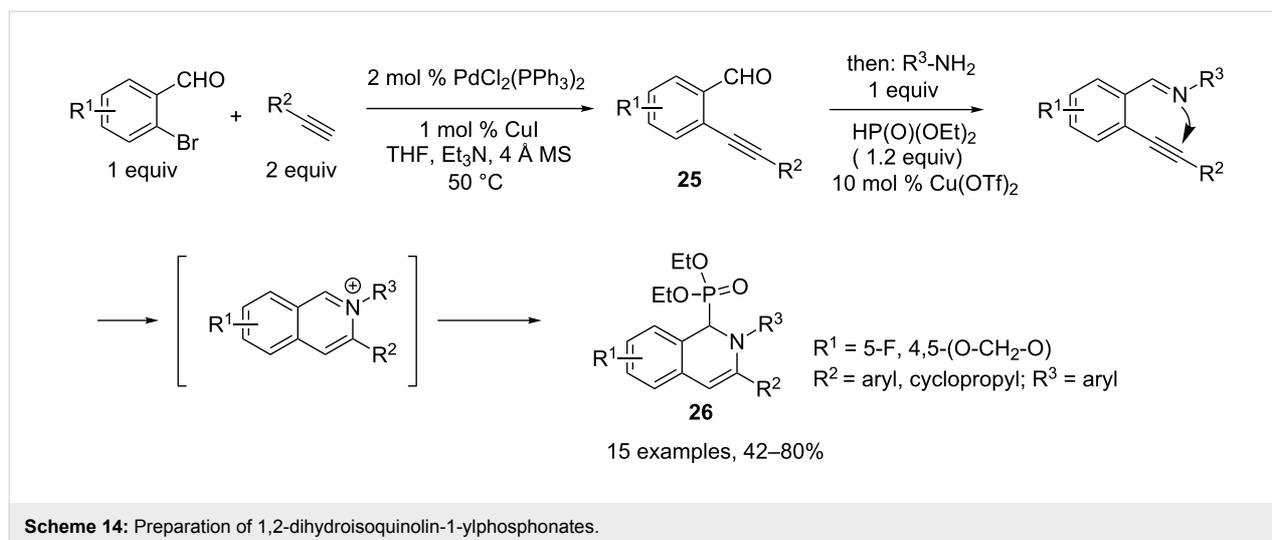
Imine as a nucleophilic partner

A tandem four-component reaction allowing access to 1,2-dihydroisoquinolin-1-ylphosphonates **26** was reported by Wu and coworkers. Initial Sonogashira coupling was effected between a 2-bromobenzaldehyde and an alkyne in the presence of catalytic amounts of PdCl₂(PPh₃)₂ and CuI. After complete conversion of the aldehyde into the coupling product **25** (TLC control), a primary amine and diethylphosphite were added to the reaction medium with concomitant addition of 10 mol % of Cu(OTf)₂ necessary to complete the cyclization step. The proposed mechanism involves formation of an imine intermediate, which attacks the triple bond activated by the copper(II) complex. The resulting iminium was finally trapped by addition of diethylphosphite. Moderate to good yields were obtained

depending on the nature of the various components (Scheme 14) [13].

Amines as hetero-Michael donors

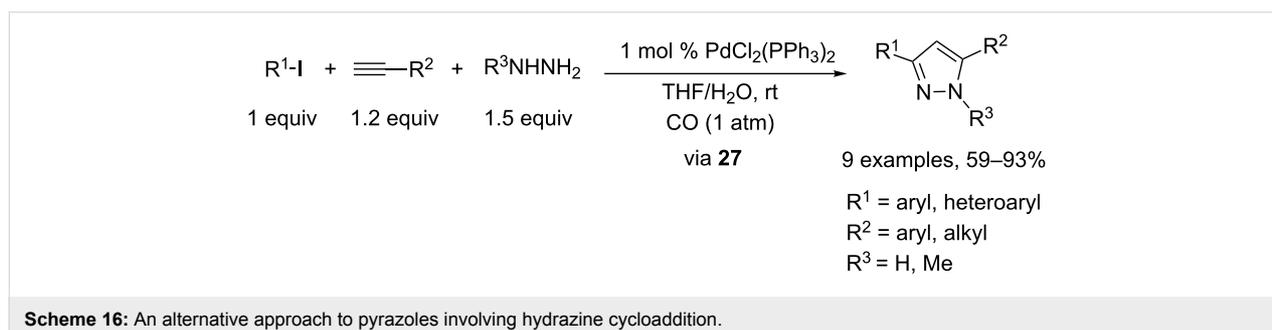
Many multicomponent approaches to nitrogen heterocycles have been developed based on the reaction of nitrogen-centered nucleophiles with α,β -unsaturated ketones generated in situ by Pd-catalyzed Sonogashira cross-coupling reactions. For instance, by building on their expertise in this area [14] Müller and coworkers recently developed a very effective and modular three-component strategy to assemble a series of 3,5-bis(hetero)aromatic pyrazoles in a consecutive fashion from terminal alkynes, acid chlorides, and hydrazine derivatives. Classical approaches to these valuable compounds are notably

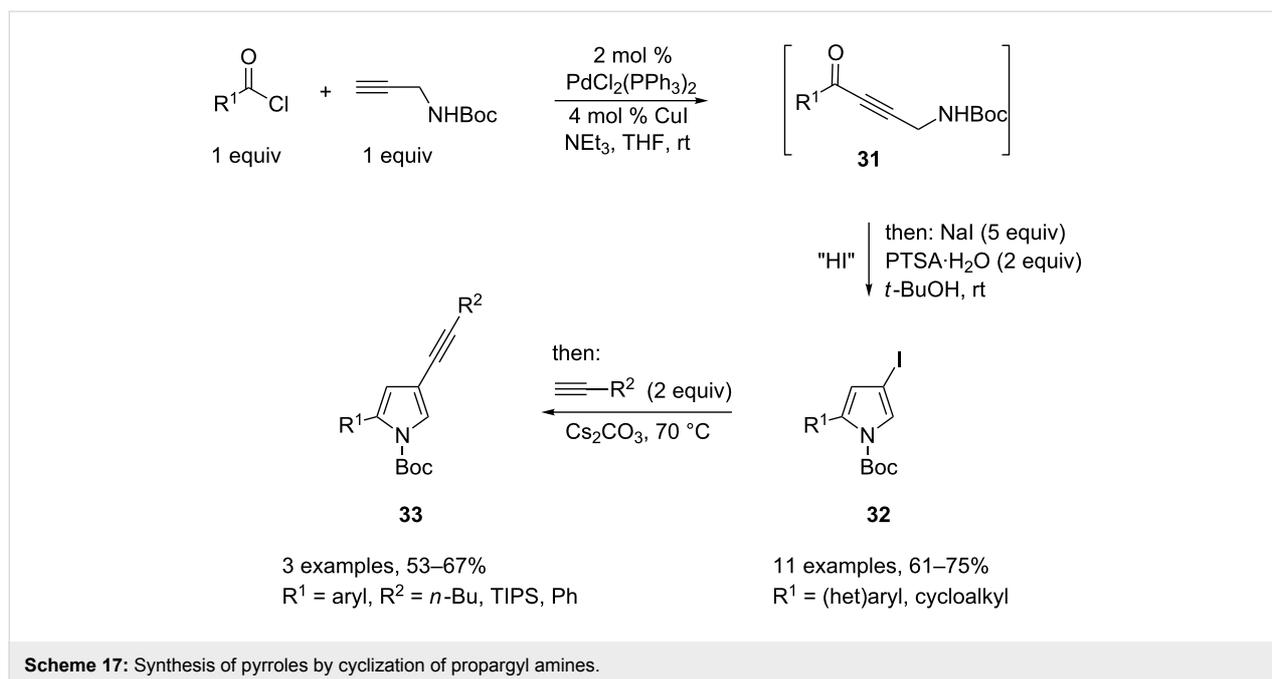


based on the cyclocondensation of hydrazine derivatives with 1,3-disubstituted three-carbon units, including α,β -unsaturated ketones, and particularly alkynones. In situ generation of the latter is an interesting means of overcoming the poor commercial availability of these compounds and also offers the flexibility needed for library production (Scheme 15). Thus various (hetero)aryl acid chlorides and terminal alkynes were heated in

THF in the presence of Et_3N and catalytic amounts of $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI . The resulting ynone **27** were then treated in situ with diversely substituted hydrazine derivatives to produce, upon microwave heating, a series of pyrazoles **28–30** (Scheme 15). As previously established for this type of cycloaddition, one of the two possible regioisomers was obtained preferentially depending on the hydrazine derivatives used, *N*-alkyl- and *N*-arylhydrazines giving opposite regioselectivities [15].

The carbonylative coupling of terminal alkynes with aryl (and heteroaryl) halides was proposed by Mori and coworkers as a different approach to α,β -alkynyl ketone derivatives as pyrazole precursors. They established a four-component domino process combining various organic halides, terminal alkynes, hydrazines, and carbon monoxide at room temperature. In this case, all components are mixed at the very beginning of the process, in aqueous THF, under ambient pressure of CO and in the presence of 1 mol % $\text{PdCl}_2(\text{PPh}_3)_2$ as the sole catalyst. However, one drawback of this approach is that it is, so far, limited to simple hydrazine and *N*-methylhydrazine (Scheme 16). From a mechanistic point of view, it is interesting to note that the intermediacy of α,β -alkynyl ketones in the four-





component process could not be confirmed (TLC). In addition, their reaction with hydrazines was shown to be ineffective under the present solvent system in the presence or absence of palladium catalyst. This may suggest that if α,β -alkynyl ketones are formed, they immediately react with hydrazine to form pyrazole by a specific rate acceleration in the one-pot process [16].

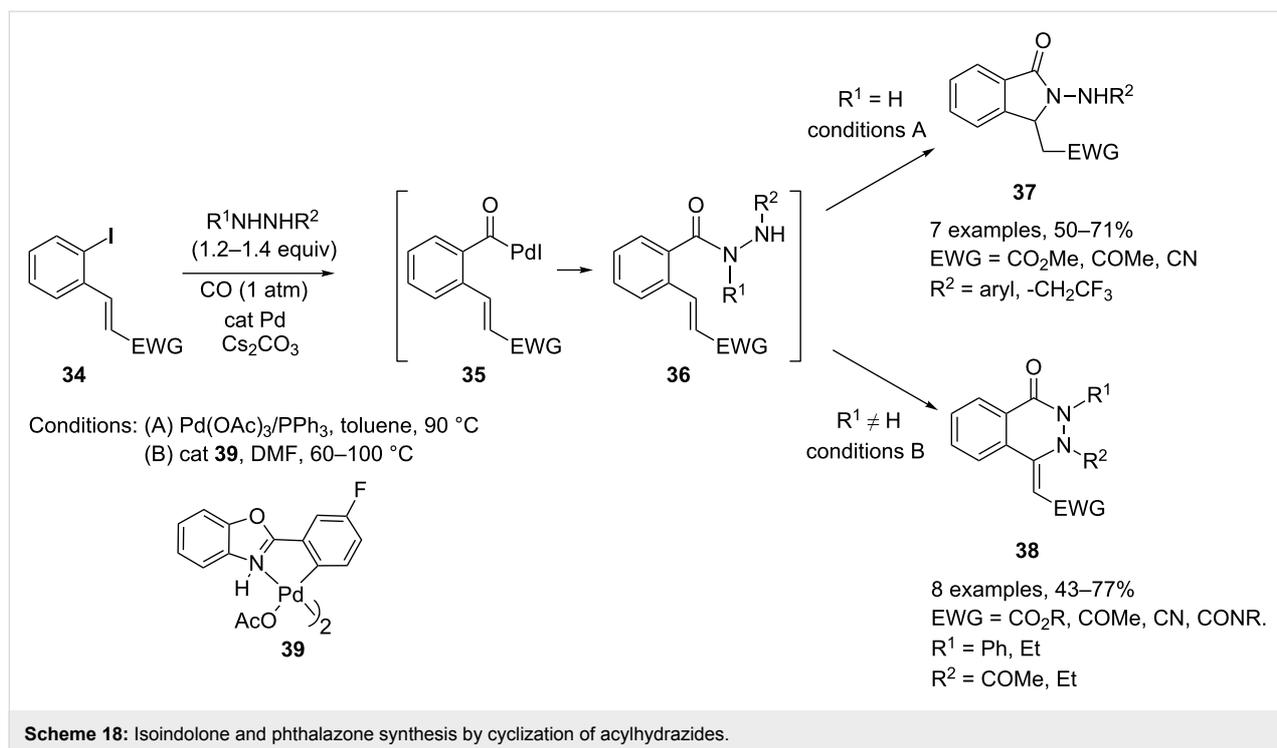
The Sonogashira cross-coupling of acid chlorides with terminal alkynes has also been demonstrated as a valuable tool to generate, in situ, ynones bearing a pendant amine group **31**, which will undergo addition–intramolecular cyclocondensation processes leading to the formation of pyrrole derivatives. For instance, a series of (hetero)aryl-, alkynyl-, and cycloalkyl acid chlorides were cross-coupled with *N*-Boc-protected propargyl-amine at room temperature, and the resulting ynones were then treated in situ with sodium iodide and PTSA to yield 2-substituted *N*-Boc-4-iodopyrroles **32** in good overall yields. Interestingly, this product may be further transformed in situ into the corresponding *N*-Boc-4-alkynylpyrroles **33** by a further Sonogashira coupling that makes use of the still-operative palladium complex. To do so, a terminal alkyne and caesium carbonate were added to the reaction mixture containing the newly formed 4-iodopyrrole, and the reaction temperature was increased to 70 °C (Scheme 17) [17].

Grigg and coworkers reported a three-component cascade process for the synthesis of isoindolones and phthalazones starting from *ortho*-halogenated cinnamates **34** and related compounds in the presence of hydrazine derivatives and carbon

monoxide. The process is thought to begin with carbonylation of the starting aryl iodide to give an acylpalladium species **35**, which is intercepted by the hydrazine nucleophile to give an acylhydrazide intermediate **36**. The latter undergoes intramolecular Michael addition to give either *N*-aminoisoindolones **37** or mono-*N*- and di-*N,N'*-phthalazones **38**, depending essentially on whether a monosubstituted or 1,2-disubstituted hydrazine derivative is used. A proper choice of catalyst and reaction conditions is also needed to improve the efficiency of each reaction (Scheme 18) [18].

Consecutive one-pot transformations initiated by Heck reaction and terminated by intramolecular aza–Michael addition were developed by Hanson and coworkers to access a series of benzo-fused sultams. A range of α -bromobenzenesulfonyl chlorides **40** were first coupled with various amines in DMF at room temperature in the presence of Et_3N to generate intermediate sulfonamides **41**. Subsequent in situ addition of a Michael acceptor in large excess together with Et_3N , Bu_4NCl , and catalytic $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ led to the production of the desired sultams **42** upon heating at 110 °C. A series of sultam derivatives of bioactive, related isoindol-1-one amides **43** were also prepared by entering acrylic acid into the Heck–aza–Michael process and coupling a second amine derivative (after removal of excess acrylic acid) with the aid of an oligomeric alkyl carbodiimide **44** (Scheme 19) [19].

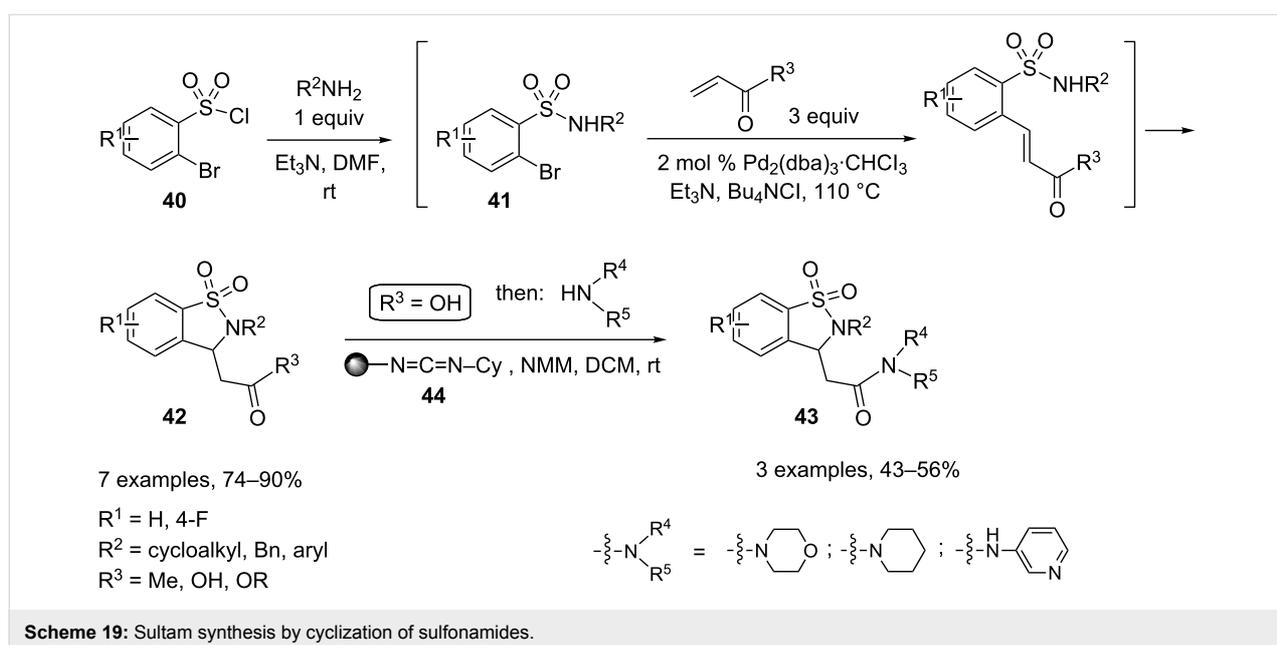
Interestingly, Willis and coworkers have shown that aryl *N*-aminosulfonamides may be accessed by three-component coupling of aryl iodides, hydrazines, and DABCO·(SO_2)₂ as a

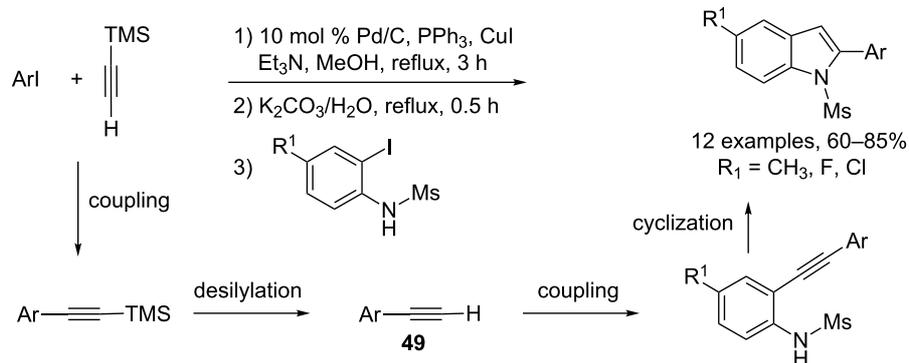


convenient source of sulfur dioxide. However, this Pd-catalyzed aminosulfonylation process proved inefficient with primary amines (Scheme 20) [20].

Multicomponent synthesis of nitrogen-containing heterocycles may also be initiated by an aza-Michael addition and terminated by a palladium-catalyzed ring-closure process [21]. For instance, Balme and coworkers reported a Pd-catalyzed three-

component assembly of highly functionalized 4-benzyl- and allyl-pyrrolidines **46** based on a combination of allylamines (in situ transformed to their sodium salts by treatment with NaH), *gem*-disubstituted alkenes **45** as Michael acceptors, and unsaturated halides (or triflate). Equal amounts of each of the three partners were reacted at room temperature in the presence of a catalytic quantity of a palladium(0) catalyst generated in situ by reduction of PdCl₂(PPh₃)₂ with *n*-butyllithium. The key step in



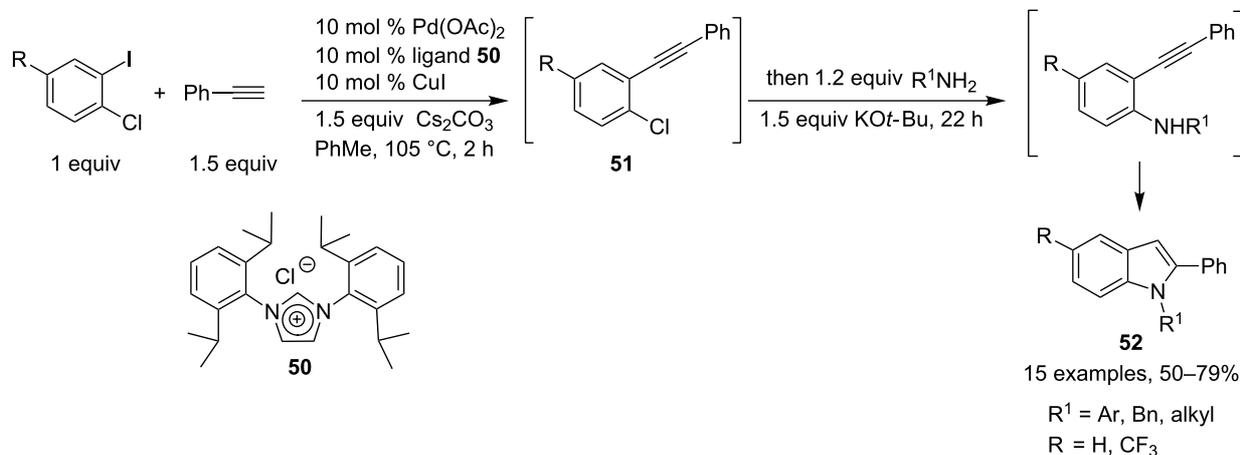


Scheme 22: Synthesis of indoles through a sequential C–C coupling/desilylation–coupling/cyclization reaction.

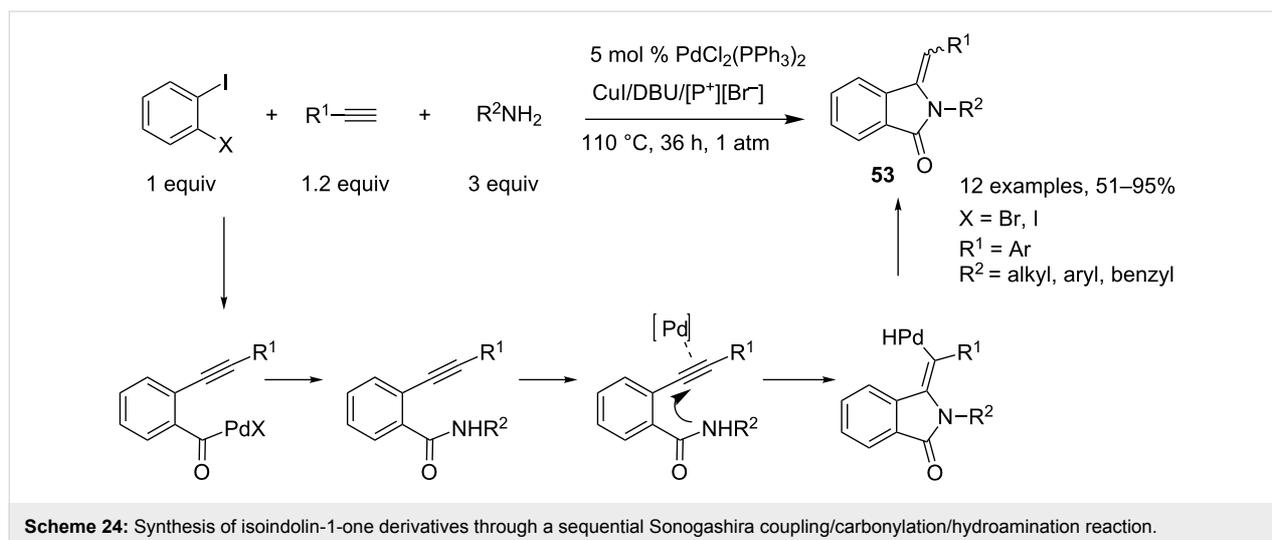
tion between (trimethylsilyl)acetylene (TMSA) with an aryl iodide, followed by a desilylation reaction. The subsequent addition of the third partner, an *o*-iodoaniline derivative, allowed a Pd/Cu tandem C–C/C–N-bond-forming reaction. The main advantage of this multicomponent reaction is to suppress the isolation of the pure form of the arylalkyne derivatives, which often represents a problem due to their ability to dimerize. This one-pot four-step reaction proceeded well with a series of electron-rich and electron-poor aryl iodide derivatives, and the best results were obtained when Pd/C–PPh₃ was used as the catalyst system (Scheme 22).

Another attractive palladium-mediated multicomponent approach towards the synthesis of indole derivatives involving the cyclization of a 2-alkynylaniline intermediate is based on a sequential, site-selective Pd-catalyzed cross-coupling approach starting from 1-chloro-2-iodobenzenes, phenylacetylene and a variety of primary amines [28,29]. The sequential three-component reaction was performed with the aid of an N-heterocyclic

carbene-palladium complex generated in situ, derived from imidazolium salt **50** and Pd(OAc)₂, and with CuI as the catalyst system. A first Sonogashira coupling reaction occurred, in the presence of Cs₂CO₃ as base, leading to *ortho*-alkynylchloroarene intermediates **51**. A subsequent amination was possible due to the high catalytic activity of this palladiumcarbene complex in the coupling of aryl chlorides. This was followed by an intramolecular alkyne–hydroamination (addition of an N–H bond across a carbon–carbon multiple bond) leading to the corresponding indole derivatives **52**. The amination/alkyne–hydroamination sequence requires the addition of 1.5 equiv of *t*-BuOK to reach completion. A variety of amines were involved in this one-pot sequential three-component reaction allowing the introduction of different protecting groups of the indole moiety. This site-selective, Pd/Cu-catalyzed cross-coupling approach was also performed on 1-chloro-2-iodo-4-(trifluoromethyl)benzene as *o*-dihaloarene partner and the corresponding polysubstituted indoles were isolated in good yields as single regioisomers (Scheme 23).



Scheme 23: Synthesis of indoles by a site selective Pd/C catalyzed cross-coupling approach.

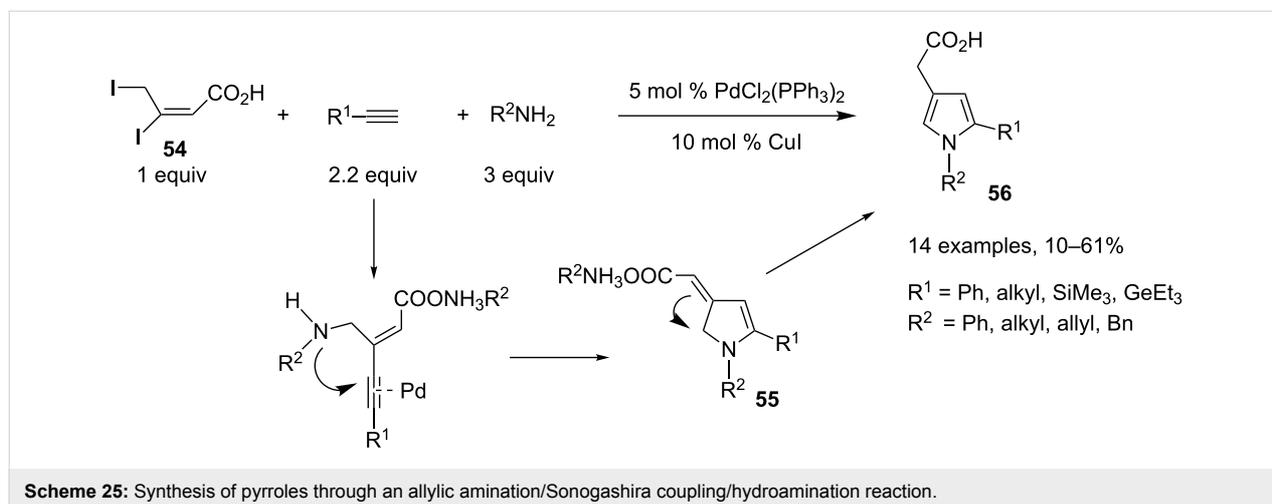


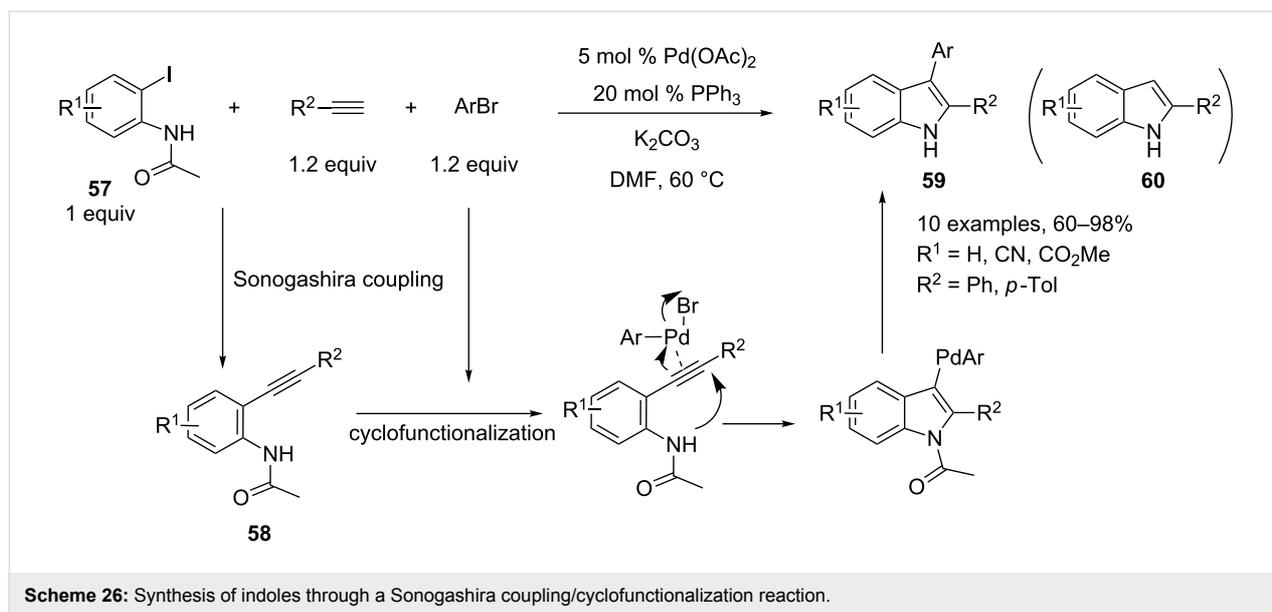
Based on this concept, Alper and coworkers reported the synthesis of isoindolin-1-one derivatives **53** through a four-component reaction starting from ortho-dihaloarenes and conducted in phosphonium salt-based ionic liquids (PSILs) with $\text{PdCl}_2(\text{PPh}_3)_2/\text{CuI}/\text{DBU}$ as the catalyst system [30]. In this case, the palladium-mediated Sonogashira coupling reaction leading to 1-halo-2-alkynylbenzene derivatives is followed by a carboxyamidation in the presence of carbon monoxide and primary amines [31]. This is followed by an in situ intramolecular hydroamination of the resulting amide on the triple bond, leading to substituted 3-methyleneisoindolin-1-ones in high selectivities in favor of the (*Z*)-isomers (Scheme 24).

A palladium-mediated three-component process for the preparation of substituted pyrroles involving a dihalogeno substrate and a sequential Sonogashira coupling followed by an hydroamination was developed by Duchêne and Parrain [32]. In this one-pot sequence, the first reaction is an allylic amination

between the 3,4-diiodobut-2-enoic acid (**54**) and a primary amine, which can be in competition with the intramolecular lactonization reaction. The best yields of the expected pyrroles were obtained when the three-component reaction was conducted, with five equivalents of the amine partner, at room temperature in DMF, with $\text{PdCl}_2(\text{PPh}_3)_2/\text{CuI}$ as the catalyst system. The initial C–N allylic amination, followed by a Sonogashira cross-coupling and an intramolecular hydroamination furnished a dihydroexoalkylidene pyrrole **55**, which rearranges into pyrrole **56**. This Pd/Cu-mediated three-component approach is influenced by the nature of the nitrogen nucleophile, and the reaction failed with tosylamine and benzylcarbamate, whereas aryl-, alkyl- and benzylamines were used successfully in this reaction (Scheme 25).

A three-component reaction involving in the first step a Sonogashira coupling of *o*-haloanilines **57** with terminal alkynes and leading to *o*-alkynylaniline intermediates **58** was developed by





Lu and co-workers [33]. This one-pot reaction is based on a stepwise synthesis of indole derivatives reported by Cachi's group, and involves, in the last step, a palladium-mediated cyclization of *o*-alkynylaniline derivatives in the presence of aryl halides [34]. In this process, oxidative addition of the aryl halide to the Pd(0) catalyst generates an organopalladium reagent, which activates the alkyne moiety towards nucleophilic attack of the amino group. A reductive elimination generates the indole derivatives **59**.

In this one-pot three-component reaction, the same palladium complex catalyzes the Sonogashira coupling and the cyclofunctionalization reaction. However, the presence of a strong electron-withdrawing substituent on the amino group is needed for the intramolecular cyclization reaction. Therefore, a protocol for a copper-free Sonogashira coupling was developed in order to suppress the concurrent formation of 2-substituted indoles **60** by direct cyclization of *o*-alkynylaniline intermediates under the classical Sonogashira reaction conditions. Interestingly, aryl bromides were used as a third partner and may be added at the beginning of this one-pot reaction since no competition between the Sonogashira coupling with these substrates and iodoanilides is observed. A variety of 2,3-disubstituted indoles **59** were obtained under mild conditions in good yields (Scheme 26).

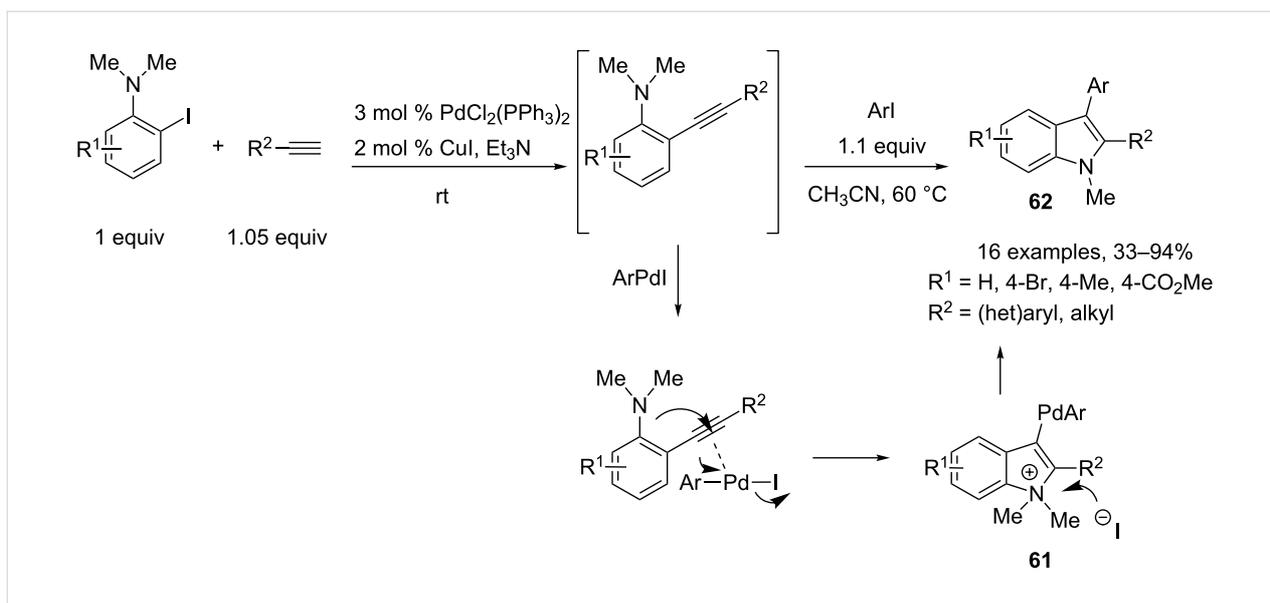
A similar three-component reaction was further developed under microwave irradiation by Larock and coworkers [35]. In this case, *N,N*-dimethyl-2-iodoanilines, terminal alkynes and various aryl iodides were involved in the reaction due to the high nucleophilicity of the *N,N*-dialkylamino moiety. Here, the reaction needs to be performed in two steps, the aryl iodide in acetonitrile being added after the completion of the first Sono-

gashira coupling reaction. Regarding the mechanism of the reaction, the intramolecular attack of the amino nucleophile affords here indolium species **61**. Removal of a methyl group by the iodide anion generated in situ, followed by reductive elimination allows the preparation of various 2,3-disubstituted indole derivatives **62** (Scheme 27).

Amines as coupling partners through Buchwald–Hartwig amination

Other strategies used for the palladium-mediated three-component preparation of substituted indole derivatives involve an efficient Buchwald–Hartwig amination as the key step. Xi and co-workers developed an elegant one-pot synthesis of 2-alkynylindoles **64** involving *o*-bromo-(2,2-dibromovinyl)benzenes **63**, arylamines and terminal alkynes as starting partners [36]. It should be noted that the three components are present at the same time in the reaction system and the best results for this Pd-catalyzed tandem Sonogashira/double C–N coupling reaction were obtained when Pd(OAc)₂ was used as the catalyst along with a bulky bidentate phosphine ligand such as Xantphos in the presence of Cs₂CO₃ as base. Most likely, the reaction proceeds through a Pd-catalyzed Sonogashira coupling leading to a mono-alkynylated product, followed by an intermolecular Buchwald–Hartwig amination and a subsequent intramolecular amination. This Pd-catalyzed tandem coupling reaction allows the preparation of a variety of 2-alkynylindoles **64** (Scheme 28).

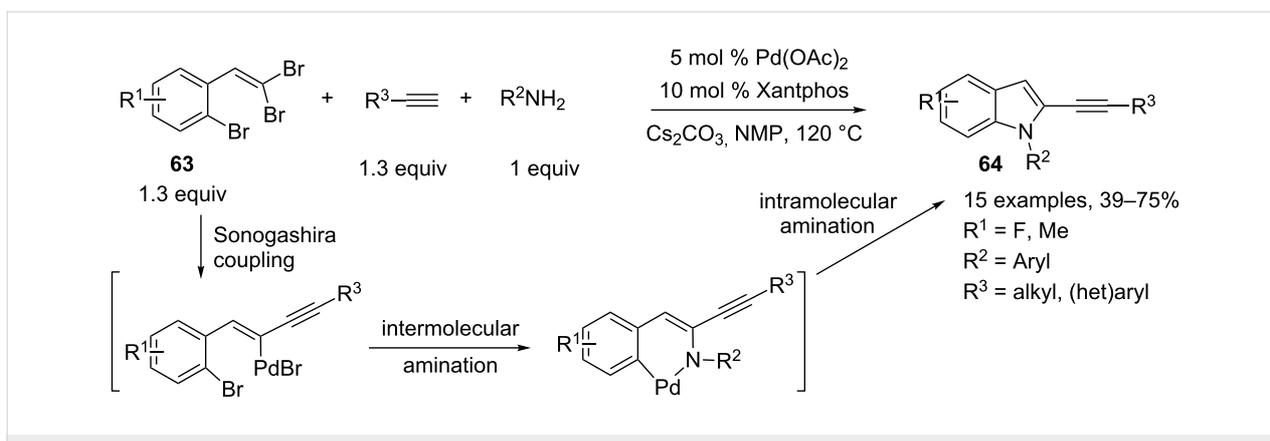
An elegant three-component process based on a Pd-catalyzed cascade sequence, involving an alkenyl amination, a C-arylation and a subsequent intramolecular N-arylation, was developed by Barluenga and coworkers for the preparation of indole

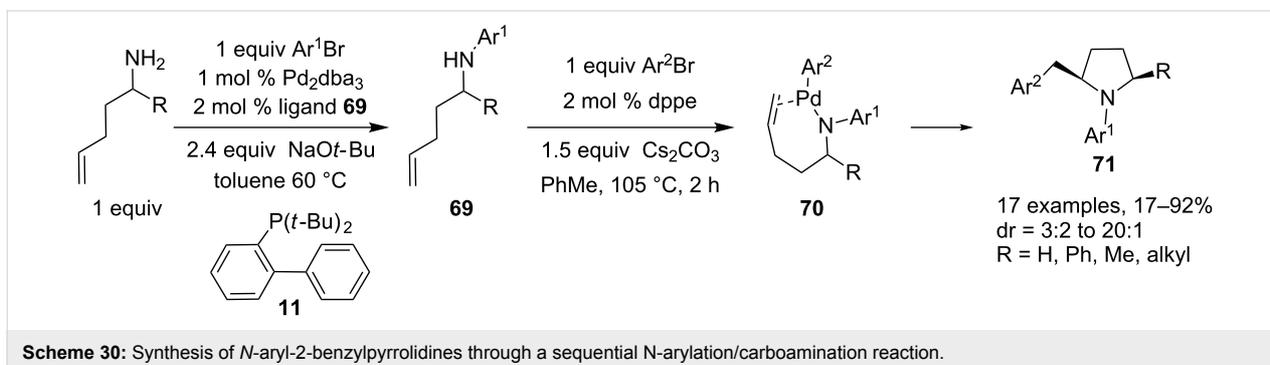
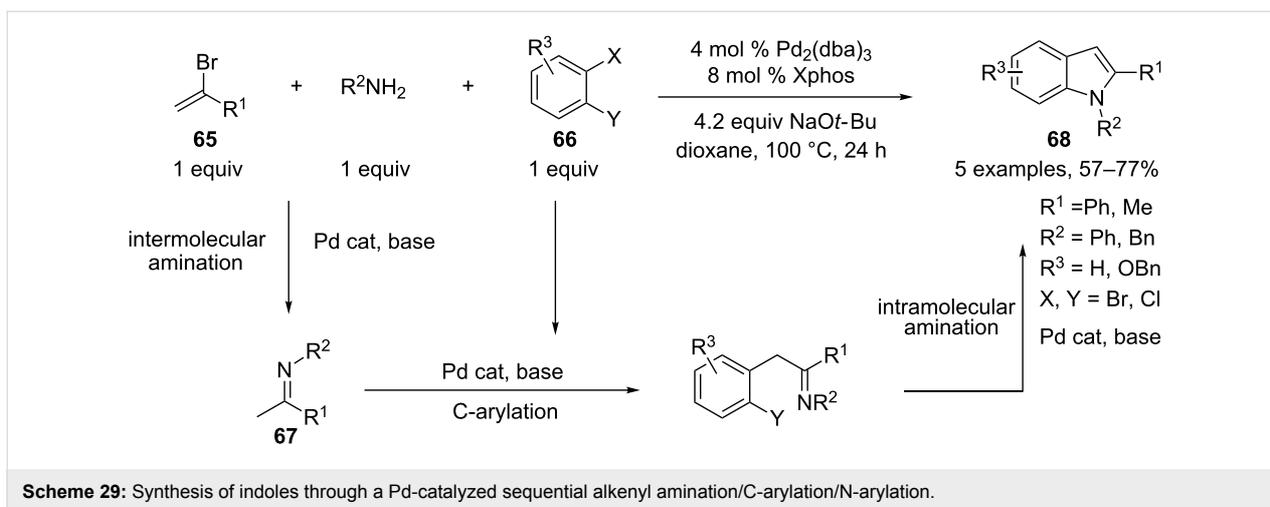


derivatives **68** [37]. Here, equimolecular amounts of haloalkene **65**, *o*-dihaloarene **66**, and amines are mixed at the start of the reaction. The higher reactivity of the haloalkene toward oxidative addition with palladium, when compared to the haloarene, allowed the unique formation of the imine intermediate **67**. This was followed by the formation of the corresponding aza-allylic anion by deprotonation in basic media. A subsequent Pd-mediated intermolecular alkylation with the dihalogeno substrate followed by an intramolecular N-arylation furnished 2-substituted indoles **68**. In this cascade reaction, the palladium catalyst intervenes in three different coupling reactions: Intermolecular N-alkenylation, C-arylation and intramolecular N-arylation (Scheme 29).

The palladium-mediated amination reaction coupled with a nitrogen–carbon bond-forming reaction was also used for the

stereoselective synthesis of *N*-aryl-2-benzylpyrrolidines **71** starting from linear 4-pentenylamine and its derivatives [38]. In this tandem reaction, two different aryl bromides are sequentially added to the primary aliphatic amine in the presence of a palladium(0) catalyst. The first selective, Pd-catalyzed mono-*N*-arylation leading to the corresponding γ -(*N*-arylamino)alkenes **69** is followed by a carboamination reaction, developed by the same group, after addition of the second aryl bromide [39]. A plausible mechanism for this cyclization/coupling reaction involves formation of intermediate **70** by reaction of the organopalladium complex with the newly formed γ -(*N*-arylamino)alkene **69**. A *syn*-insertion of the alkene into the Pd–N bond in **70** followed by reductive elimination furnishes *N*-aryl-2-benzylpyrrolidine derivatives **71**. In this process, both reactions are catalyzed by zerovalent palladium and the choice of the phosphine ligand for the *N*-arylation of amines and the





carboamination reactions is of great significance and an *in situ* modification of the catalyst by phosphine ligand exchange was necessary to achieve the selective diarylation in good yields (Scheme 30).

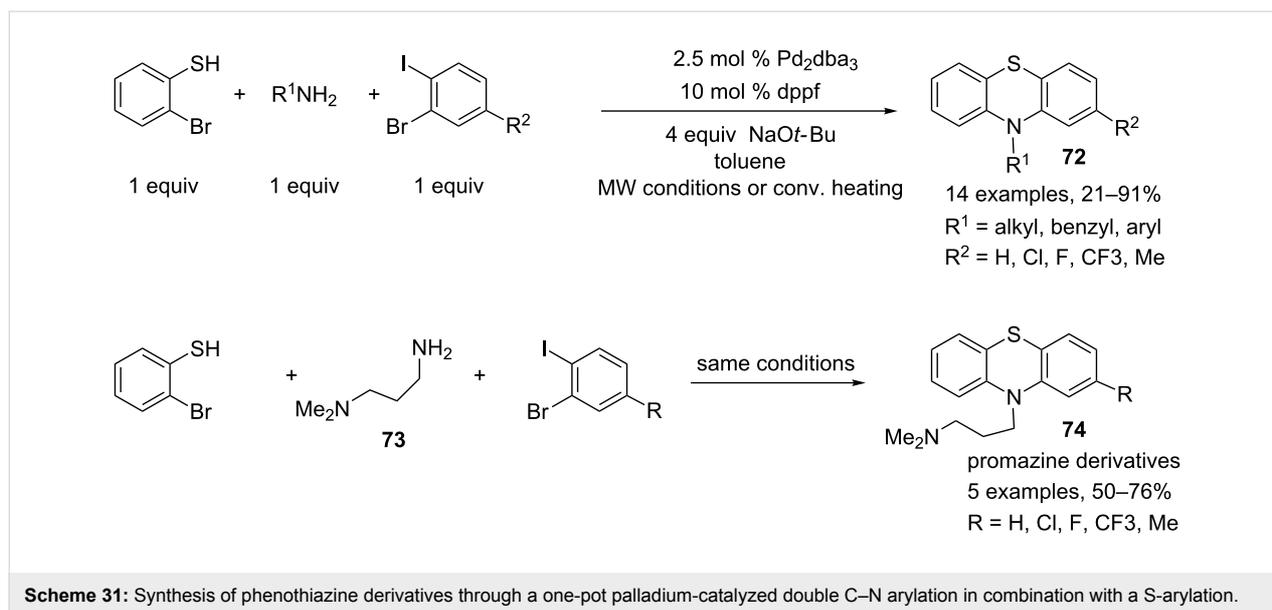
A three-component reaction involving a palladium-catalyzed double *N*-arylation in combination with a *S*-arylation in a single operation was developed for the preparation of phenothiazine derivatives **72** starting from primary amines, 2-bromothiophenol and substituted 1-bromo-2-iodobenzenes [40]. Ferrocene ligands, such as dppf, and Pd₂dba₃ as the palladium source were found to be the most suitable and efficient catalyst systems for the preparation of a series of phenothiazine derivatives. This one-pot procedure worked with a wide variety of primary amines including allyl-, benzyl-, alkyl- and arylamines, and antipsychotic promazine as well as some analogues **74** were synthesized when 3-(dimethylamino)-1-propylamine (**73**) was used as the amine component (Scheme 31).

Amines as coupling partners through a Pd-mediated allylic amination

The allene carbopalladation process with organic halides is known to generate a π -allylpalladium intermediate, which can

be trapped by intermolecular carbo- or heteronucleophiles to produce the corresponding three-component adduct. This strategy was used by Ma and coworkers for the selective preparation of five-membered nitrogen heterocycles starting from allene-bearing nucleophilic centers [41]. In this context, the same authors developed a new synthesis of substituted imidazolidinones **75** through a palladium-catalyzed, three-component reaction of 2,3-allenylamines, organic halides and isocyanates [42]. In this process, there is first a carbopalladation of the functionalized allene with the aryl iodide, followed by reaction of the internal aza-nucleophile with the highly electrophilic isocyanate derivative, before premature trapping of the initially formed π -allylpalladium intermediate that would lead to 2,5-dihydropyrrole or vinylic azacyclopropane derivatives. This is followed by a five-membered ring cyclization leading to poly-substituted imidazolidinones **75** in rather good yields and excellent selectivity (Scheme 32).

A conceptually related strategy was developed by Yoshida, Itami and Tonogaki [43]. In this case, the palladium-catalyzed allenation with an aryl iodide is performed on the allenylboronate pinacol ester **76** in the presence of benzylamine to afford the functionalized alkenylboronate **77** in quantitative

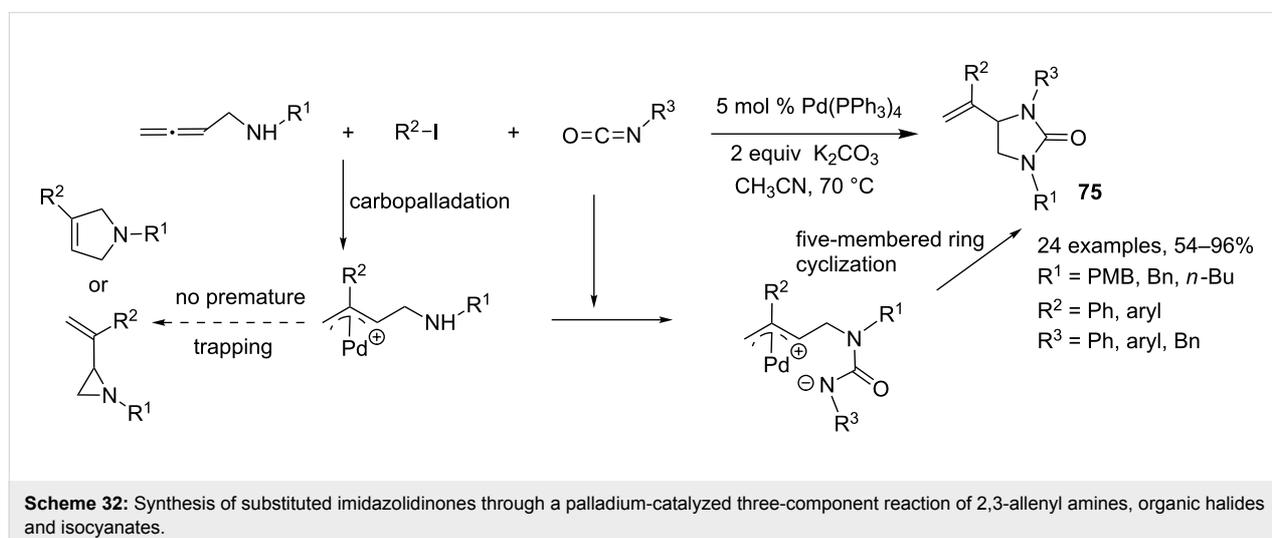


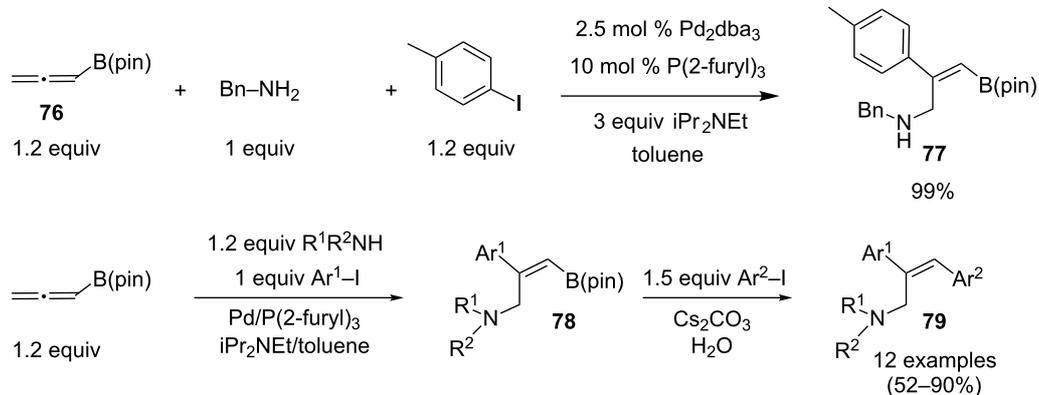
yields and with complete regio- and stereoselectivity. A four-component reaction was further developed through an in situ post C–B arylation by adding a second aryl iodide, with Cs_2CO_3 and water, to the newly formed alkenylboronate **78**. The subsequent Suzuki–Miyaura coupling led to the formation of 2,3-diarylated amines **79** and the best results were obtained with secondary amines, the remaining N–H functionality interfering with the C–B arylation step with primary amines as coupling partners (Scheme 33).

This palladium-catalyzed three-component coupling was applied to the synthesis of rolipram, which is a phosphodiesterase-4 inhibitor. In this process, the Pd-mediated three-component reaction that gives access to the alkenylboronate **80** was followed by a palladium-mediated carbonylative cycliza-

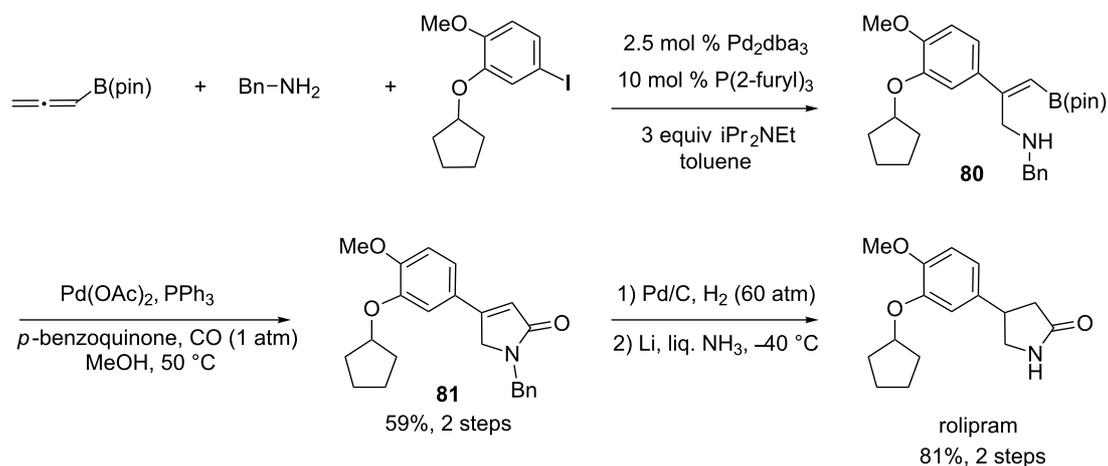
tion reaction. Hydrogenation of the resulting unsaturated lactam **81** and removal of the *N*-benzyl group afforded rolipram (Scheme 34).

Alper and coworkers developed several multicomponent approaches for the synthesis of nitrogen-containing heterocycles based on a palladium-mediated carbonylation reaction [44]. An interesting, related strategy for the preparation of unsaturated seven-membered ring lactams **84**, starting from a Baylis–Hillman adduct bearing an aryl bromide moiety **82**, with primary amines and carbon monoxide, was developed by the same group [45]. The sequence involves first a selective palladium(0)-catalyzed amination on the Baylis–Hillman acetates with primary amines leading to allylic amines **83**. This is followed by oxidative addition of the palladium species to the aryl

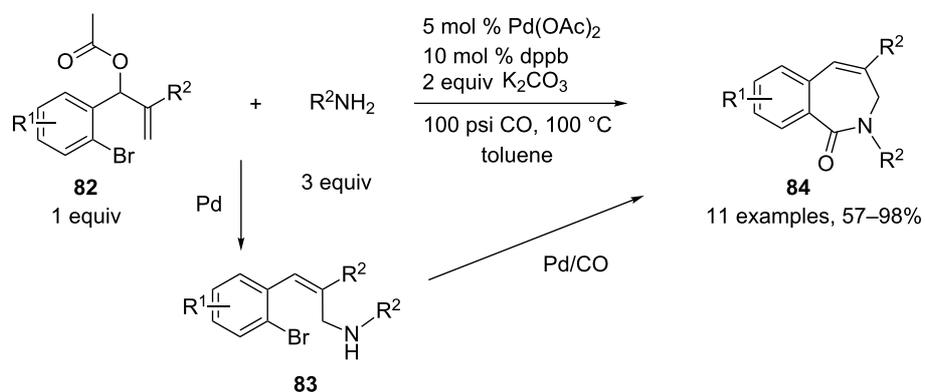




Scheme 33: Synthesis of 2,3-diarylated amines through a palladium-catalyzed four-component reaction involving an allenylboronate pinacol ester.



Scheme 34: Synthesis of rolipram involving a Pd-catalyzed three-component reaction.



Scheme 35: Synthesis of seven-membered ring lactams through a Pd-catalyzed amination/intramolecular cyclocarbonylation.

bromide, which undergoes CO insertion to form the corresponding acylpalladium, which in turn is intercepted by the allylamine to give, after reductive elimination, the seven-membered

ring lactams **84** in good to excellent yields. A wide range of amine components are compatible with this one-pot procedure (Scheme 35).

Conclusion

In summary, this review highlights the usefulness of amines as key building blocks in the development of Pd-mediated multi-component approaches to polyfunctionalized nitrogen acyclic or cyclic compounds. Amines may be involved in several bond-forming transformations, including aza-Michael additions, hydroaminations of alkynes, Buchwald–Hartwig aminations, and allylic aminations, thereby allowing the creation of several covalent bonds in a single operation. Imine derivatives are also of high synthetic value as they may act either as electrophilic or nucleophilic partners. It is expected that further useful, new multicomponent processes in which amines play a central role will be developed in the near future.

References

- Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
- Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590–594. doi:10.1002/anie.200352123
- Siamaki, A. R.; Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1135–1138. doi:10.1021/jo701875b
- Dhawan, R.; Dghaym, R. D.; Cyr, D. J. S.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 3927–3930. doi:10.1021/ol061308j
- Worrall, K.; Xu, B.; Bontemps, S.; Arndtsen, B. A. *J. Org. Chem.* **2011**, *76*, 170–180. doi:10.1021/jo101858d
- Tsukamoto, H.; Ueno, T.; Kondo, Y. *Org. Lett.* **2007**, *9*, 3033–3036. doi:10.1021/ol071107v
- Tsukamoto, H.; Kondo, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 4851–4854. doi:10.1002/anie.200800823
- Kobayashi, T.; Nakashima, M.; Hakogi, T.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3809–3812. doi:10.1021/ol061405c
- Jarusiewicz, J.; Choe, Y.; Yoo, K. S.; Park, C. P.; Jung, K. W. *J. Org. Chem.* **2009**, *74*, 2873–2876. doi:10.1021/jo900163w
- Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 1644–1647. doi:10.1002/anie.200805519
- Arefalk, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2005**, *70*, 938–942. doi:10.1021/jo048187q
- Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2006**, *8*, 5971–5974. doi:10.1021/ol0624528
- Zhou, H.; Jin, H.; Ye, S.; He, X.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 4616–4618. doi:10.1016/j.tetlet.2009.05.106
- Müller, T. J. J.; D'Souza, D. M. *Pure Appl. Chem.* **2008**, *80*, 609–620. doi:10.1351/pac200880030609
And references cited therein.
- Willy, B.; Müller, T. J. J. *Eur. J. Org. Chem.* **2008**, 4157–4168. doi:10.1002/ejoc.200800444
- Mohamed Ahmed, M. S.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487–4489. doi:10.1021/ol051841j
- Merkul, E.; Boersch, C.; Frank, W.; Müller, T. J. J. *Org. Lett.* **2009**, *11*, 2269–2272. doi:10.1021/ol900581a
- Grigg, R.; Sridharan, V.; Shah, M.; Mutton, S.; Kilner, C.; MacPherson, D.; Milner, P. *J. Org. Chem.* **2008**, *73*, 8352–8356. doi:10.1021/jo800822p
- Rolfe, A.; Young, K.; Hanson, P. R. *Eur. J. Org. Chem.* **2008**, 5254–5262. doi:10.1002/ejoc.200800651
- Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 16372–16373. doi:10.1021/ja1081124
- Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115–2134. doi:10.1055/s-2003-42082
- Martinon, L.; Azoulay, S.; Monteiro, N.; Kündig, E. P.; Balme, G. *J. Organomet. Chem.* **2004**, *689*, 3831–3836. doi:10.1016/j.jorganchem.2004.07.039
- Martinon, L. Ph.D. Thesis, University of Lyon/University of Geneva, France/Switzerland, 2006.
- Lemaire-Audoire, S.; Savignac, M.; Genêt, J.-P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, *36*, 1267–1270. doi:10.1016/0040-4039(95)00003-U
- Li, J. J.; Gribble, G. W. Metal-Catalyzed Cross-Coupling Reactions for Indoles. In *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*; Gribble, G. W., Ed.; Topics in Heterocyclic Chemistry, Vol. 26; Springer: Berlin, 2011; pp 193–234. doi:10.1007/7081_2010_36
- Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. doi:10.1021/cr040639b
- Layek, M.; Lakshmi, U.; Kalita, D.; Barange, D. K.; Islam, A.; Mukkanti, K.; Pal, M. *Beilstein J. Org. Chem.* **2009**, *5*, No. 46. doi:10.3762/bjoc.5.46
- Ackermann, L. *Org. Lett.* **2005**, *7*, 439–442. doi:10.1021/ol047649j
- Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311–11316. doi:10.1016/j.tet.2005.09.095
- Bradaric, C. J.; Downard, A.; Kennedy, C.; Robertson, A. J.; Zhou, Y. *Green Chem.* **2003**, *5*, 143–152. doi:10.1039/b209734f
- Cao, H.; McNamee, L.; Alper, H. *Org. Lett.* **2008**, *10*, 5281–5284. doi:10.1021/ol8021403
- Lamandé-Langle, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Chem. Commun.* **2010**, *46*, 5157–5159. doi:10.1039/C0CC00500B
- Lu, B. Z.; Zhao, W.; Wei, H.-X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271–3274. doi:10.1021/ol061136q
- Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915–3918. doi:10.1016/S0040-4039(00)74818-0
- Chen, Y.; Markina, N. A.; Larock, R. C. *Tetrahedron* **2009**, *65*, 8908–8915. doi:10.1016/j.tet.2009.07.075
- Liang, Y.; Meng, T.; Zhang, H.-J.; Xi, Z. *Synlett* **2011**, 911–914. doi:10.1055/s-0030-1259699
- Barluenga, J.; Jiménez-Aquino, A.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1529–1532. doi:10.1002/anie.200604407
- Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575–2578. doi:10.1021/ol050647u
- Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605–3608. doi:10.1002/anie.200460060
- Dahl, T.; Tornøe, C. W.; Bang-Andersen, B.; Nielsen, P.; Jorgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1726–1728. doi:10.1002/anie.200705209
- Ma, S.; Jiao, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4737–4740. doi:10.1002/anie.200290033
For a three component strategy involving carbopalladation of γ -allenic malonates.
- Shu, W.; Yu, Q.; Jia, G.; Ma, S. *Chem.–Eur. J.* **2011**, *17*, 4720–4723. doi:10.1002/chem.201003611
- Tonogaki, K.; Itami, K.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2006**, *128*, 1464–1465. doi:10.1021/ja057778a
- Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 3642–3644. doi:10.1021/ol101428v

45. Cao, H.; Vieira, T. O.; Alper, H. *Org. Lett.* 2011, 13, 11–13.
doi:10.1021/ol102699a

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Pseudo five-component synthesis of 2,5-di(hetero)arylthiophenes via a one-pot Sonogashira–Glaser cyclization sequence

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Keywords:

C–C coupling; copper; multicomponent reactions; palladium;
thiophenes

Beilstein J. Org. Chem. **2011**, *7*, 1499–1503.

doi:10.3762/bjoc.7.174

Received: 27 May 2011

Accepted: 10 October 2011

Published: 04 November 2011

This article is part of the Thematic Series "Multicomponent reactions".

Associate Editor: D. O'Hagan

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Abstract

Based upon a consecutive one-pot Sonogashira–Glaser coupling–cyclization sequence a variety of 2,5-di(hetero)arylthiophenes were synthesized in moderate to good yields. A single Pd/Cu-catalyst system, without further catalyst addition, and easily available, stable starting materials were used, resulting in a concise and highly efficient route for the synthesis of the title compounds. This novel pseudo five-component synthesis starting from iodo(hetero)arenes is particularly suitable as a direct access to well-defined thiophene oligomers, which are of peculiar interest in materials science.

Introduction

Over the past decades 2,5-di(hetero)aryl substituted thiophenes [1,2] have constantly attracted a lot of interest, especially as charge-transport materials in electronic [3] and optoelectronic [4-6] devices, but also in drug design as antitumor [7] or anti-inflammatory agents [8] or in plaque imaging [9]. Most commonly the methodological access to these targets has been based upon Pd- or Ni-catalyzed coupling of dihalo thiophenes with organometallic (hetero)aryl derivatives by virtue of Suzuki [10] or Stille [11] coupling. Even though this strategy for the synthesis of symmetrical 2,5-diarylated thiophenes has proven to be efficient and general, all of these synthetic routes

share the drawback of ultimately requiring two different halogenated (hetero)arenes and the separate conversion into an organometallic derivative in an additional step. From a practical point of view halogen–metal exchange, transmetalation and isolation occasionally turns out to be tedious and in many cases the use of polar functionality in the substrate is considerably restricted.

In recent years interesting examples of palladium-catalyzed direct C–H activation and arylation of (hetero)aromatics have been reported [12,13]. Although these procedures only employ

a single halogenated substrate and avoid the stoichiometric formation of organometallic intermediates the substrate scope is limited to activated heteroaromatic C–H bonds. In addition, sophisticated catalyst systems must be applied, and the efficiency is also variable.

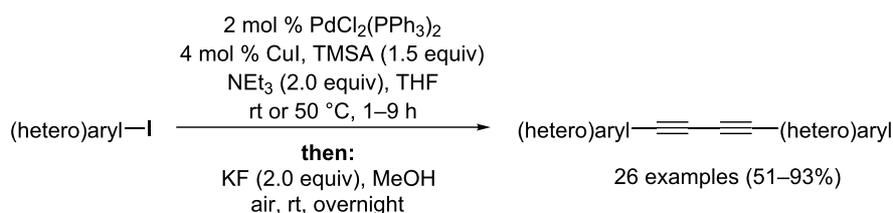
Just recently we reported a very straightforward one-pot synthesis of symmetric 1,4-di(hetero)arylated 1,3-butadiynes starting from (hetero)aryl iodides by virtue of a sequentially Pd/Cu-catalyzed [14] Sonogashira–Glaser process (Scheme 1) [15].

According to this general one-pot access to 1,4-di(hetero)aryl-1,3-butadiynes we reasoned that it should be possible to address the butadiyne functionality towards heterocyclization, again in a one-pot fashion. Here, we communicate the first pseudo five-component synthesis of 2,5-di(hetero)arylthiophenes by virtue of a one-pot Sonogashira–Glaser cyclization sequence.

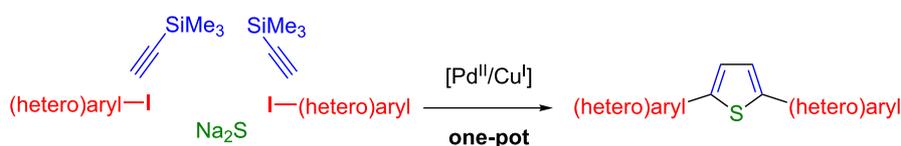
Results and Discussion

The conversion of 1,4-diaryl-1,3-butadiynes into 2,5-diarylthiophenes by base-mediated cyclization with sodium sulfide or sodium hydrogen sulfide is a literature-known procedure [16–23]. Therefore, we reasoned that the concatenation of our sequentially Pd/Cu-catalyzed Sonogashira–Glaser reaction [15] with the sulfide-mediated cyclization should lead to a straightforward one-pot pseudo five-component synthesis of 2,5-di(hetero)arylthiophenes (Scheme 2).

We first set out to identify an optimal cosolvent for all four steps taking advantage of the high yield Sonogashira–Glaser coupling synthesis [15] of 1,4-diphenylbutadiyne starting from iodobenzene (**1a**) (Table 1). In addition, the final cyclization step to give 2,5-diphenylthiophene (**2a**) was performed under microwave heating at 120 °C for a hold time of 2 h.



Scheme 1: Concept of a Sonogashira–Glaser coupling sequence.



Scheme 2: Concept of a Sonogashira–Glaser cyclization synthesis of 2,5-di(hetero)arylthiophenes.

Table 1: Evaluation of different solvents.^a

entry	solvent	cavity temperature [°C] (hold time in the cyclization step)	conversion ^b (yield of 2a [%] ^c)
1	THF	120 (2 h)	complete (61)
2	1,4-dioxane	120 (2 h)	complete (59)
3	DMSO	120 (2 h)	complete (11)
4	DMF	120 (2 h)	complete (64)
5	DMF	90 (4 h)	complete (n. i.) ^d
6 ^e	DMF	90 (8 h)	complete (n. i.) ^d

^aReaction conditions: Iodobenzene (2 mmol) in degassed solvent (10 mL) was reacted for 1.5 h at rt with TMSA (3 mmol) in the presence of PdCl₂(PPh₃)₂ (0.04 mmol), CuI (0.08 mmol), and NEt₃ (2 mmol). Then KF (3 mmol) and methanol (5 mL) were added and the reaction mixture was stirred in the open reaction vessel at rt for 16 h. After the addition of Na₂S·9H₂O (3 mmol) and KOH (3 mmol) the sealed reaction vessel was heated in a microwave oven. ^bConversion in the final step (monitored by TLC). ^cGiven yields refer to isolated and purified products. ^dn. i.: Not isolated. ^eThe final step was performed in an oil bath at 90 °C for 8 h to achieve complete conversion.

The solvent screening revealed that THF (tetrahydrofuran) (Table 1, entry 1), 1,4-dioxane (Table 1, entry 2), and DMF (*N,N*-dimethylformamide) (Table 1, entry 4) are equally suitable solvents giving rise to essentially comparable yields. DMSO (dimethylsulfoxide) (Table 1, entry 3), however, turned out to give inferior yields, resulting in an increased formation of byproducts already during the desilylation and the oxidative coupling step (as monitored by TLC). A lower reaction temperature resulted in a prolonged reaction time under microwave conditions to achieve complete conversion (Table 1, entry 5), whereas conductive heating at the same temperature even doubled this reaction time (Table 1, entry 6). As a consequence, DMF as a solvent and dielectric heating at 120 °C for 2 h in the final step were identified as the optimal settings for the sequence.

With these optimized conditions in hand, the substrate scope of this novel pseudo five-component synthesis of 2,5-di(hetero)arylthiophenes was studied (Scheme 3). Starting from (hetero)aryl iodide **1** all reactions were carried out on a 2 mmol scale to give symmetrical 2,5-di(hetero)arylthiophenes **2** as stable, crystalline solids (with the exception of **2b**) in moderate to good yield (Figure 1). The structural assignments of all thiophenes **2** were unambiguously supported by ¹H and ¹³C NMR spectroscopy, mass spectrometry, and combustion analysis. Due to poor solubility no NMR spectra of compounds **2m**, **2n** and **2o** could be recorded, yet, the assignment of the molecular structure is supported by mass spectrometry and combustion analysis.

The scope of this new one-pot pseudo five-component Sonogashira–Glaser cyclization synthesis of symmetrical 2,5-di(hetero)arylthiophenes **2** is fairly broad with respect to the applied (hetero)aryl iodides **1**. The product analysis of the target structures **2** reveals that aryl substituents can be electroneutral (**2a** and **2l–2n**), electron-rich (**2b**, **2c**, **2f**, **2k**, **2o**, **2p**) as well as electron-poor (**2d**, **2e** and **2h–2j**). Substituents in *ortho*- (**2b**), *meta*- (**2c–2g**), and *para*-positions (**2h**, **2i**) are tolerated. Even bulky bi- or tricyclic substrates are transformed without any complications (**2l–2p**). Polar substituents such as hydroxy

groups (**2f**) are tolerated as well. Furthermore, several different 5- and 6-membered S- and N-heteroaryl iodides give rise to the formation of the corresponding 2,5-di(heteroaryl)thiophenes (**2j–2k** and **2o**) in good yields.

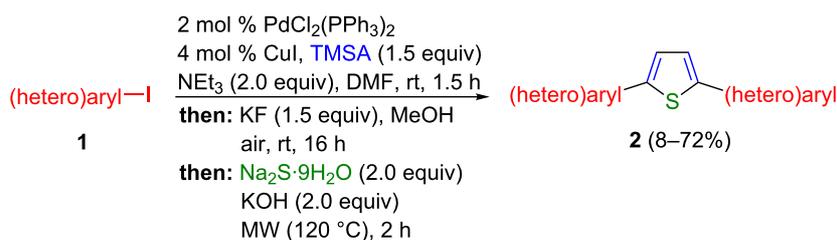
Deviating from the general procedure, in the case of *m*-bromoiodobenzene (**1d**) only 1 equiv of TMSA was added in order to minimize a second alkynylation at the bromine position in the initial Sonogashira coupling step, which resulted in a moderate yield of the dibromo derivative (**2d**). Upon reaction of the *m*-iodo-nitrobenzene (**1g**) a concomitant reduction of the nitro groups to the amines was observed, giving rise to the dianilino thiophene **2g**.

Most interestingly, even the linear five-ring-containing derivatives “PPTPP” (**2n**) and “T5” (**2o**), which are important charge-transport molecules in materials science [3], were easily accessed in a one-pot procedure. Starting from the stable and readily available aryl iodides **1n** and **1o**, the presented new methodology allowed the synthesis of both molecules in a quick, simple and economic one-pot reaction. Moreover, the usual preparation and isolation of boronic acids or even more sensitive zinc organometallics was circumvented. In addition the use of the rather expensive diiodothiophene as a coupling partner was avoided [24–26]. “PPTPP” (**2n**) and “T5” (**2o**) were readily purified by Soxhlet extraction.

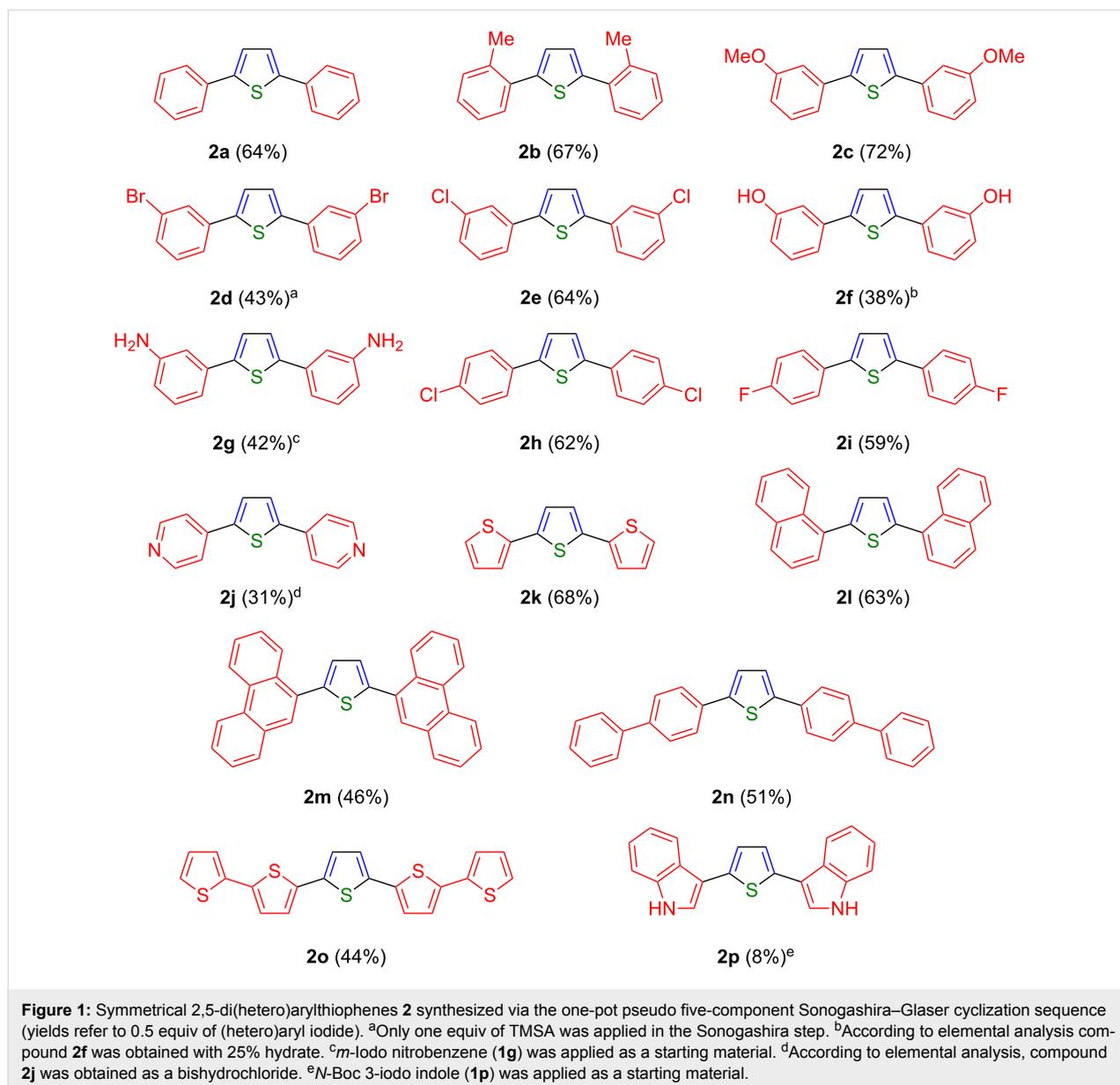
Upon reaction of *N*-Boc-3-iodoindole (**1p**) a complete cleavage of the protection group and the formation of several byproducts were observed leading to a significantly lower isolated yield of the corresponding thiophene **2p**.

Conclusion

In summary we have developed an economical and efficient one-pot sequence for transforming (hetero)aryl iodides into symmetrical 2,5-di(hetero)arylthiophenes based upon an initial sequentially Pd/Cu-catalyzed Sonogashira–Glaser process followed by a subsequent sulfide-mediated cyclization. A broad range of functional groups is tolerated and the iodo substrates are either commercially available or easily accessible. This



Scheme 3: Pseudo five-component Sonogashira–Glaser cyclization synthesis of symmetrical 2,5-di(hetero)arylthiophenes **2**.



strikingly simple methodology is highly practical and leads to a straightforward protocol for the preparation of the title compounds. Studies addressing more-sophisticated 2,5-disubstituted thiophenes for surface modification and also mesoporous hybrid materials are currently underway.

Experimental

2c: An 80 mL microwave reaction vessel, equipped with a rubber septum, was charged with 1-iodo-3-methoxybenzene (**1c**) (468 mg, 2.00 mmol), PdCl₂(PPh₃)₂ (28 mg, 0.04 mmol, 2 mol %), CuI (16 mg, 0.08 mmol, 4 mol %), and degassed DMF (10.0 mL). The reaction mixture was flushed for 10 min with nitrogen by using a cannula. After addition of trimethylsilylacetylene (0.43 mL, 3.00 mmol) and dry triethylamine

(0.55 mL, 4.00 mmol) the solution was stirred at rt for 1.5 h. Then KF (174 mg, 3.00 mmol), and methanol (5.00 mL) were subsequently added and the reaction mixture was stirred under aerobic atmosphere in the opened reaction vessel overnight at rt. After the addition of sodium sulfide nonahydrate (960 mg, 4 mmol), potassium hydroxide (224 mg, 4 mmol), and methanol (5 mL) the vessel was heated to 120 °C under microwave irradiation for 2 h. After cooling to rt the mixture was adsorbed on neutral aluminium oxide and filtered through a short plug of neutral aluminium oxide with THF as an eluent. The solvents were removed in vacuo and the residue was adsorbed on Celite® and purified by column chromatography on silica gel (hexane) to give 215 mg (0.72 mmol, 72 %) of **2c** as a light-yellow solid. *R*_f 0.35 (*n*-hexane/ethyl acetate 10:1); mp 73 °C;

^1H NMR (CDCl_3 , 500 MHz) δ 3.87 (s, 6H), 6.83–6.87 (m, 2H), 7.16–7.18 (m, 2H), 7.22–7.25 (m, 2H), 7.29 (s, 2H), 7.31 (t, $^3J = 7.9$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.5 (CH_3), 111.4 (CH), 113.2 (CH), 118.4 (CH), 124.3 (CH), 130.1 (CH), 135.7 (C_{quat}), 143.6 (C_{quat}), 160.1 (C_{quat}); EIMS m/z (%): 297 (22), 296 ($[\text{M}]^+$, 100), 253 (27), 210 (16), 148 (15); UV–vis (CH_2Cl_2), λ_{max} [nm] (ϵ): 331 (36700); IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3008 (w), 2960 (w), 2924 (w), 2852 (w), 2833 (w), 1776 (w), 1593 (m), 1581 (m), 1473 (m), 1458 (m), 1436 (m), 1423 (m), 1334 (w), 1319 (m), 1286 (m), 1255 (m), 1197 (m), 1176 (m), 1159 (m), 1120 (m), 1033 (s), 975 (m), 839 (m), 804 (s), 786 (s), 775 (s), 723 (m), 678 (s), 624 (m); Anal. calcd for $\text{C}_{18}\text{H}_{16}\text{O}_2\text{S}$ (296.4): C, 72.94; H, 5.44; found: C, 73.10; H 5.73.

Supporting Information

Supporting Information File 1

Experimental procedures, spectroscopic and analytical data of all compounds **2**.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-174-S1.pdf>]

Supporting Information File 2

Copies of NMR spectra of compounds **2a–I** and **2p**.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-174-S2.pdf>]

Acknowledgements

The financial support of this work by the Fonds der Chemischen Industrie is gratefully acknowledged. The authors also thank the BASF SE and Merck Serono for the generous donation of chemicals.

References

- Mishra, A.; Ma, C.-Q.; Bäuerle, P. *Chem. Rev.* **2009**, *109*, 1141–1276. doi:10.1021/cr8004229
- Barbarella, G.; Melucci, M.; Sotgiu, G. *Adv. Mater.* **2005**, *17*, 1581–1593. doi:10.1002/adma.200402020
- Yamao, T.; Shimizu, Y.; Terasaki, K.; Hotta, S. *Adv. Mater.* **2008**, *20*, 4109–4112. doi:10.1002/adma.200800942
- Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011–2014. doi:10.1021/ol049386z
- Campbell, N. L.; Duffy, W. L.; Thomas, G. I.; Wild, J. H.; Kelly, S. M.; Bartle, K.; O'Neill, M.; Minter, V.; Tufn, R. P. *J. Mater. Chem.* **2002**, *12*, 2706–2721. doi:10.1039/B202073B
- Kitamura, T.; Lee, C. H.; Taniguchi, Y.; Fujiwara, Y.; Sano, Y.; Matsumoto, M. *Mol. Cryst. Liq. Cryst.* **1997**, *293*, 239–245. doi:10.1080/10587259708042774
- Bey, E.; Marchais-Oberwinkler, S.; Werth, R.; Negri, M.; Al-Soud, Y. A.; Kruchten, P.; Oster, A.; Frotscher, M.; Birk, B.; Hartmann, R. W. *J. Med. Chem.* **2008**, *51*, 6725–6739. doi:10.1021/jm8006917
- Pairet, M.; Van Ryn, J., Eds. *COX-2 Inhibitors*; Birkhäuser Verlag: Basel, Switzerland, 2004.
- Chandra, R.; Kung, M.-P.; Kung, H. F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1350–1352. doi:10.1016/j.bmcl.2005.11.055
- Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867. doi:10.1039/C39790000866
- Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638. doi:10.1021/ja00479a077
- Borghese, A.; Geldhof, G.; Antoine, L. *Tetrahedron Lett.* **2006**, *47*, 9249–9252. doi:10.1016/j.tetlet.2006.10.130
- Derridj, F.; Gottumukkala, A. L.; Djebbar, S.; Doucet, H. *Eur. J. Inorg. Chem.* **2008**, 2550–2559. doi:10.1002/ejic.200800143
- Müller, T. J. J. *Top. Organomet. Chem.* **2006**, *19*, 149–205. doi:10.1007/3418_012
- Merkul, E.; Urselmann, D.; Müller, T. J. J. *Eur. J. Org. Chem.* **2011**, 238–242. doi:10.1002/ejoc.201001472
- Kowada, T.; Kuwabara, T.; Ohe, K. *J. Org. Chem.* **2010**, *75*, 906–913. doi:10.1021/jo902482n
- Morisaki, F.; Kurono, M.; Hirai, K.; Tomioka, H. *Org. Biomol. Chem.* **2005**, *3*, 431–440. doi:10.1039/B409095K
- Al-Taweel, S. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1041–1046. doi:10.1080/10426500211734
- Schroth, W.; Dunger, S.; Billig, F.; Spitzner, R.; Herzschuh, R.; Vogt, A.; Jende, T.; Israel, G.; Barche, J.; Ströhl, D.; Sieler, J. *Tetrahedron* **1996**, *52*, 12677–12698. doi:10.1016/0040-4020(96)00752-1
- Potts, K. T.; Nye, S. A.; Smith, K. A. *J. Org. Chem.* **1992**, *57*, 3895–3901. doi:10.1021/jo00040a032
- Acheson, R. M.; Lee, G. C. M. *J. Chem. Res., Miniprint* **1986**, 3020–3036.
- Schulte, K. E.; Reisch, J.; Herrmann, W.; Bohn, G. *Arch. Pharm.* **1963**, *296*, 456–467. doi:10.1002/ardp.19632960708
- Schulte, K. E.; Reisch, J.; Hörner, L. *Angew. Chem.* **1960**, *72*, 920. doi:10.1002/ange.19600722317
- Hotta, S.; Lee, S. A.; Tamaki, T. *J. Heterocycl. Chem.* **2000**, *37*, 25–29. doi:10.1002/jhet.5570370105
- Dingemans, T. J.; Murthy, N. S.; Samulski, E. T. *J. Phys. Chem. B* **2001**, *105*, 8845–8860. doi:10.1021/jp010869j
- Melucci, M.; Barbarella, G.; Zambianchi, M.; Di Pietro, P.; Bongini, A. *J. Org. Chem.* **2004**, *69*, 4821–4828. doi:10.1021/jo035723q

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Synthesis of (–)-julocrotine and a diversity oriented Ugi-approach to analogues and probes

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Full Research Paper

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Keywords:

diversity oriented synthesis; julocrotine; leishmania; Mitsunobu reaction; Ugi reaction

Beilstein J. Org. Chem. **2011**, *7*, 1504–1507.

doi:10.3762/bjoc.7.175

Received: 01 September 2011

Accepted: 21 October 2011

Published: 07 November 2011

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

An improved total synthesis of (–)-julocrotine in three steps from Cbz-glutamine, in 51% overall yield, is presented. To demonstrate the potential of the heterocyclic moiety for diversity oriented synthesis, a series of (–)-julocrotine analogues was synthesized by employing the heterocyclic precursor as an amino input in Ugi four-component reactions (Ugi-4CR) [1].

Introduction

Julocrotine (**1**) is a natural glutarimide alkaloid isolated from several plants of the genus *Croton* [2-4], including *Croton cuneatus* Klotzsch, which is used by Amazonia natives in anti-inflammatory and analgesic medicines. The structure of this glutarimide-containing alkaloid was first proposed in 1960, based upon a series of degradative experiments, but only confirmed in 2008 by X-ray analysis [5-7]. Most interestingly, it was found to inhibit the growth of promastigote and amastigote forms of the protozoan *Leishmania amazonensis* (*L.*) with no cytotoxicity against the host cell [8]. This parasite causes cutaneous leishmaniasis, a neglected disease that affects more than 12 million people in tropical countries [9].

In addition, the glutarimide motif can be considered as a privileged structure. Compounds with this pharmacophore often exhibit a wide range of biological properties including anti-inflammatory [10], antitumor [11,12], and anticonvulsive properties [13].

Because of the low yields of julocrotine obtained through isolation from natural sources and the necessity to gain access to larger quantities of this substance for further biological screening, Silva and Joussef developed a straightforward total synthesis in six steps [14]. Starting from L-glutamic acid, their chiral-pool approach yielded the desired optically active natural

product in 41% overall yield. After analyzing the structure of (–)-julocrotine, we set out to synthesize it in only three steps from commercially available L-Cbz-glutamine, in a sequence of cyclization (a), N-alkylation (b), and the removal of the protecting group followed by acylation with (S)-2-methylbutanoic acid (c) [15] (Figure 1).

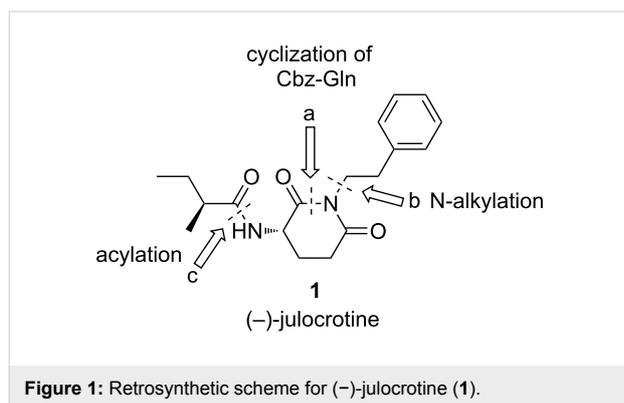


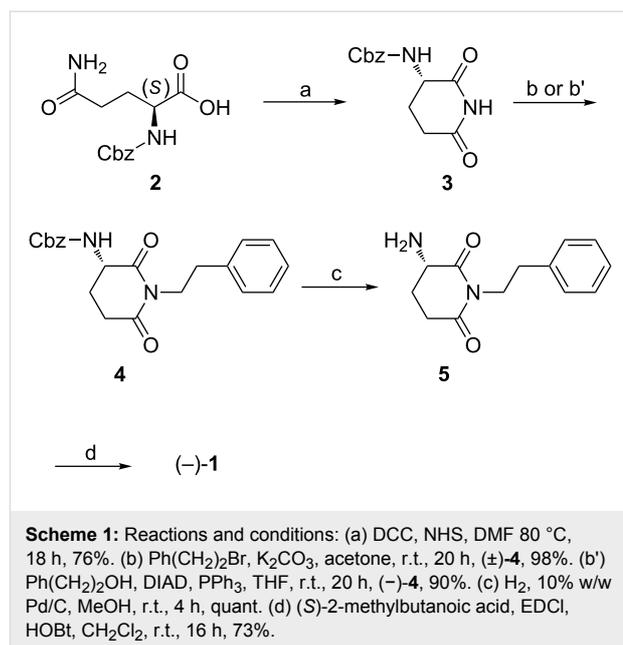
Figure 1: Retrosynthetic scheme for (–)-julocrotine (1).

Based on this flexible route, we also envisioned the synthesis of derivatives utilizing post-cyclization transformations by multi-component reactions. This diversity-driven approach benefits from the fact that the heterocyclic moiety may be considered a privileged structural element for bioactivity.

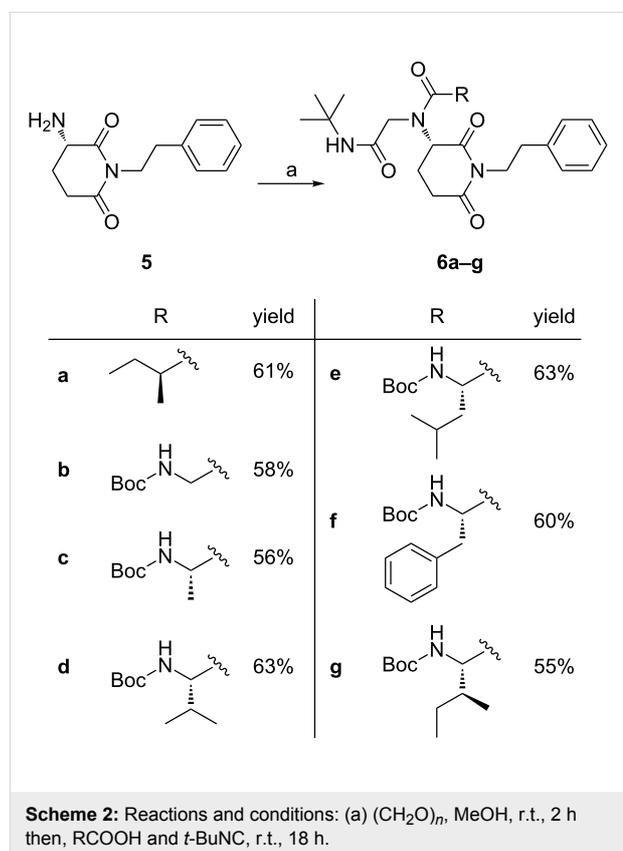
Results and Discussion

The synthetic approach, illustrated in Scheme 1, starts from Cbz-glutamine **2**, which reacted in the presence of dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (NHS) in DMF to afford Cbz-glutarimide **3** in 76% yield in optically pure form [16]. To alkylate the imide-moiety, glutarimide **3** was reacted with phenylethyl bromide in the presence of potassium carbonate at room temperature. The desired compound **4** was obtained in 98% isolated yield, but analysis revealed racemization. Indeed, the equilibration at the chiral center of **4** can be observed even in the presence of weak bases such as potassium carbonate [17]. Thus, we decided to use a base-free N-alkylation protocol, namely the Mitsunobu reaction of **3** and the readily available 2-phenylethanol [18]. This protocol gave the desired optically active product in 90% yield ($[\alpha]_D^{20} -29.2$). The key intermediate **4** was hydrogenated on Pd/C at room temperature to afford **5**, which was coupled with (S)-2-methylbutanoic acid in the presence of EDCI and HOBt to afford (–)-julocrotine (**1**) in 73% yield, over two steps. The HRMS, ^1H and ^{13}C NMR spectra, optical rotation, and melting point of **1** were consistent with the reported data [2,14,15].

For the diversity oriented synthesis the advanced intermediate **5** was used as the amino component in an Ugi-4CR with (S)-2-methylbutanoic acid, hydrophobic amino acids, formaldehyde



and *tert*-butyl isocyanide (Scheme 2). These analogues possess a protease-resistant peptoid scaffold and this might lead to an enhanced activity [19,20]. In this endeavor, all Ugi reactions were initiated by pre-imine formation of **5** and reaction with formaldehyde as the oxo-component, after which the multicom-



ponent reaction was completed by the addition of (*S*)-2-methylbutanoic acid, Boc-Gly, Boc-Ala, Boc-Val, Boc-Leu, Boc-Phe and Boc-Ile and *tert*-butyl isocyanide. Following this procedure, the desired optically active compounds **6a–g** were obtained in 55–63% yields. Their structures were confirmed by ¹H, ¹³C NMR and HRMS spectra.

Finally, the Ugi-4CR was utilized for the synthesis of a molecular probe prototype of **1**, which can be used for intercalation studies (Scheme 3). For this propose, the natural product scaffold should be attached through a spacer to a reporter tag, which is normally a luminescent group or a dye. The advanced intermediate **5** was converted to the respective imine as depicted in Scheme 2 and then reacted with (*S*)-2-methylbutanoic acid and isonitrile **7** to afford the intermediate **8** in 61% yield. This compound was then hydrogenated to afford **9** and then directly coupled with 1-pyrenemethylamine, by using EDCI as coupling reagent, to yield the designed probe prototype **10** in 80% yield (from **8**).

Pyrene derivative **10** exhibited strong blue luminescence in both solution and solid phase. This probe may be used for tracking the (–)-julocrotine in biological systems, in particular in promastigote and amastigote forms of protozoan *Leishmania amazonensis* (*L.*). It could be helpful to elucidate the to-date unknown mode of action of this natural product in the parasite.

Conclusion

In summary, a highly efficient method to synthesize (–)-julocrotine (**1**) in three steps from Cbz-glutamine **2** was developed. The approach affords the natural product in 51% overall yield. The versatility of the developed protocol was demonstrated in the synthesis of seven julocrotine analogues and a molecular probe utilizing Ugi-4CRs. The desired compounds **6a–g** and **10** were obtained in good yields.

Supporting Information

Supporting Information File 1

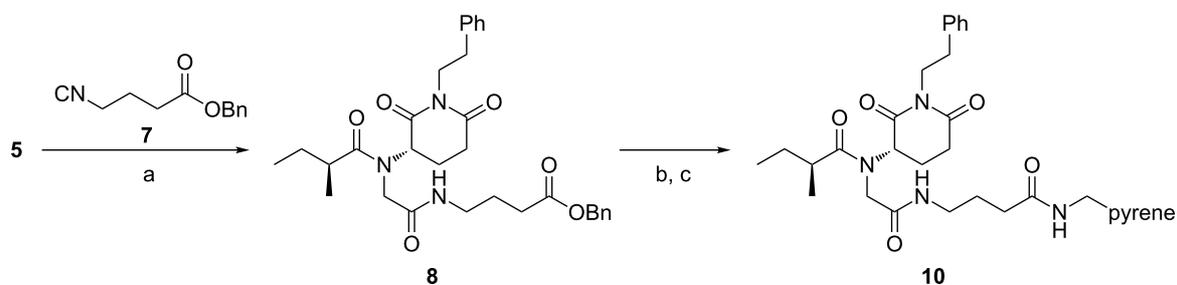
Experimental procedures and analytical data.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-175-S1.pdf>]

Acknowledgements

The authors thank Dr. Jürgen Schmidt and Mr. Torsten Geißler for the HRMS and emission spectra and Ms. Leah M. Harris for a kind revision of this manuscript. R.A.W.N.F. is grateful to CNPq for a Ph.D. fellowship.

References

- Hulme, C.; Dietrich, J. *Mol. Diversity* **2009**, *13*, 195–207. doi:10.1007/s11030-009-9111-6
- Anastasi, C. A. *Asoc. Quim. Argent.* **1925**, *13*, 348–356.
- Aboagye, F. A.; Sam, G. H.; Massiot, G.; Lavaud, C. *Fitoterapia* **2000**, *71*, 461–462. doi:10.1016/S0367-326X(00)00141-6
- Suárez, A. I.; Blanco, Z.; Delle Monache, F.; Compagnone, R. S.; Arvelo, F. *Nat. Prod. Res.* **2004**, *18*, 421–426. doi:10.1080/14786410310001622004
- Nakano, T.; Djerassi, C.; Corral, R. A.; Orazi, O. O. *Tetrahedron Lett.* **1959**, *1*, 8–12. doi:10.1016/S0040-4039(01)99446-8
- Nakano, T.; Djerassi, C.; Corral, R. A.; Orazi, O. O. *J. Org. Chem.* **1961**, *26*, 1184–1191. doi:10.1021/jo01063a051
- Moreira, R. Y. O.; Brasil, D. S. B.; Alves, C. N.; Guilhon, G. M. S. P.; Santos, L. S.; Arruda, M. S. P.; Müller, A. H.; Barbosa, P. S.; Abreu, A. S.; Silva, E. O.; Rumjanek, V. M.; Souza, J., Jr.; da Silva, A. B. F.; de A. Santos, R. H. *Int. J. Quantum Chem.* **2008**, *108*, 513–520. doi:10.1002/qua.21355
- Guimarães, L. R. C.; Rodrigues, A. P. D.; Marinho, P. S. B.; Müller, A. H.; Guilhon, G. M. S.; Santos, L. S.; do Nascimento, J. L. M.; Silva, E. O. *Parasitol. Res.* **2010**, *107*, 1075–1081. doi:10.1007/s00436-010-1973-0



Scheme 3: Reactions and conditions: (a) (CH₂O)_n, MeOH, r.t., 2 h then, (*S*)-2-methylbutanoic acid and **7**, r.t. 18 h, 61%. (b) H₂, 10% w/w Pd/C, MeOH, r.t., 10 h. (c) 1-pyrenemethylamine hydrochloride, Et₃N, EDCI, DMAP, CH₂Cl₂, r.t., 24 h, 80% over two steps.

9. Leishmaniasis: The magnitude of the problem, World Health Organization.
http://www.who.int/leishmaniasis/burden/magnitude/burden_magnitude/en/index.html (accessed July 25, 2011).
10. Michalska, D.; Morzyk, B.; Bienko, D. C.; Wojciechowski, W. *Med. Hypotheses* **2000**, *54*, 472–474. doi:10.1054/mehy.1999.0879
11. Matsuda, F.; Kawasaki, M.; Terashima, S. *Tetrahedron Lett.* **1985**, *26*, 4639–4642. doi:10.1016/S0040-4039(00)98773-2
12. Choi, B.-G.; Seo, H.-K.; Chung, B.-H.; Choi, S.-U.; Lee, C.-O. *Arch. Pharmacol Res.* **1994**, *17*, 467–469. doi:10.1007/BF02979127
13. Lee, J.; Son, K.; Kim, M.; Jung, G.; Choi, J.; Lee, E.-S.; Park, M. *Arch. Pharmacol Res.* **1999**, *22*, 491–495. doi:10.1007/BF02979158
And references cited therein.
14. Silva, L. L.; Joussef, A. C. *J. Nat. Prod.* **2011**, *74*, 1531–1534. doi:10.1021/np200234e
15. Teng, B.; Zheng, J.; Huang, H.; Huang, P. *Chin. J. Chem.* **2011**, *29*, 1312–1318. doi:10.1002/cjoc.201180248
During the preparation of this manuscript the above mentioned article, applying a similar strategy for the synthesis of (-)-julocrotine, was published.
16. Kaldor, S. W.; Hammond, M.; Dressman, B. A.; Labus, J. M.; Chadwell, F. W.; Kline, A. D.; Heinz, B. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2021–2026. doi:10.1016/0960-894X(95)00345-T
17. Sondheimer, E.; Holley, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 3767–3770. doi:10.1021/ja01571a041
18. Sen, S. E.; Roach, S. L. *Synthesis* **1995**, 756–758. doi:10.1055/s-1995-4012
19. Miller, S. M.; Simon, R. J.; Ng, S.; Zuckermann, R. N.; Kerr, J. M.; Moos, W. H. *Drug Dev. Res.* **1995**, *35*, 20–32. doi:10.1002/ddr.430350105
20. Kreye, O.; Westermann, B.; Wessjohann, L. A. *Synlett* **2007**, 3188–3192. doi:10.1055/s-2007-990912

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[doi:10.3762/bjoc.7.175](https://doi.org/10.3762/bjoc.7.175)

Regioselectivity in the multicomponent reaction of 5-aminopyrazoles, cyclic 1,3-diketones and dimethylformamide dimethylacetal under controlled microwave heating

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Keywords:

aminopyrazoles; dimedone; DMFDMA; regioselectivity

Beilstein J. Org. Chem. **2012**, *8*, 18–24.

doi:10.3762/bjoc.8.3

Received: 05 October 2011

Accepted: 13 December 2011

Published: 04 January 2012

This article is part of the Thematic Series "Multicomponent reactions".

Guest Editor: T. J. J. Müller

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Abstract

The multicomponent reaction of 5-aminopyrazole derivatives with cyclic 1,3-dicarbonyl compounds and dimethylformamide dimethylacetal (DMFDMA) in DMF at 150 °C under controlled microwave heating afforded regioselectively 8,9-dihydropyrazolo[1,5-*a*]quinazolin-6(7*H*)-ones **6** rather than the corresponding dihydropyrazolo[5,1-*b*]quinazolin-8(5*H*)-ones **4**.

Introduction

Several naturally occurring and synthetic compounds containing quinazoline derivatives are of considerable interest in fields related to the organic and medicinal chemistry of natural products [1,2]. The quinazoline ring system represents the core skeleton of an important class of heterocyclic compounds

possessing a wide range of biological activities [3,4]. Multicomponent reactions (MCR) occupy an interesting position in organic synthesis because of their atom economy, simple procedures and convergent character [5-7]. An unresolved issue in multicomponent reactions is whether their selectivity is chemo-

or regioselectivity, or both, due to the several possible parallel reaction pathways, which result in the formation of different products [8-10]. Many factors modulate the selectivity of synthetic transformations, such as temperature, pressure, solvent, catalyst and type of reaction control, i.e., either kinetic or thermodynamic [11-13]. It has been reported that the use of microwave or ultrasound irradiation provides an additional parameter for synthetic selectivity [14-17].

Results and Discussion

The multicomponent reaction of 5-aminopyrazoles, dimedone and aromatic aldehydes was reported to afford several different tricyclic products. Thus, in an early report [18], the reaction of the three components in ethanol under conventional heating afforded mainly the corresponding pyrazolo[3,4-*b*]quinolin-5-ones. This finding was later supported by other authors [19]. Recently, the results of an interesting study dealing with such reactions were described by Chebanov et al. [20] Specifically, these researchers performed the reaction at 150 °C in the presence of triethylamine by employing a sealed vessel under microwave or conventional heating, and which thus afforded pyrazoloquinolinones (Hantzsch-type dihydropyridines). On the other hand, the use of sonication at room temperature under neutral conditions favours the formation of isomeric pyrazolo[5,1-*b*]quinazolin-8(4*H*)-ones (Biginelli-type dihydropyrimidines) [9]. Employing more nucleophilic bases to catalyse the reaction afforded the corresponding pyrazolo[4,3-*c*]quinazolin-9-ones [20]. It was concluded that, under ambient and neutral conditions, the reaction proceeds under kinetic control, and the Biginelli-type dihydropyrimidines are the predominant isomers. Increasing the reaction temperature in the presence of triethylamine as base produces the more thermodynamically stable dihydropyridine (Hantzsch-type product). In addition, the nature of the catalyst plays an important role [20].

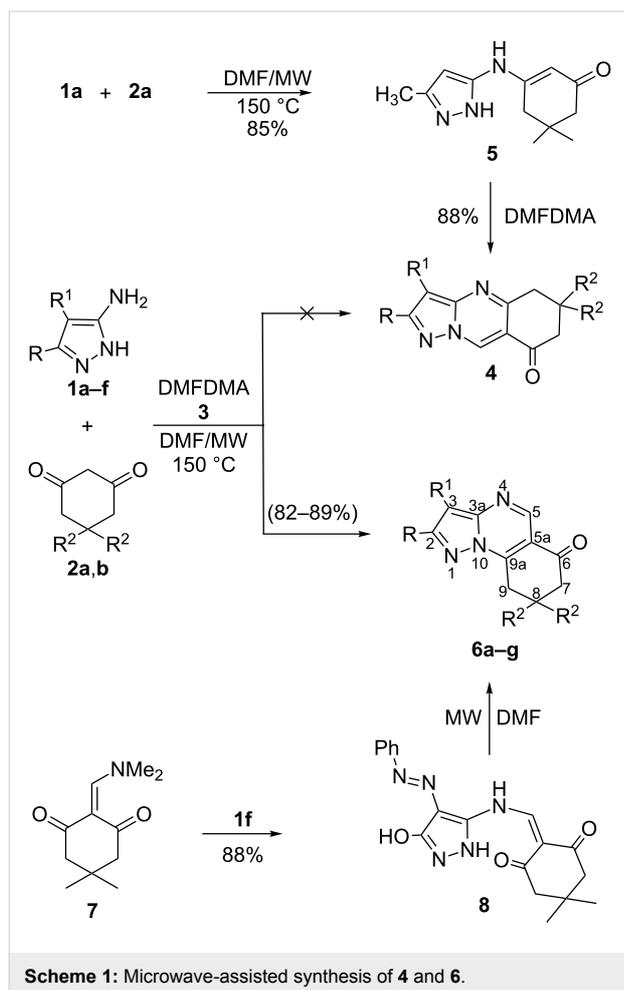
A one-pot three component reaction of 5-amino-1*H*-pyrazole-4-carbonitrile, dimedone and triethylorthoesters in toluene under reflux was recently reported to afford the corresponding pyrazolo[1,5-*a*]quinazolin-6-one derivatives [21]. Although it is well established that 5-amino-pyrazoles have nonequivalent nucleophilic reaction centres in the aminopyrazole scaffold (N1, C4, NH₂), which can lead to the formation of several different tricyclic reaction products, no general basis on which to determine the preferred tautomeric form of the final product has been established.

In continuation of our studies in which we performed multicomponent reactions using controlled microwave heating [22-24], we report herein the results of our investigation concerning the regioselectivity in multicomponent reactions of 5-aminopyrazoles, cyclic 1,3-diketones and dimethylformamide dimethylacetal (DMFDMA) under controlled microwave heating.

We began this study by treating 5-amino-3-methylpyrazole (**1a**) and dimedone (**2a**) with DMFDMA (**3**) in DMF under microwave heating at 150 °C for 15 min. After being cooled to room temperature, the precipitated solid product was isolated in 88% yield (Table 1). The mass spectrum of the reaction product showed a molecular ion peak $m/z = 229.12$ (100%). The ¹H NMR revealed a singlet signal at $\delta = 6.70$ ppm integrated for one proton, which was assigned to the pyrazoloquinazolinone C₃ proton, and which indicates the lack of involvement of such a proton in the condensation leading to the tricyclic system. Although, it was previously reported [20] that, due to reduced steric hindrance, the multicomponent reaction of 5-amino-3-methyl-pyrazole, aromatic aldehydes and dimedone under controlled microwave irradiation at 150 °C involves the participation of C₃-H of the pyrazole ring in such a cyclocondensation reaction, this is not favoured in our case. In addition two

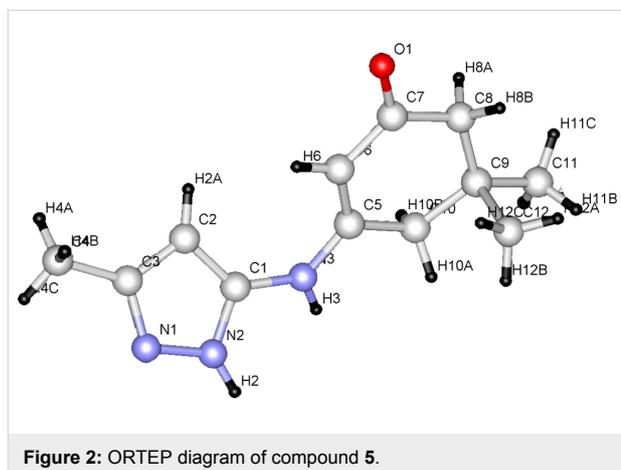
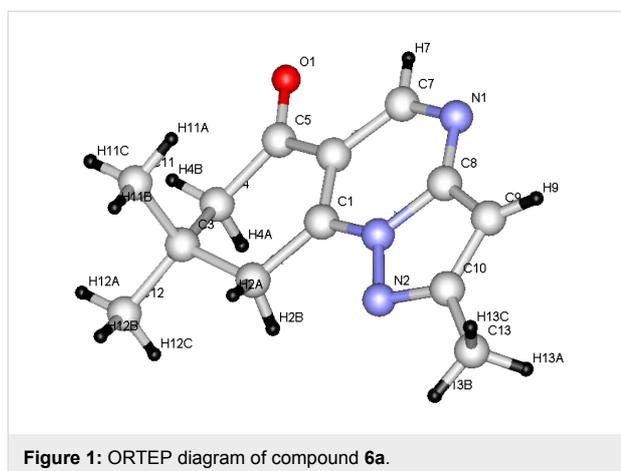
Table 1: Microwave-assisted synthesis of **4** and **6**.

entry	compound	5-aminopyrazole, 1 ;	cyclic 1,3-diketone, 2 ;	product	yield (%)
1	1a	R = CH ₃ , R ¹ = H	2a ; R ² = CH ₃	6a	88
2	1a	R = CH ₃ , R ¹ = H	2b ; R ² = H	6b	85
3	1b	R = NH ₂ , R ¹ = CO ₂ Et	2b ; R ² = H	6c	89
4	1c	R = CH ₃ , R ¹ = C ₆ H ₅	2a ; R ² = CH ₃	6d	83
5	1d	R = C ₆ H ₅ , R ¹ = H	2b ; R ² = H	6e	82
6	1e	R = C ₆ H ₅ , R ¹ = H	2a ; R ² = CH ₃	6f	83
7	1f	R = OH, R ¹ = C ₆ H ₅ N=N-	2a ; R ² = CH ₃	6g	84



signals were assigned to two CH₂ groups and three methyl functions, and a singlet at $\delta = 8.75$ ppm corresponding to one proton at C₅. The pyrazolo[1,5-*a*]-quinazolin-8(5*H*)-one **6a** was established as the reaction product, rather than with isomeric **4a**, which was prepared by first reacting **1a** with dimedone (**2a**) in DMF under microwave heating at 150 °C for 10 min to afford **5**. Subsequently, treating compound **5** with DMFDMA (**3**), under the same experimental conditions, gave compound **6a** in excellent yield (Scheme 1 and Table 1). Furthermore, the structures of compounds **5** and **6a** were unambiguously confirmed by single-crystal X-ray diffraction [25,26] (Figure 1, Figure 2 and Table 1, Table 2, Table 3).

With this result in hand, we went on to study the scope of such multicomponent reactions with several substituted 5-aminopyrazoles and cyclic 1,3-diketones. Thus, the reaction of **1b-f** with **2a,b** and **3**, under the same experimental conditions, afforded the corresponding pyrazolo[5,1-*b*]quinazolin-8(5*H*)-ones **6b-g**, respectively. The structures of **6b-g** were deduced from their ¹H NMR, ¹³C NMR, mass spectra and elemental analyses.



Compound **6g** was also obtained by an alternative route: Compound **8** was prepared by reacting enaminone **7** with 5-aminopyrazole derivative **1f** in DMF under microwave heating at 150 °C for 2 min (Table 1). When this compound was refluxed in DMF under microwave heating for 13 min it under-

Table 2: Selected bond lengths and bond angles for compound **6a**.

bond lengths		bond angles	
atom numbers	geometric parameter (Å)	atom numbers	geometric parameter (°)
N1–C8	1.372 (3)	C7–N1–C8	116.15 (19)
N1–C7	1.309(3)	N2–N3–C1	125.03 (16)
N2–C10	1.344 (3)	C1–N3–C8	122.51 (18)
N3–C8	1.397 (3)	N3–C1–C6	116.10 (17)
N3–C1	1.490 (3)	C8–C9–C10	106.29 (17)
N1–C6	1.377 (3)	C1–C6–C5	119.42 (19)
N6–C7	1.421 (3)	N1–C7–C6	124.5 (3)
		N1–C8–C9	133.29 (19)
		N3–N2–C10	103.65 (17)
		N2–N3–C8	112.41(16)
		N1–C8–N3	121.56 (18)

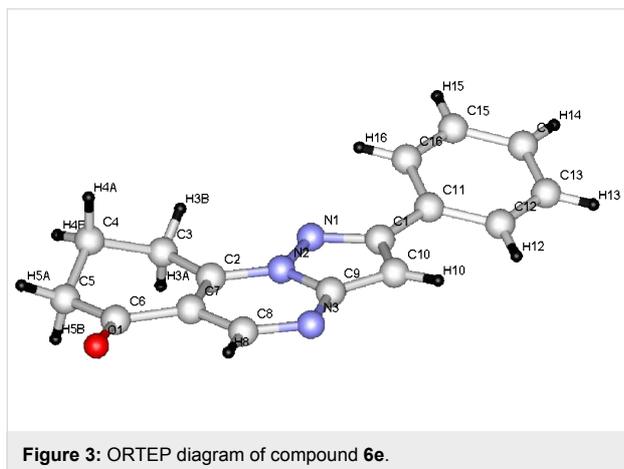
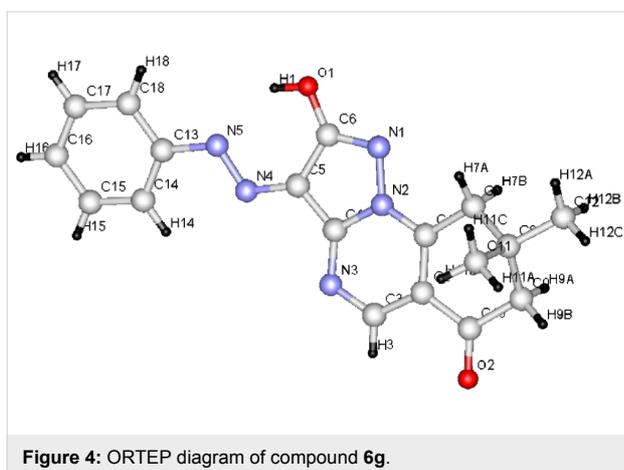
Table 3: Selected bond lengths and bond angles for compound **6e**.

bond lengths		bond angles	
atoms numbers	geometric parameter (Å)	atom numbers	geometric parameter (°)
N3–C9	1.360 (3)	C8–N3–C9	116.10 (19)
N3–C8	1.3147(3)	N1–N2–C2	124.94 (19)
N1–C1	1.346 (3)	N2–C1–C3	124.71 (18)
N2–C9	1.396 (3)	N2–C2–C7	116.23 (18)
N2–C2	1.364 (3)	C1–C10–C9	120.9 (17)
C2–C7	1.363 (3)	C2–C7–C8	124.7 (2)
C7–C8	1.428 (3)	N3–C8–C7	105.78 (17)
		N3–C9–C10	133.37 (19)
		N2–N1–C1	103.94 (14)
		N1–N2–C9	112.01(15)
		N2–C9–N3	120.99 (18)

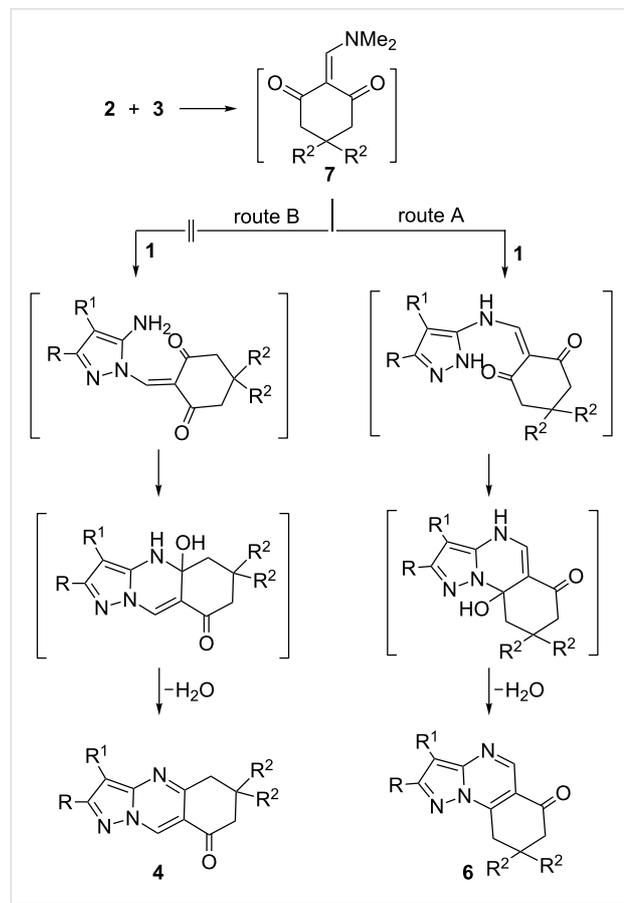
Table 4: Selected bond lengths and bond angles for compound **6g**.

bond lengths		bond angles	
atoms numbers	geometric parameter (Å)	atom numbers	geometric parameter (°)
N3–C4	1.330 (2)	C3–N3–C4	116.18 (10)
N3–C3	1.321(19)	N1–N2–C1	124.04 (12)
N1–C6	1.343 (17)	C1–N2–C4	121.41 (12)
N2–C4	1.393 (18)	N2–C1–C2	116.52 (13)
N2–C1	1.343 (19)	C4–C5–C6	105.52 (13)
C1–C7	1.491 (2)	C1–C2–C10	119.58 (13)
C1–C2	1.394 (2)	N3–C3–C2	123.90 (14)
		N3–C4–C5	132.56 (14)
		N2–N1–C6	104.27 (11)
		N1–N2–C4	114.50(11)
		N2–C4–N3	123.02 (13)

went cyclization to give **6g** (Scheme 1). Moreover, the structure of compounds **6b–g** was unequivocally established by single-crystal X-ray diffraction of compounds **6e,g** (Figure 3, Figure 4 and Table 3, Table 4) [27,28].

**Figure 3:** ORTEP diagram of compound **6e**.**Figure 4:** ORTEP diagram of compound **6g**.

A proposed mechanism to account for the formation of products **6** is illustrated in Scheme 2. The base-catalyzed reaction of cyclic 1,3-diketones **2** with DMFDMA **3** gave the enaminone **7**, which subsequently reacted with 5-aminopyrazole **1** at the

**Scheme 2:** A proposed mechanism to account for the formation of products **6**. The factors that determine the nature of the end product are, however, at present unclear.

exocyclic amino function, followed by cyclization through water loss to give **6** (route A). Formation of isomeric product **4**, which would be formed by route B, was ruled out based on spectral and X-ray diffraction data.

From the data of the X-ray crystal structure it can be concluded that the bridged head nitrogen has bond angles closer to those of sp^3 nitrogen. One may thus conclude that the lone pair on this nitrogen atom does not contribute much to the actual state of the molecule and that charge-separated ions also do not contribute significantly; although, the pyrazolo[5,1-*b*]quinazolin ring is almost planar.

Conclusion

In summary, we can reveal that the reaction of substituted 5-aminopyrazoles, cyclic 1,3-diketones and dimethylformamide dimethylacetal (DMFDMA, **3**) proceeds by initial attack of the exocyclic amino function. Although an attack by the ring nitrogen has been proposed for the reaction of 5-aminopyrazoles with acrylonitrile [29], here steric factors hinder such an attack and the reaction occurs exclusively, in every case studied, at the amino function.

Experimental

General information. All the reactions were carried out in a Milestone START Microwave Labstation (temperature control by IR sensor). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured on a Bruker DPX instrument by using $\text{DMSO-}d_6$ as solvent and TMS as internal standard. Chemical shifts are expressed as δ in ppm. Coupling constants (J) are given in Hertz (Hz). The melting points were measured in a Gallenkamp melting-point apparatus and are not corrected. Mass spectra were measured by using VG Autospec Q MS 30 and MS 9 (AEI) spectrometer with the EI (70 eV) mode.

General procedure for the synthesis of pyrazoloquinazolinones (**6a–g**)

A solution of 5-aminopyrazole derivative **1a–f** (1 mmol), cyclic 1,3-diketones (**2a,b**) (1 mmol) and dimethylformamide dimethylacetal (DMFDMA, **3**) (1 mmol) in DMF (10 mL) was heated under reflux in a Milestone Microwave Labstation at 150 °C for 15 min. After concentration and cooling to room temperature, the resulting solid product so formed was collected by filtration, washed well with EtOH, dried and recrystallized from EtOH.

2,8,8-Trimethyl-8,9-dihydropyrazolo[5,1-*b*]quinazolin-6(7*H*)-one (6a): Greenish yellow plates, 201 mg (88% yield); mp 134–135 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 1.12 (s, 6H, 2CH₃), 2.48 (s, 3H, CH₃), 2.56 (s, 2H, CH₂ at C-9), 3.32 (s, 2H, CH₂ at C-7), 6.70 (s, 1H, CH at C-3), 8.75 (s, 1H, CH at C-5);

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 14.55, 27.89, 32.36, 36.46, 38.87, 50.08, 98.04, 112.39, 146.03, 149.34, 152.21, 157.52, 194.82; EIMS m/z : 229.1 (M^+), 214, 173, calcd. for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}$ 229.28; Anal. calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}$: C, 68.1; H, 6.59; N, 18.33; found: C, 68.22; H, 6.62; N, 18.35%.

2-Methyl-8,9-dihydropyrazolo[5,1-*b*]quinazolin-6(7*H*)-one (6b): Yellow plates, 170 mg (85% yield); mp 154–155 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.21–2.27 (m, 2H, CH₂ at C-8), 2.66 (t, $J = 6.8$ Hz, 2H, CH₂ at C-9), 3.40 (t, $J = 6.4$ Hz, 2H, CH₂ at C-7), 6.71 (s, 1H, CH at C-3), 8.77 (s, 1H, CH at C-5); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 14.53, 19.95, 33.37, 36.54, 97.91, 113.3, 146.3, 149.0, 153.9, 157.42, 194.81; EIMS m/z 201.12 (M^+), calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$ 201.22; Anal. calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$: C, 65.66; H, 5.51; N, 20.88; found: C, 65.68; H, 5.49; N, 20.67%.

Ethyl 2-amino-6-oxo-6,7,8,9-tetrahydropyrazolo[5,1-*b*]quinazolin-3-carboxylate (6c): Yellow crystals, 243 mg (89% yield); mp 184–185 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 1.31 (t, $J = 7.2$ Hz, 3H, CH₃), 2.10–2.20 (m, 2H, CH₂ at C-8), 2.63 (t, $J = 6.8$ Hz, 2H, CH₂ at C-9), 3.25 (t, $J = 6.8$ Hz, 2H, CH₂ at C-7), 4.31 (q, $J = 6.8$ Hz, 2H, CH₂), 6.7 (br s, 2H, NH₂), 8.82 (s, 1H, CH at C-5); EIMS m/z 274.1 (M^+), 228, 174.1, calcd for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_3$ 274.28; Anal. calcd for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_3$: C, 56.93; H, 5.14; N, 20.43; found: C, 57.12; H, 5.23; N, 20.45%.

2,8,8-Trimethyl-3-phenyl-8,9-dihydropyrazolo[5,1-*b*]quinazolin-6(7*H*)-one (6d): Pale yellow crystals, 253 mg (83% yield); mp 279–280 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 1.15 (s, 6H, 2 CH₃), 2.49 (s, 2H, CH₂ at C-9), 2.58 (s, 3H, CH₃ at C-2), 2.63 (s, 2H, CH₂ at C-7), 7.13–7.55 (m, 5H, Ph-H), 8.83 (s, 1H, CH at C-5); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 14.41, 24.42, 27.90, 36.42, 38.87, 50.15, 112.99, 119.22, 125.88, 126.67, 128.30, 129.20, 132.43, 140.64, 144.52, 159.05, 194.70; EIMS m/z 305.2 (M^+), 299, 179.1, calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$ 305.37; Anal. calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$: C, 74.73; H, 6.27; N, 13.76; found: C, 74.66; H, 6.35; N, 13.82%.

2-Phenyl-8,9-dihydropyrazolo[1,5-*a*]quinazolin-6(7*H*)-one (6e): Pale yellow crystals, 215 mg (82% yield); mp 197–198 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.25 (m, 2H, CH₂ at C-8), 2.64 (t, $J = 5.6$ Hz, 2H, CH₂ at C-9), 3.41 (t, $J = 5.6$ Hz, 2H, CH₂ at C-7), 7.39 (br s, 1H, CH at C-3), 7.48 (m, 3H, Ph-H), 8.08 (d, $J = 7.2$ Hz, 2H, Ph-H), 8.78 (s, 1H, CH at C-5); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 19.97, 23.46, 36.63, 79.19, 95.49, 114.10, 126.44, 129.0, 129.69, 131.85, 146.77, 149.69, 154.39, 157.60, 162.32, 194.84; EIMS m/z 263.1 (M^+), 235.1, 152.1, calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}$ 263.11; Anal. calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}$: C, 72.99; H, 4.98; N, 15.96; found: C, 72.94; H, 5.18; N, 16.32%.

8,8-Dimethyl-2-phenyl-8,9-dihydropyrazolo[1,5-*a*]quinoxalin-6(7*H*)-one (6f): Pale yellow crystals, 242 mg (83% yield); mp 244–245 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.18 (s, 6H, 2 CH₃), 2.59 (s, 2H, CH₂ at C-9), 3.44 (s, 2H, CH₂ at C-7), 7.34 (s, 1H, CH at C-3), 7.50 (m, 3H, Ph-H), 8.09 (m, 2H, Ph-H), 8.81 (s, 1H, CH at C-5); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 28.47, 32.73, 37.17, 50.86, 95.94, 113.79, 127.02, 129.29, 129.97, 132.53, 146.90, 150.61, 152.87, 158.37, 194.85; Anal. calcd for C₁₈H₁₇N₃O: C, 74.20; H, 5.88; N, 14.42; found: C, 74.32; H, 5.91; N, 14.44%.

2-Hydroxy-8,8-dimethyl-3-(phenyldiazenyl)-8,9-dihydropyrazolo[1,5-*a*]quinoxalin-6(7*H*)-one (6g): Orange crystals, 295 mg (88% yield); mp 254–255 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.14 (s, 6H, 2 CH₃), 2.66 (s, 2H, CH₂ at C-9), 3.26 (s, 2H, CH₂ at C-7), 7.45 (t, *J* = 7.2 Hz, 1H, Ph-H), 7.55 (t, *J* = 7.6 Hz, 2H, Ph-H), 7.85 (d, *J* = 7.6 Hz, 2H, Ph-H), 8.95 (s, 1H, CH at C-5); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 27.96, 32.25, 36.44, 50.14, 79.20, 115.14, 115.74, 121.33, 129.34, 129.80, 144.26, 148.99, 151.95, 152.61, 162.10, 194.3; EIMS *m/z* 335.1 (M⁺), 307.1, 258.1, calcd for C₁₈H₁₇N₅O₂ 335.14; Anal. calcd for C₁₈H₁₇N₅O₂: C, 64.47; H, 5.11; N, 20.88; found: C, 64.43; H, 5.33; N, 20.95%.

Synthesis of (*Z*)-5,5-dimethyl-3-[(3-methyl-1*H*-pyrazol-5-yl)amino]cyclohexanone (5)

A solution of **1a** (1 mmol) and **2a** (1 mmol) in DMF (10 mL) was heated under reflux in a Milestone Microwave Labstation at 150 °C for 10 min. After concentration and cooling to room temperature, the resulting solid product so formed was collected by filtration, washed well with EtOH, dried and recrystallized from EtOH to afford a pure sample of compound **5** as yellow crystals, 186 mg (85% yield); mp 233–235 °C.

Synthesis of 4a: A solution of **1a** (1 mmol) and **2a** (1 mmol) in DMF (10 mL) was heated under reflux in a Milestone Microwave Labstation at 150 °C for 10 min. After concentration and cooling to room temperature, the resulting solid product so formed was collected by filtration, washed well with EtOH, dried and recrystallized from EtOH to afford a pure sample of (*Z*)-3,3-dimethyl-5-(3-methyl-1*H*-pyrazol-5-ylimino)cyclohexanone (**5**) as yellow crystals, 186 mg (85% yield); mp 233–235 °C.

Reaction of 5 with dimethylformamide dimethylacetal (DMFDMA, 3): A solution of **5** (1 mmol) and DMFDMA (**3**) (1 mmol) in DMF (10 mL) was heated under reflux in a Milestone Microwave Labstation at 150 °C for 10 min. After evaporation to dryness under reduced pressure, the resulting solid product was collected by filtration, washed well with EtOH, dried and recrystallized from EtOH to give **4a**.

Alternative synthesis of 6g: Synthesis of 2-((3-hydroxy-4-(phenyldiazenyl)-1*H*-pyrazol-5-ylamino)methylene)-5,5-dimethylcyclohexane-1,3-dione (8): A solution of **1f** (1 mmol), enaminone **7** (1 mmol) in DMF (10 mL) was heated under reflux in a Milestone Microwave Labstation at 150 °C for 2 min. After concentration and cooling to room temperature, the precipitated product was collected by filtration, washed well with EtOH, dried and recrystallized from EtOH to give a pure sample of **8** as orange crystals, 303 mg (88% yield); mp 255–256 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.01 (s, 6H, 2 CH₃), 2.40 (s, 2H, CH₂), 3.26 (s, 2H, CH₂), 7.24–7.85 (m, 6H, 5 Ph-H and *CH*-NH), 11.76 (s, 1H, NH), 12.59 (s, 1H, pyrazole NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 27.95, 30.70, 50.12, 109.66, 115.16, 115.74, 121.31, 126.16, 129.32, 129.64, 129.80, 144.34, 148.97, 152.57, 158.40, 194.23, 195.33; EIMS *m/z* 353.2 (M⁺), 335.1, 242.1, calcd. for C₁₈H₁₉N₅O₃ 353.15; Anal. calcd for C₁₈H₁₉N₅O₃: C, 61.18; H, 5.42; N, 19.82; found: C, 61.23; H, 5.45; N, 19.92%.

Cyclization of 8. A solution of **8** (1 mmol) in DMF (10 mL) was heated under reflux in a Milestone Microwave Labstation at 150 °C for 13 min. The reaction mixture was evaporated to dryness in vacuo. The precipitated solid product was filtered off, washed with a small amount of EtOH, dried and recrystallized from EtOH to give an analytical pure sample of **6g** (identical with an authentic sample, MS, ¹H NMR and ¹³C NMR).

Acknowledgements

K. U. Sadek is grateful to the Alexander von Humboldt Foundation for donation of a Milestone START Microwave Labstation, which was of great help in finishing this work. M. H. Elnagdi and Moustafa Sherief Moustafa are grateful to Kuwait University Research Administration for the financial support of project SC1/10, and the analytical facilities provided by SAF projects No. GS 03/08 (Single crystal X-ray crystallography-Rigaku Rapid II) & GS 01/01 & GS 01/03 & GS 01/05 are greatly appreciated.

References

- Kessler, M.; Baudry, M.; Lynch, G. *Brain Res.* **1989**, *489*, 377. doi:10.1016/0006-8993(89)90875-5
- McQuaid, L. A.; Smith, E. C. R.; South, K. K.; Mitch, C. H.; Schoepp, D. D.; True, R. A.; Calligaro, D. O.; O'Malley, P. J.; Lodge, D.; Ornstein, P. L. *J. Med. Chem.* **1992**, *35*, 3319. doi:10.1021/jm00096a002
- Orvieto, F.; Branca, D.; Giomini, C.; Jones, P.; Koch, U.; Ontoria, J. M.; Palumbi, M. C.; Rowley, M.; Toniatti, C.; Muraglia, E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4196. doi:10.1016/j.bmcl.2009.05.113
- Watson, C. Y.; Whish, W. J. D.; Threadgill, M. D. *Bioorg. Med. Chem.* **1998**, *6*, 721. doi:10.1016/S0968-0896(98)00029-7
- Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366. doi:10.1055/s-1999-2612

6. Kantevari, S.; Vuppapapati, S. V. N.; Nagarapu, L. *Catal. Commun.* **2007**, *8*, 1857. doi:10.1016/j.catcom.2007.02.022
7. Sami, S.; Nandi, G. C.; Kumar, R.; Singh, M. S. *Tetrahedron Lett.* **2009**, *50*, 7096. doi:10.1016/j.tetlet.2009.10.022
8. Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
9. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. doi:10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U
10. Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. doi:10.1002/ejoc.200400511
11. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A*, 5th ed.; Springer: New York, 2007.
12. Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. doi:10.1021/cr068388p
13. Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547. doi:10.1055/s-2005-918922
14. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. doi:10.1002/anie.200400655
15. de la Hoz, A.; Diaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. doi:10.1039/b411438h
16. Bonrath, W.; Paz Schmidt, R. A. Ultrasound in Synthetic Organic Chemistry. In *Advances in Organic Synthesis*; Atta-ur-Rahman, Ed.; Bentham Sciences: Oak Park, IL, 2005; Vol. 1, pp 81–117.
17. Gravotto, G.; Cintas, P. J. *Chem. Soc. Rev.* **2006**, *35*, 180. doi:10.1039/b503848k
18. Quiroga, J.; Mejía, D.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *Tetrahedron* **2001**, *57*, 6947. doi:10.1016/S0040-4020(01)00649-4
19. Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Shishkina, S. V.; Shishkin, O. V.; Kobzar, K. M.; Kappe, C. O. *Org. Lett.* **2007**, *9*, 1691. doi:10.1021/ol070411l
20. Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Knyazeva, I. V.; Groth, U.; Glasnov, T. N.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 5110. doi:10.1021/jo800825c
21. Ghotekar, B. K.; Jachak, M. N.; Toche, R. B. *J. Heterocycl. Chem.* **2009**, *46*, 708. doi:10.1002/jhet.128
22. Sadek, K. U.; Shaker, R. M.; Abd Elrady, M.; Elnagdi, M. H. *Tetrahedron Lett.* **2010**, *51*, 6319. doi:10.1016/j.tetlet.2010.09.114
23. Abd El Latif, F. M.; Barsy, M. A.; Aref, A. M.; Sadek, K. U. *Green Chem.* **2002**, *4*, 196. doi:10.1039/b110723m
24. Mekheimer, R. A.; Sadek, K. U. *J. Heterocycl. Chem.* **2009**, *46*, 149. doi:10.1002/jhet.13
25. CCDC 825123 contains the supplementary crystallographic data for compound **6a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>
26. CCDC 833076 contains the supplementary crystallographic data for compound **5**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>
27. CCDC 827653 contains the supplementary crystallographic data for compound **6e**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>
28. CCDC 826742 contains the supplementary crystallographic data for compound **6g**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>
29. Elnagdi, M. H. *Tetrahedron* **1974**, *30*, 2791. doi:10.1016/S0040-4020(01)97447-2

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