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Authors	Ivan Lyutin, Vasilisa Krivovicheva, Grigory Kantin and Dmitry Dar'in
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ORCID® iDs	Grigory Kantin - https://orcid.org/0000-0001-9141-680X; Dmitry Dar'in - https://orcid.org/0000-0002-0413-7413

Access to 2-Oxoazetidine-3-carboxylic Acids Derivatives via Thermal Microwave-Assisted Wolff Rearrangement of 3-Diazotetramic Acids in the Presence of Nucleophiles

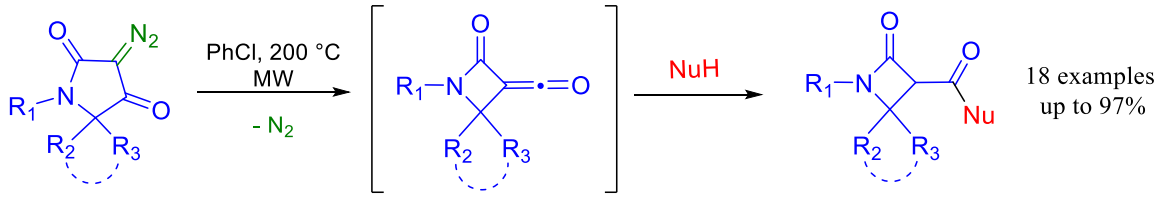
Ivan Lyutin,[1] Vasilisa Krivovicheva,[1] Grigory Kantin,[1] Dmitry Dar'in*[1,2]

[1] Institute of Chemistry, Saint Petersburg State University, 26 Universitetskiy pr., Peterhof, Saint Petersburg 198504, Russian Federation

[2] Saint Petersburg Research Institute of Phthisiopulmonology, 2-4 Ligovsky pr., Saint Petersburg 191036, Russian Federation

* Correspondence: Corresponding author at: Department of Medicinal Chemistry, Institute of Chemistry, Saint Petersburg State University, 26 Universitetskiy pr., Peterhof 198504 Russian Federation, E-mail address: d.dariin@spbu.ru

In commemoration of the 300th anniversary of St Petersburg State University's founding



Keywords: β-lactams; Wolff rearrangement; diazo tetramic acids; nucleophiles; thermolysis; spirocycles.

Abstract

In this work, we report an efficient approach to 2-oxoazetidine-3-carboxylic acid derivatives based on thermally promoted Wolff rearrangement of diazo tetramic acids in the presence of nucleophiles. The method allows easy variation of the substituent in the exocyclic acyl group by introducing different *N*-, *O*- and *S*-nucleophilic reagents into the reaction. The reaction of chiral diazo tetramic acids leads exclusively to *trans*-diastereomeric β-lactams. The use of variously substituted diazo tetramic acids, including spirocyclic derivatives, as well as a wide range of nucleophiles provides access to a structural diversity of medically relevant 2-oxoazetidine-3-carboxylic acids amides and esters.

Introduction

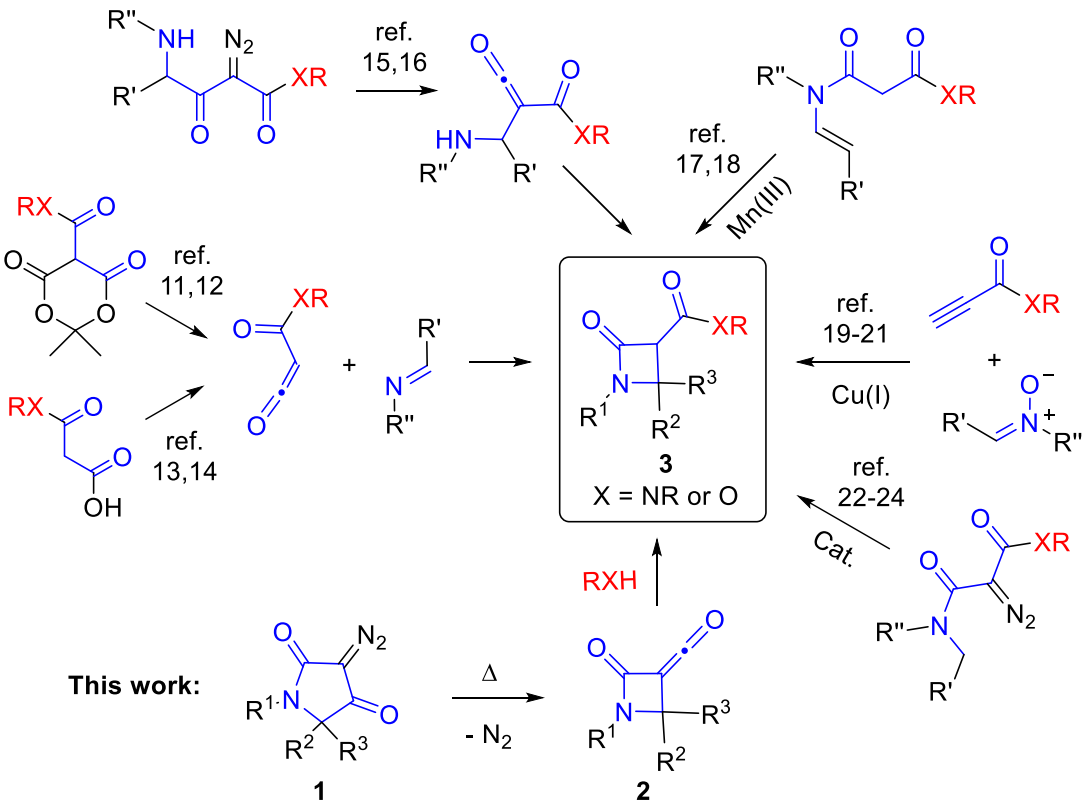
The importance of the β-lactam (azetidin-2-one) scaffold to medicinal chemistry and drug design is self-evident. This four-membered heterocycle is a key fragment of many antibiotics,[1] including penicillin and its analogues, as well as other pharmacologically important

molecules.[2] Therefore, the search for new efficient and versatile methods for the preparation of structurally diverse β-lactam derivatives is of great importance and relevance.

Continuing the investigation of the reactivity and synthetic potential of diazo tetramic acids (**1**), we have recently shown that these diazo reagents can act as precursors of β-lactam ketenes **2** generated by thermally promoted Wolff rearrangement.[3] The interaction of such ketenes with nucleophiles of different nature could serve as a source of libraries of structurally diverse 2-oxoazetidine-3-carboxylic acid derivatives **3** (Scheme 1).

The 2-oxoazetidine-3-carboxylic acid derivatives (mainly amides) exhibit various types of biological activity, among which the following can be highlighted: inhibition of β-lactamases,[4, 5] antitubercular properties,[6] antiproliferative and antibacterial activity,[7] herbicidal properties,[8, 9] inhibition of neutral amino acid transporter (SLC6A19).[10] Hence, developing new synthetic methods to create structurally diverse 2-oxoazetidine-3-carboxylic acid derivatives is a highly valuable endeavour that could have a positive impact on the future drug discovery.

Most synthetic approaches to amides and esters of 2-oxoazetidine-3-carboxylic acids reported in the literature are based on the construction of the β-lactam ring (Scheme 1). The main methods include the [2+2] cycloaddition of acyl ketenes, generated by various methods, with imines[11-14] and the Wolff rearrangement of γ-amino-α-diazo-β-keto esters followed by intramolecular cyclization.[15, 16] Additionally, the manganese(III)-promoted cyclization of *N*-alkenyl malonamides[17, 18] and the Cu(I)-catalyzed reaction of propiolic acid derivatives with nitrones (Kinugasa reaction)[19-21] should also be mentioned, as well as intramolecular C-H insertion using diazo monomalonamides under the action of various catalysts which is a very efficient method for preparing β-lactam esters.[22-24]



Scheme 1. Synthetic routes to 2-oxoazetidine-3-carboxylic acids derivatives.

At the same time, from the point of view of easy variation of the substituent in the exocyclic acyl group (RX), a method allowing the introduction of this moiety at the last step of synthesis would be in great demand. We proposed that, besides modifying the 2-oxoazetidine-3-carboxylic acids themselves, such an approach could involve diazo tetramic acids, subjected to thermal Wolff rearrangement, with various nucleophiles.

The application of the Wolff rearrangement in organic synthesis as a route to generate ketenes is being actively investigated, involving both acyclic and carbocyclic diazocarbonyl compounds.[25] At the same time, the use of diazo heterocyclic reagents (including diazo tetramic acids) in this transformation, with the formation of heterocyclic ring contraction products, is represented in the literature only by isolated examples.[26-30] In addition, photoinitiation is mainly used, while the possibilities of thermolysis remain virtually unexplored.

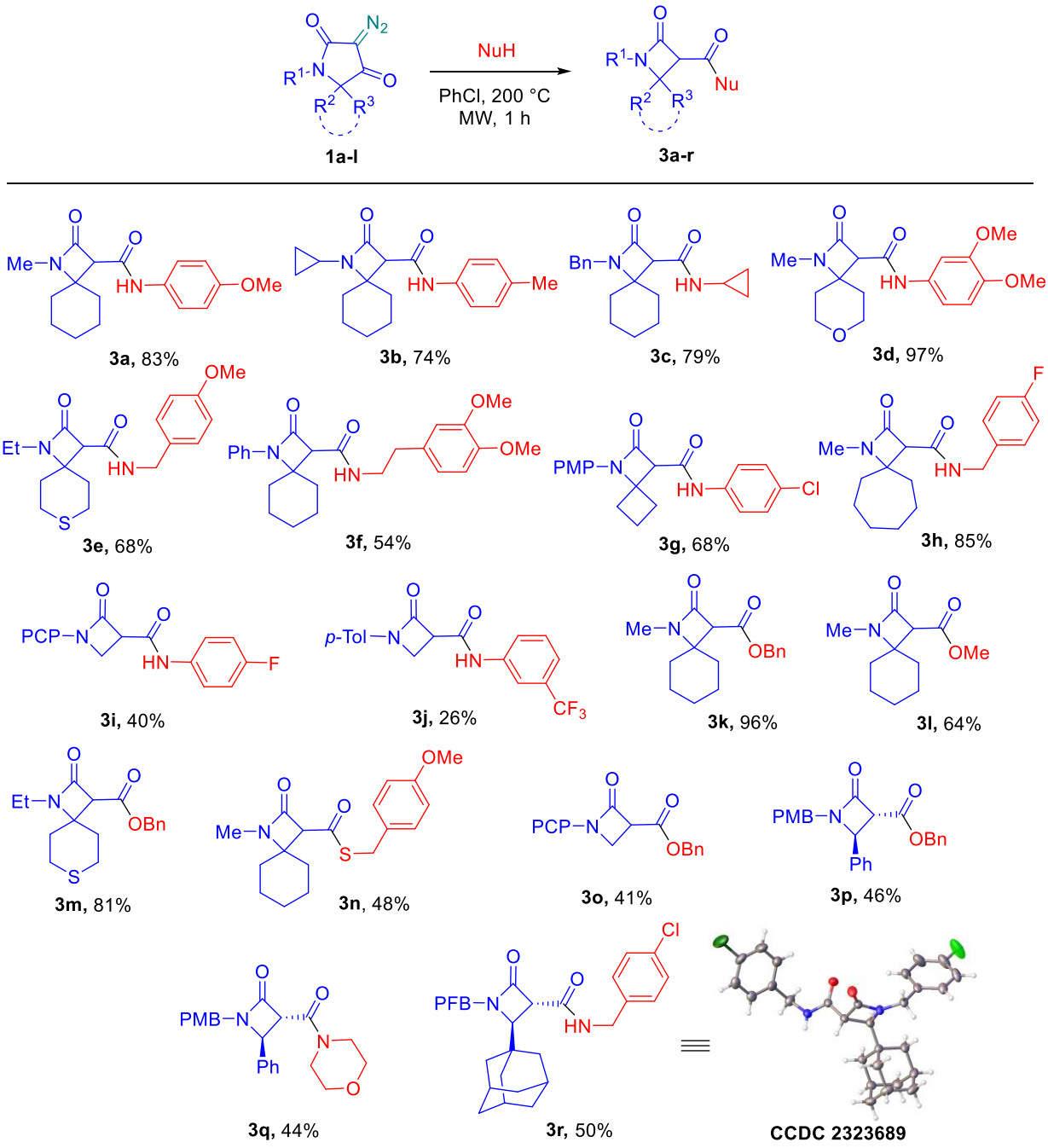
Herein, we report our findings obtained while investigating a synthetic approach to 2-oxoazetidine-3-carboxylic acid derivatives based on the thermally promoted Wolff rearrangement of diazo tetramic acids.

Results and Discussion

Diazo tetramic derivatives **1** are available in a wide variety using the techniques described previously.[31] The conditions for their thermal decomposition were tested in a previous

study.[3] The reaction requires rather severe heating under microwave irradiation (200 °C, chlorobenzene, sealed vial), ensuring complete conversion of the diazo compound in a rather short time.

Initial experiments using *p*-anisidine as a nucleophile showed that the target β-lactam derivative **3a** could be obtained in high yield after simple chromatographic separation of the reaction mixture (Scheme 2). We further introduced various aromatic and aliphatic amines as well as alcohols and mercaptan into the reaction. In order to demonstrate the structural diversity of the compounds obtained, a wide range of diazo tetramic acids **1** of different structures was used. It can be observed that the 5-monosubstituted diazo derivatives, and especially those with no substituents in position 5, form the target products in lower, often moderate yields (see **3i,j,o** and **3p,q,r**) compared to the 5,5-disubstituted (spirocyclic) analogues. This result may be related to the lower stability of the less substituted β-lactam derivatives under thermolysis conditions. Additional alkyl substituents sterically shield the ring and prevent unwanted nucleophilic attack leading to product degradation.



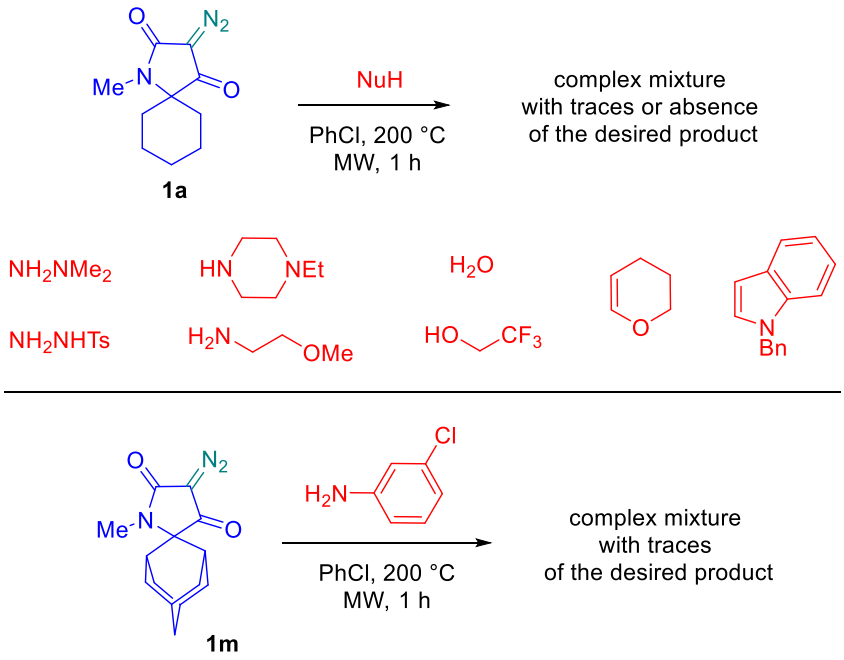
Scheme 2. Scope of diazo tetramic acids **1** thermolysis in the presence of various nucleophiles. PMP = *p*-methoxyphenyl, PCP = *p*-chlorophenyl, PMB = *p*-methoxybenzyl, PFB = *p*-fluorobenzyl.

In reactions with alcohols and *p*-methoxybenzyl mercaptan, the corresponding esters **3k-m,o,p** and thioester **3n** were successfully obtained in moderate to high yields. The synthesis of compound **3k** was additionally carried out on a scaled-up scale (1.5 mmol *vs*. 0.25 mmol), allowing sufficient amounts to be obtained for further modifications (*vide infra*). However, a marked decrease in yield (78% *vs*. 96%) was observed upon scaling up.

In the case of products with two stereogenic centers (**3p-r**), the formation of a single *trans*-diastereomer was observed. According to literature data, the vicinal coupling constants in the

3,4-disubsituted β-lactam cycle have characteristic values for the two diastereomers, lying in the intervals 5.5–6.0 Hz and 1.5–2.5 Hz for the *cis* and *trans* forms, respectively.[32, 33] This makes it easy to assign the stereochemistry of the products obtained. Additional confirmation was gained from X-ray analysis data for structure **3r** (Scheme 2).

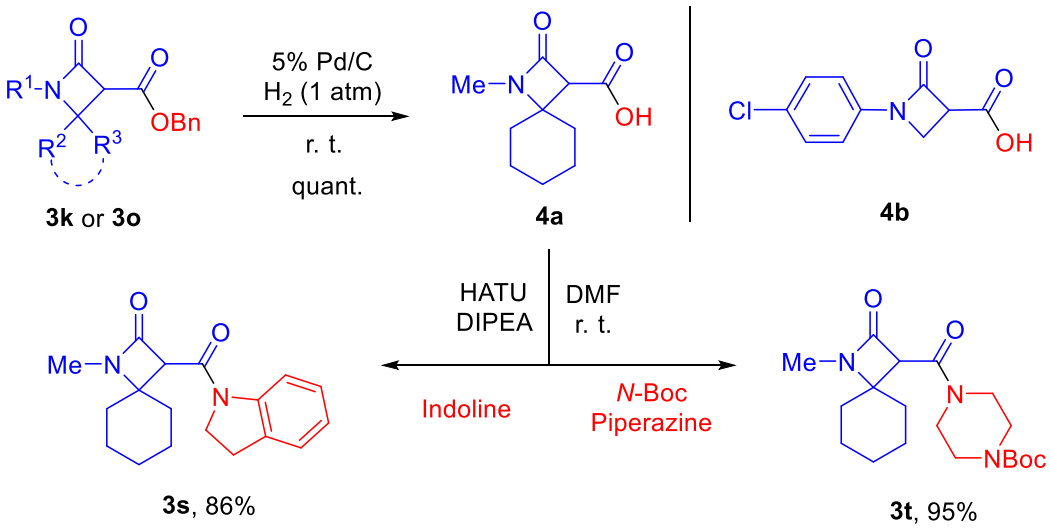
In some cases, we were unable to isolate the target product of the reaction, which was either observed in trace amounts or was not detected in the reaction mixture at all, making it extremely difficult to interpret (Scheme 3). Negative results were observed for dimethyl and tosyl hydrazine, *N*-ethylpiperazine and β-methoxyethylamine. Attempts to obtain directly 2-oxoazetidine carboxylic acid (or its decarboxylation product) or its trifluoroethyl ester by running the synthesis with water or trifluoroethanol were also unsuccessful. Acylation of the π-excessive double bonds of *N*-alkyl indole and dihydropyran by the in situ generated ketene was also unsuccessful. Of the diazo tetramic acids, only the spiro adamantane derivative **1m** was not able to form the desired β-lactam. These reactions gave complex mixtures of unidentified products.



Scheme 3. Negative results with several *N*-, *O*- and *C*-nucleophiles and with diazo reagent **1m**.

The benzyl esters **3k** and **3o** were converted into the corresponding acids **4a,b** by hydrogenolysis under mild conditions, which proceeded in quantitative yields (Scheme 4). It should be noted that this method of preparing β-lactam acids compares favorably with the alkaline hydrolysis of their methyl and ethyl esters, which does not always give high yields of the target compounds. When stored individually or in solution at room temperature, the acids **4** gradually decompose and undergo decarboxylation and other accompanying processes. The example of acid **4a**

demonstrates the possibility of easy amidation to form new β-lactam derivatives **3s** and **3t** (Scheme 4).



Scheme 4. Preparation of acids **4** by hydrogenolysis of benzyl esters and examples of acid **4a** amidation.

Conclusion

We have developed a straightforward access to 2-oxoazetidine-3-carboxylic acid derivatives based on the thermally promoted Wolff rearrangement of diazo tetramic acids in the presence of different nucleophiles. The proposed method allows easy variation of the substituent at the exocyclic carbonyl group by preformed ring contraction and interaction of the intermediate ketene with the selected nucleophile. Various aromatic and aliphatic amines as well as alcohols and thiols can be used as nucleophiles. 5-Monosubstituted diazo tetramic acids give exclusively *trans*-diastereomeric β-lactam products. The use of variously substituted diazo tetramic acids, including their spirocyclic derivatives, provides access to a new structural diversity of medically relevant β-lactam derivatives. The possibility of transforming the obtained benzyl esters into 2-oxoazetidine-3-carboxylic acids and their subsequent amidation has been demonstrated.

Deposition Number CCDC 2323689 (for **3r**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Supporting Information

Supporting Information File 1

General experimental information, X-ray crystallographic data, synthetic procedures, analytical data and NMR spectra for the reported compounds.

Acknowledgements

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ORCID® iDs

Dmitry Dar'in - https://orcid.org/0000-0002-0413-7413

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