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Base-Catalyzed Synthesis of Flavones *via* Thiol-Assisted Sequential Demethylation/Cyclization of 1-(2-methoxyphenyl)prop-2-yn-1-ones

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Abstract

Flavone and analogues represent an important class of biologically and pharmacologically active substances commonly found in the composition of diverse plants as part of the class of secondary metabolites. Herein, we have demonstrated an efficient and regioselective synthetic strategy for the preparation of functionalized flavones through sequential demethylation/6-*endo*-dig intramolecular cyclization of propyn-1-ones, using catalytic amounts of base in the presence of a thiol, by employing NMP as the solvent. The reactions proceeded smoothly under transition-

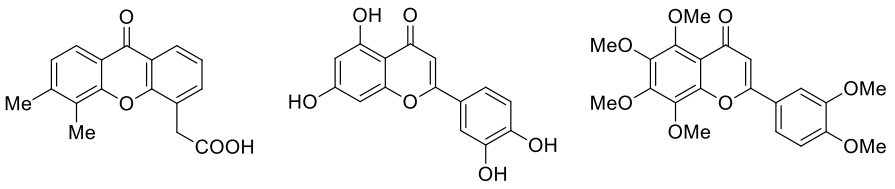
metal-free and open to air conditions, furnishing the desired six-membered heterocycles in moderate to excellent yields, in short reaction time.

Keywords

Flavone; Demethylation; Cyclization; Base-catalysis; Thiol

Introduction

Flavonoids consist in one of the most important family of heterocycles which are ubiquitous in the molecular structure of natural products, especially found in the composition of several herbs, flowers, and cereal grains, as part of the class of secondary metabolites [1] and well known to present anti-inflammatory and antioxidant effects [2]. Among them, 4*H*-chromen-4-one or flavone derivatives are known to present a range of biological and pharmacological properties [3] such as phytotoxic (potentially new herbicides) [4], antibacterial [5], and potential anticancer activity [6]. Vadimezan [7], Luteolin [8], and Nobiletin [9] (Figure 1) are examples of pharmacologically active flavones that present, among others, anticancer properties.

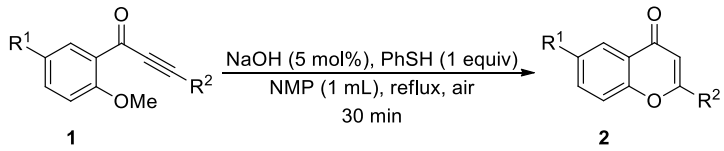


Vamedizan **Luteolin** **Nobiletin**

Figure 1: Pharmacologically active flavone derivatives.

Due their recognized potential to become therapeutic agents, the scientific community has been focused on the development of synthetic strategies to obtain these target substances and consequently several protocols have successfully fulfilled this role [10]. Classical methods include cyclization processes by using

different substrates such as chalcones [11], *o*-alkynoylphenols [12], and 1,3-dicarbonylic compounds [13]. More recently, cyclization approaches promoted by transition-metal salts and electrophilic species have shown high efficiency for the preparation of functionalized flavones [14]. Moreover, reaction systems based on oxidants under metal-free conditions have been employed to promote the cyclodehydrogenation of 2-hydroxychalcones [15]. Despite to the efficacy of the reported protocols, some of them require expensive transition-metal catalysts, additional oxidation steps by using strong oxidants, inert atmosphere, environmentally harmful solvents, and long reaction periods. Alternatively, herein we report the base-catalyzed regioselective synthesis of flavone derivatives **2** via tandem demethylation/6-*endo*-dig intramolecular cyclization of 1-(2-methoxyphenyl)prop-2-yn-1-ones **1** in the presence of thiol, under transition-metal-free and open to air conditions, and short reaction time (Scheme 1).



1 2

Scheme 1: Demethylation/Cyclization of 1-(2-methoxyphenyl)prop-2-yn-1-ones.

Results and Discussion

At the beginning of our studies, we have focused into find out the best set of reaction parameters to promote the cyclization of the 1-(2-methoxyphenyl)-3-phenylprop-2-yn-1-one **1a**, which was chosen as standard substrate due its easy synthesis and good availability. Firstly, the substrate **1a** (0.25 mmol) was submitted to the reaction in the presence of benzenethiol (1 equiv), K_2CO_3 (5 mol%) as the base in NMP (1 mL) as the solvent, under argon at reflux temperature for 30 minutes (Table 1, entry 1). This protocol was previously related to regioselective cleavage of aryl alkyl ethers [16].

Through these conditions the expected flavone **2a** was successfully isolated in 86% yield. In view of this excellent result, we were encouraged to continue with optimization studies and the influence of the temperature was the first evaluated parameter (Table 1, entries 2-4). These experiments have shown that the reaction is strongly dependent on thermal factors since no product was observed and the starting material was totally recovered by varying the temperature from 25 °C to 150 ºC. On the other hand, no influence in the reaction behavior was noticed under aerobic conditions and the desired product **2a** was obtained in 90% yield by carrying out the reaction in an open reaction flask (Table 1, entry 5). The presence of the thiol as well as the base was determinant for the conversion of the substrate and no reaction was observed in the absence of either of these two reagents (Table 1, entries 6 and 7).

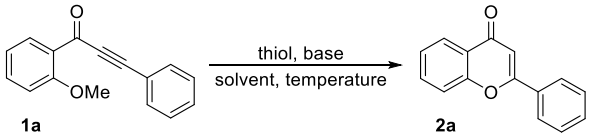
The influence of different solvents was also examined (Table entries 8-13). Aprotic polar solvents such as DMSO and DMF lead to the expected product in 83 and 47% yield, respectively, while MeCN did not furnish any product (Table 1, entries 8-10). Polar protic solvents like EtOH and glycerol were also inefficient to form the cyclized product (Table 1, entries 11 and 12). Except for glycerol, these reactions were conducted under the reflux temperature of each solvent which could indicate that not only the nature of the solvent, but also thermic aspects influence these reactions. Though, the presence of a solvent proved to be crucial to the reaction efficiency since when the reaction was carried out using 0.5 mL of benzenethiol in absence of any solvent, no cyclization was observed and the substrate was recovered (Table 1, entry 13).

The use of different inorganic bases was also evaluated (Table 1, entries 14-17). When NaOH, KOH, $NaHCO_3$, and Li_2CO_3 were employed as bases the cyclized product was obtained in reasonable yields, although only by using NaOH an

improvement in the reaction yield was observed and the flavone **2a** was isolated in 95% yield (Table 1, entry 14). Subsequently, some experiments were carried out to verify the reaction behavior by using different amounts of benzenethiol as well as alkyl and aryl-substituted thiols (Table 1, entries 19-22). By using ethanethiol and arylthiols bearing electron-donating (*p*-MeO) and electron withdrawing (*p*-Cl) groups lower yields of the **2a** were achieved (Table 1, entries 20-22). Interestingly, these results are in agreement with the previous observations on the electronic effects of the substituents described by Chakraborti and co-workers [16]. The reaction efficiency has significantly decreased when less than one equivalent of benzenethiol was employed (Table 1, entry 18) and the presence of more than one equivalent also furnished the product in lower yield (Table 1, entry 19). In order to become the cyclization system more attractive in terms of economy we have tried to use only 0.5 mL of NMP as the solvent (Table 1, entry 23), but only 40% yield was obtained after 30 minutes. In addition, the reaction time also demonstrates high influence in the cyclization process since lower yields were observed when the reactions were quenched in less than 30 minutes (Table 1, entries 24 and 25).

Accordingly to the optimization studies the best reaction condition to promote the demethylation/cyclization of the propyn-1-one **1a** consists in the use of NaOH (5 mol%) as the base in the presence of 1 equivalent of benzenethiol in NMP (1 mL) as the solvent, under ambient atmosphere at reflux temperature for 30 minutes. Through this protocol the desired flavone **2a** has been selectively obtained in 95% yield (Table 1, entry 14). The use of catalytic amounts of base, short reaction period and NMP as the solvent, which is considered a biodegradable molecule [17], represents an advantage of this method by concerning economic and environmental aspects.

Table 1: Effect of different reaction parameters on cyclization of **1a**[a].



1a 2a

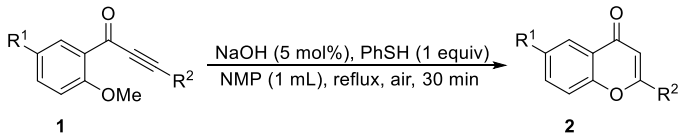
Entry	Thiol (equiv)	Base	Solvent	T ºC	Yield %
1	PhSH (1)	K_2CO_3	NMP	202	86[b]
2	PhSH (1)	K_2CO_3	NMP	r.t.	-[b]
3	PhSH (1)	K_2CO_3	NMP	100	-[b]
4	PhSH (1)	K_2CO_3	NMP	150	-[b]
5	PhSH (1)	K_2CO_3	NMP	202	90
6	-	K_2CO_3	NMP	202	-
7	PhSH (1)	-	NMP	202	-
8	PhSH (1)	K_2CO_3	DMSO	189	83
9	PhSH (1)	K_2CO_3	DMF	153	47
10	PhSH (1)	K_2CO_3	MeCN	82	-
11	PhSH (1)	K_2CO_3	EtOH	78	-
12	PhSH (1)	K_2CO_3	Glycerol	202	-[c]
13	PhSH (19.6)	K_2CO_3	-	169	-[d]
14	**PhSH (1)**	**NaOH**	**NMP**	**202**	**95**
15	PhSH (1)	KOH	NMP	202	68
16	PhSH (1)	$NaHCO_3$	NMP	202	39
17	PhSH (1)	Li_2CO_3	NMP	202	44
18	PhSH (0.6)	NaOH	NMP	202	4
19	PhSH (1.8)	NaOH	NMP	202	81
20	EtSH (1)	NaOH	NMP	202	38
21	4-Cl-C_6H_4SH (1)	NaOH	NMP	202	73
22	4-MeO-C_6H_4SH (1)	NaOH	NMP	202	16

23	PhSH (1)	NaOH	NMP	202	40[e]
24	PhSH (1)	NaOH	NMP	202	46[f]
25	PhSH (1)	NaOH	NMP	202	70[g]

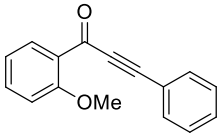
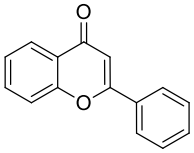
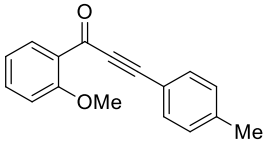
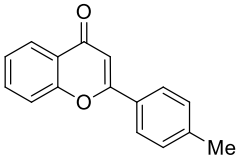
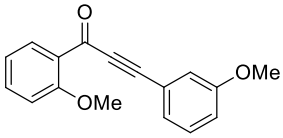
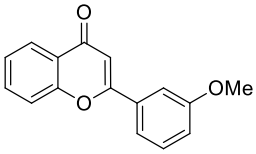
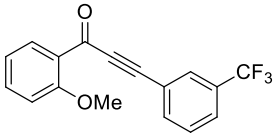
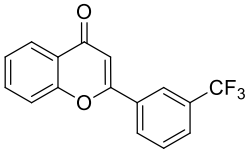
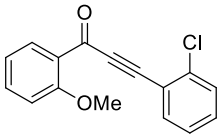
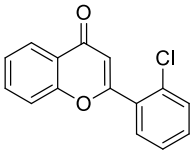
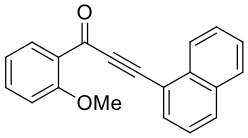
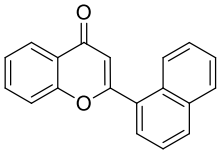
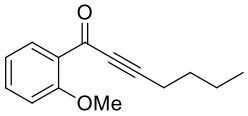
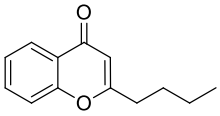
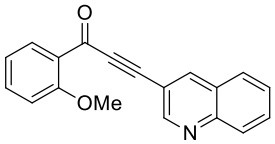
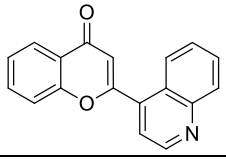
[a]The reaction was carried out using **1a** (0.25 mmol) and the base (5 mol%) in a solvent (1 mL) under air for 30 minutes; yields for isolated product; [b]The reaction was carried out under argon atmosphere; [c]Only traces of **2a** were detected by GC-MS analysis; [d]0.5 mL of PhSH was used; [e]NMP (0.5 mL) was used; [f]The reaction mixture was quenched after 10 minutes; [g]The reaction mixture was quenched after 20 minutes.

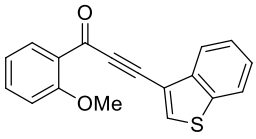
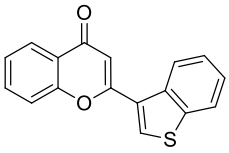
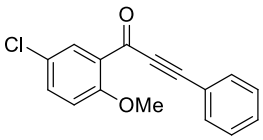
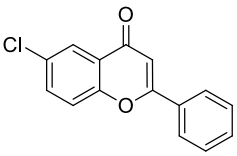
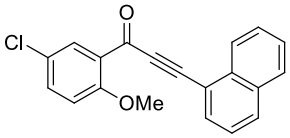
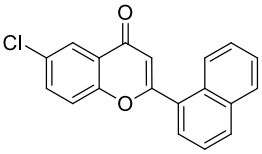
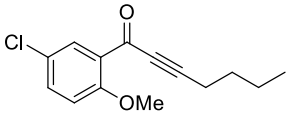
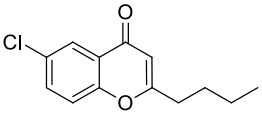
To confirm the coverage and generality as well as to study the limitations of the methodology, we have extended the optimized conditions to several propyn-1-ones **1** bearing different substituents bonded to the carbon-carbon triple bond and into the anisole ring (Table 2). The reaction showed tolerance to electron-donating and electron-withdrawing groups into the aromatic ring bonded to the C*sp* leading to the corresponding products **2b-e** in moderate to good yield (Table 2, entries 2-5). The reaction seems to be no sensitive to steric effects from the substituents into the triple bond, since the presence of a bulky 1-naphthyl group did not provide any disturb in the reaction behavior and the product **2f** was isolated in 89% yield (Table 2, entry 6). The reaction system was also tolerant to an alkyl (*n*-Bu) group bonded to the alkyne furnishing the flavone derivative **2g** in 63% yield (Table 2, entry 7). Both substrates **1h** and **1i** bearing quinolin-4-yl and benzo[*b*]thiophen-3-yl groups bonded to the alkynylic carbon, respectively, have afforded the expected flavone derivatives **2h** and **2i** in moderate yields (Table 2, entries 8 and 9). The reaction system is also compatible in the presence of a chlorine atom into the anisole ring leading to the corresponding flavones **2j-l** in moderate to excellent yields (Table 2, entries 10-12).

Table 2: Regioselective synthesis of flavone derivatives **2**[a].



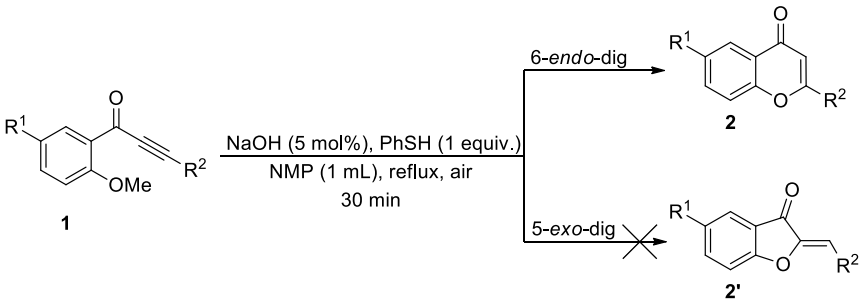
1 2

Entry	Substrate 1	Product 2	Yield %[b]
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	75
3	 **1c**	 **2c**	88
4	 **1d**	 **2d**	55
5	 **1e**	 **2e**	50
6	 **1f**	 **2f**	89
7	 **1g**	 **2g**	63
8			44

		2h	
	1h		
9			34
	1i	**2i**	
10			57
	1j	**2j**	
11			93
	1k	**2k**	41
12			
	1l	**2l**	

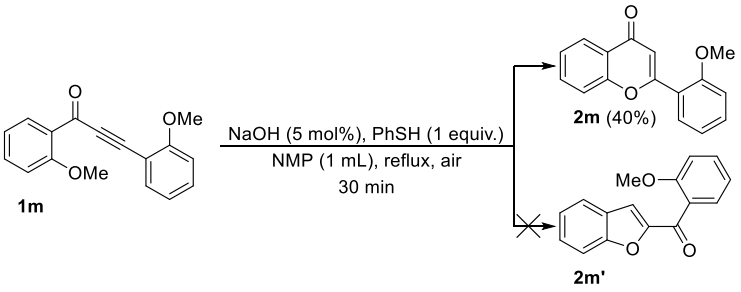
[a]The reaction was carried out using **1** (0.25 mmol), PhSH (1 equiv), NaOH (5 mol%) as the base in NMP (1 mL) as the solvent, under air at reflux temperature for 30 min; [b]Yields for isolated products.

Importantly, the demethylation/cyclization system has shown high regioselectivity affording exclusively six-membered heterocycles **2** through sequential demethylation and intramolecular 6-*endo*-dig cyclization processes. The possible competitive 5-*exo*-dig cyclization to give the benzofuranone derivatives **2'** was not observed in any experiment during the optimization studies neither in the scope development (Scheme 2).



Scheme 2: Regioselectivity of the demethylation/cyclization.

Besides that, the synthetic methodology has also proved to be regioselective in terms of the demethylation step since only the expected flavone **2m** was obtained in 40% yield when the propyn-1-one **1m** was submitted to the best reaction condition, and the benzo[*b*]furan **2m'** was not detected (Scheme 3). This result is probably explained by the major electrophilic character of the C*sp* at the *β*-position from the carbonyl group (Figure 2, A). Still, the resonance electron-donation of the methoxy group *ortho* to the carbonyl moiety decreases the electron density on the CH_3 (Figure 1), which foments the nucleophilic attack of the thiolate ion (Figure 2, B). These, in turn, leads to flavone **2m**, rather than benzo[*b*]furan **2m'**.



Scheme 3: Synthesis of the flavone **2m**.

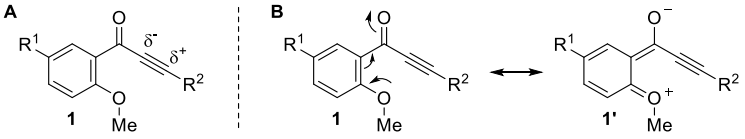
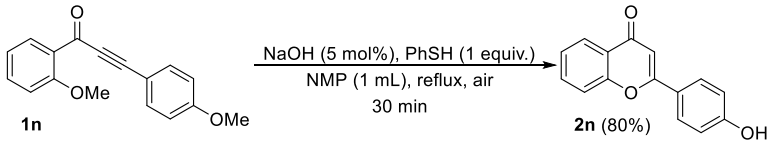
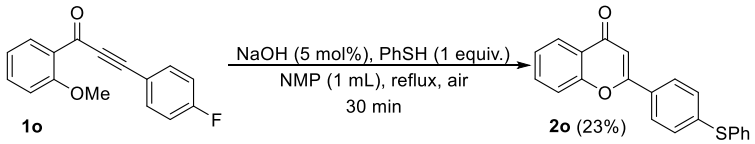


Figure 2. Electron density on the triple bond and methoxy electron-donating effect.

Still trying to extend the scope of the synthetic approach, the propyn-1-ones **1n** and **1o** bearing a methoxy group and a fluorine atom, respectively, at the *para*-position of the benzene ring bonded to the triple bond were tested under same conditions and in both reactions off-beat products were obtained. The reaction of the substrate **1n** leads to the 2-(4-hydroxyphenyl)-4*H*-chromen-4-one **2n** in 80% yield (Scheme 4) indicating the occurrence of a secondary demethylation reaction. When the propyn-1-one **1o** reacted with thiolate ion, the 2-(4-(phenylthio)phenyl)-4*H*-chromen-4-one **2o** was isolated in a moderate yield (Scheme 5). This result indicates a side aromatic nucleophilic substitution reaction through replacement of the fluorine atom by a thiophenyl group at the *para*-position of the benzene ring.



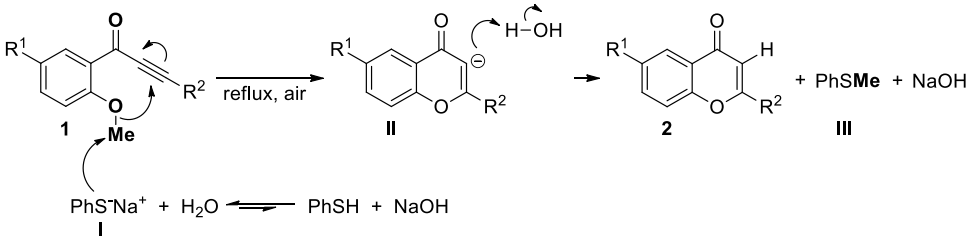
Scheme 4: Synthesis of the flavone derivative **2n**.



Scheme 5: Synthesis of the flavone derivative **2o**.

Based on the literature [16,18] and in the experimental data we believe that a plausible reaction pathway to these transformations involves a typical acid-base equilibrium between the benzenethiol and NaOH to form the thiolate anion **I**; demethylation step proceeds by the nucleophilic attack of the thiolate **I** to the methyl group of the substrate **1** and initiates the sequential cyclization reaction by the nucleophilic attack of the oxygen electron lone pair to the C*sp* of the triple bond to afford the anionic intermediate **II**, which undergoes carbanion protonation leading to the flavone derivative **2** and the thioanisole **III**, regenerating the base catalyst

(Scheme 6). To supporte this proposal, the thioanisole **III** was observed during the optimization and scope studies by GCMS analysis of the crude reaction mixtures.



Scheme 6: Plausible reaction mechanism.

Conclusion

An alternative and synthetic approach for the preparation of flavone derivatives has been described through base-catalyzed sequential demethylation/intramolecular cyclization of propyn-1-ones in the presence of thiols, using NMP as the solvent, under transition-metal-free and open to air conditions in short reaction time. The methodology has shown tolerance to several electron-donating and withdrawing groups bonded to the aromatic rings of the substrates as well as the presence of an alkyl substituent at the C*sp* of the carbon-carbon triple bond, affording the desired products in moderate to excellent yields. The intramolecular cyclization reactions have proceeded with high regioselectivity furnishing only six-membered heterocycles via 6-*endo*-dig ring closure. Regarding the economic and environmental aspects, the use of catalytic amounts of an inorganic base, a biodegradable solvent, the short reaction period, and ambient atmosphere represent advantages that deserve to be highlighted.

Supporting Information

Supporting Information File 1:

File Name: Supplementary Material

File Format: .pdf

Title: Experimental Procedures, MS and NMR Data, and Spectra

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