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Thiazolium-Mediated Multicomponent Reactions: A Facile Synthesis of 3-Aminofuran Derivatives

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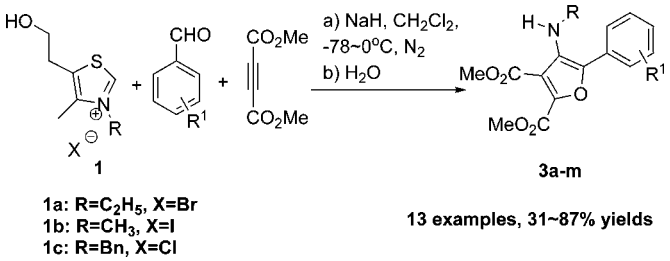
ABSTRACT



A facile synthesis of highly functionalized 3-aminofuran derivatives by the multicomponent reactions of thiazolium salts, aldehydes, and DMAD is described.

Substituted furans play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals[1] but also as useful building blocks in synthetic chemistry.[2] While many synthetic routes for furan synthesis exist, convergent annulation strategies without transition-metal catalysis are uncommon.[3,4]

The nucleophilic character of diheteroatom-substituted carbenes offers opportunities for constructing substituted heterocyclic compounds and has attracted considerable attention in recent years.[5,6] Very recently, Nair and coworkers reported interesting multicomponent reactions of diaminocarbenes with dimethyl acetylenedicarboxylate (DMAD) and aldehydes for the synthesis of oxymaleate and furanose derivatives.[7] Inspired by their account, a convergent method for furan synthesis by thiazolium salts **1** mediated multicomponent reactions was sought. Here, we report that the thiazol-2-ylidene **2**,[8] generated in situ from thiazolium

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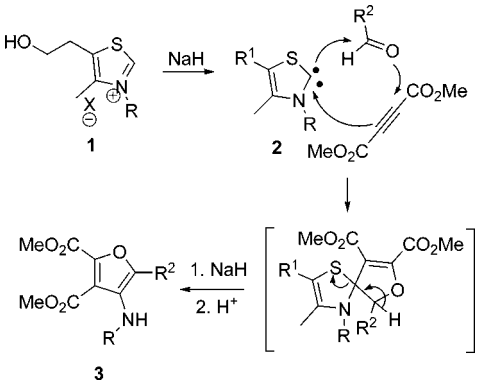
salts **1**, could undergo a sequential three-component nucleophilic attack process leading to polysubstitued 3-aminofurans **3** (Scheme 1).

Scheme 1. Thiazolium-Mediated Multicomponent Reaction for the Synthesis of 3-Aminofuran Derivatives 3



This unique tandem reaction process is particularly attractive in two factors. One is the in situ generation and sequential nucleophlic addition of thiazol-2-ylidene **2** with the aldehyde and DMAD to form the spirocyclic intermediate through the simultaneous formation of two C−C bonds and a C−O bond. The other is the selective ring opening of the spirocycle intermediate followed by hydrolyzation to furnish 3-aminofurans **3**.[9]Although the thiazolium-catalyzed acylation has shown general utility in synthetic organic chemistry,[10,11] to the best of our knowledge, the participation of thiazolium salts **1** in multicomponent reactions[12] has not been reported so far. As many thiazolium salts are commercially available or readily synthesized from commercial materials,[13] this method represents a powerful protocol for the convergent construction of substituted furans.

The reaction was initially carried out by exposing DMAD and 4-nitrobenzaldehyde to thiazol-2-ylidene **2a**, generated in situ by the deprotonation of thiazolium salt **1a** with sodium hydride in THF at 0 °C under a nitrogen atmosphere. To our surprise, a facile reaction leading to the formation of 3-aminofuran derivative **3a** occurred (eq 1).[14] The product **3a** was characterized by spectroscopic analysis. It is noteworthy that the ^{13}C NMR signals for the two ester carbonyls of **3a** were seen at δ 163.5 and 158.2 ppm.[15] Final proof for the structure assigned for **3a** was derived from single-crystal X-ray analysis (Figure 1).

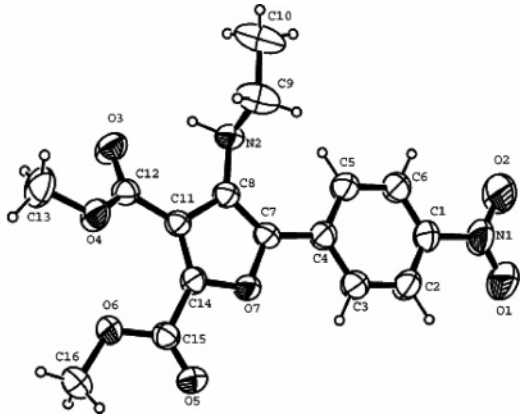
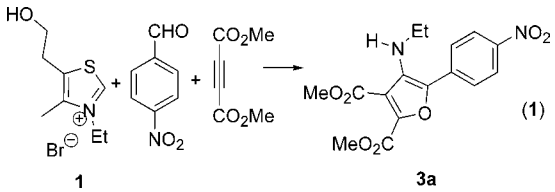


Figure 1. ORTEP representation of the crystal structure of **3a**.

An initial survey of solvents demonstrated that CH_2Cl_2 is the solvent of choice (Table 1, eq 1). Furthermore, we found

Table 1. Effect of Reaction Conditions on the Thiazolium-Mediated Multicomponent Reaction for the Synthesis of **3a**[a]



1 3a

entry	solvent	base	equiv	T (°C)	time (h)	yield[b] (%)
1	THF	NaH	4	0	3	32
2	DMSO	NaH	4	rt	5	0
3	CH_2Cl_2	*t*-BuOK	4	0	3	29
4	CH_2Cl_2	DBU	4	0	5	0
5	CH_2Cl_2	NaH	4	0	3	45
6	CH_2Cl_2	NaH	4	−78	4[c]	61
7	CH_2Cl_2	NaH	2	−78	4[c]	54

[a] Aldehyde (0.5 mmol), **1** (1 mmol), and DMAD (0.75 mmol). [b] Isolated yield based on starting aldehyde. [c] -78 °C, 2 h; then 0 °C, 2 h.

(8) The mechanism which is generally accepted for thiazolium-catalyzed reaction was proposed by Breslow, where thiazol-2-ylidene **2** was thought to act as the actual catalyst. An alternative mechanistic model based on the formation of carbene dimers was presented by Lemal et al. and extended by López Calahorra et al. in the 1980s. For the competing models, see: (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. (b) Lemal, D. M.; Lovaid, R. A.; Kawano, K. I. *J. Am. Chem. Soc.* **1964**, *86*, 2518. (c) Castells, J.; López Calahorra, F.; Domingo, L. *J. Org. Chem.* **1988**, *53*, 4433.

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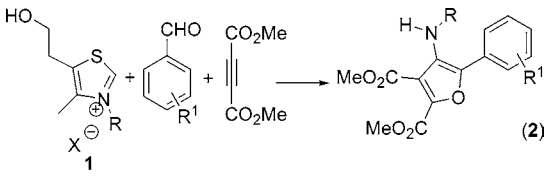
that sodium hydride is the optimum base, and we typically employ an excess (4 equiv) to ensure complete consumption of the reactants. However, it is possible to use as little as 2 equiv of sodium hydride and achieve complete conversion and moderate yield (entry 7). It was shown that the reaction temperature has a dramatic effect on the yield of **3a** (entries 6 and 7) due to the stability of carbene or reaction intermediates at lower temperatures.

In subsequent investigations, we discovered that the reaction demonstrates wide scope with respect to the aryl aldehyde, and the 3-aminofuran derivatives **3a**−**m** were obtained in moderate to good yields (Table 2, eq 2). Electron-deficient aldehydes performed much better than their electron-rich counterparts; 4-methoxybenzaldehyde required longer reaction times relative to the parent compound (entry 9). The reaction was also tolerant to the thiazolium salts. Other commercial available thiazolium salts 1**b** and 1**c** were also tested in this reaction to afford the corresponding furans. Due to the solubility of 1**b** and 1**c** in CH_2Cl_2, the yields of furans **3j**−**m** were lower than the **1a** counterparts (entries 10−13).[16]

Table 2. Multicomponent Reactions of Thiazolium Salts **1** and Aryl Aldehydes with DMAD for the Synthesis of 3-Aminofuran Derivative **3a**−**m**[a]



entry	thiazolium salt **1**	R^1	product **3**	yield[b] (%)
1	**1a**	4-NO_2	**3a**	61
2	**1a**	3-NO_2	**3b**	65
3	**1a**	2-Cl	**3c**	74
4	**1a**	4-Cl	**3d**	69
5	**1a**	4-F	**3e**	87
6	**1a**	2,3-difluoro	**3f**	81
7	**1a**	H	**3g**	62
8	**1a**	4-Me	**3h**	51
9[c]	**1a**	4-MeO	**3i**	31
10[c]	**1b**	4-F	**3j**	73
11	**1b**	H	**3k**	52
12	**1b**	4-Me	**3l**	41
13	**1c**	4-F	**3m**	32

[a] Reagents and reaction conditions: (1) NaH (2 mmol), **1** (1 mmol), CH_2Cl_2, −78 °C, 15 min; then solution of aldehyde (0.5 mmol), DMAD (0.75 mmol), 2 h; 0 °C, 2 h; (2) $NaHCO_3$ (aq). [b] Isolated yield based on starting aldehyde. [c] After 2 h at −78 °C, then 0 °C, 6 h.

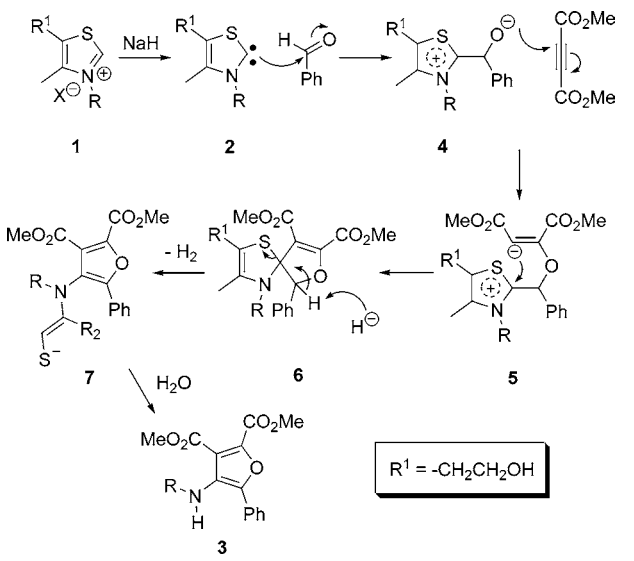
(14) Only trace benzoin condensation product was found in the reaction mixture.

(15) In contrast to 2-aminofuran analogues, the ^{13}C NMR signals for the two ester carbonyls were seen at δ 165.20 and 164.62 ppm; see ref **4a**.

(16) It should be noted that in entries 10−13 no further attempt was made to optimize these reactions

At our present level of understanding, a plausible reaction sequence that accounts for the thiazolium salt mediated multicomponent reaction is shown in Scheme 2. Thus, the initial event in this reaction is the addition of carbene **2** to the aldehyde to form an zwitterion **4**.[7] The resulting zwitterion **4** undergoes a conjugate addition to DMAD, followed by intramolecular annulation to give spirocycle intermediate **6**. Then, selective ring opening of the latter afforded free thiol **7**. It seems that an elimination to the formation of aromatic furan provides the driving force for the C−S bond breaking.[17] Finally, the unstable free thiol **7** was hydrolyzed to furnish furan derivative **3**.

Scheme 2



In conclusion, a facile and mechanistically novel protocol via thiazolium salts mediated multicomponent reactions for the synthesis of substituted 3-aminofurans has been developed. Future studies will focus on the development of related transformations, and the application of this methodology toward the synthesis of furan-containing natural products and photoluminescent materials.

Acknowledgment. We thank Prof. Dr. Y. J. Pan and Dr. J. M. Gu for HRMS and X-ray diffraction analysis, respectively.

Supporting Information Available: Crystallographic information files (CIF) for 3-aminofuran derivative **3a** and experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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