An Efficient Synthesis of 2-Aminofuran-3-carbonitriles via Cascade Stetter–γ-Ketonitrile Cyclization Reaction Catalyzed by *N*-Heterocyclic Carbene

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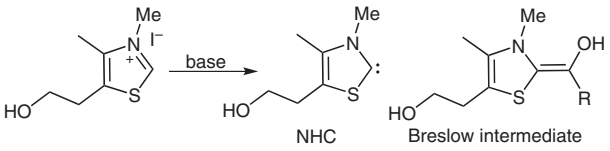
Abstract: An efficient method for the synthesis of 4,5-disubstituted 2-aminofuran-3-carbonitriles via a cascade Stetter–γ-ketonitrile cyclization reaction of aromatic aldehydes with acylidenemalononitriles, catalyzed by N-heterocyclic carbenes, has been developed. This procedure provides the corresponding products in moderate to high yields under mild conditions.

Key words: N-heterocyclic carbenes (NHCs), umpolung, cascade reaction, Stetter reaction, 2-aminofuran

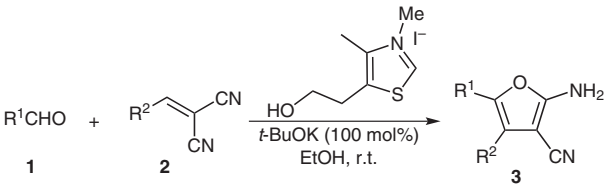
Ever since the discovery of a stable carbene,[1] the N-heterocyclic carbenes (NHCs) have attracted considerable attention due to their inversion of the classical reactivity (umpolung).[2] It is generally accepted that these umpolung reactions proceed with the addition of a Breslow intermediate (Scheme 1) to various electrophilic reagents, such as aldehydes[3] and Michael acceptors.[4] Recently, the use of some new electrophilic reagents as acceptors have been reported in umpolung reactions involving ketones,[5] aziridines,[6] nitroalkenes,[7] and imines.[8]



Scheme 1 NHC and a Breslow intermediate

Cascade reactions, which allow two or more reactions to occur consecutively in one-pot, have attracted intense interest in recent years.[9] The products of the Stetter reaction are usually 1,4-bifunctional molecules,[4] such as 1,4-diketones, 4-keto esters, and 4-keto nitriles, which are useful in many synthetic transformations.[10] However, to the best of our knowledge, few cascade reactions involving the Stetter reaction have been reported. Very recently, Gravel et al.[11] reported an NHC-catalyzed cascade Stetter–Michael reaction for the synthesis of indanes and cascade Stetter–aldol–Michael (SAM) and Stetter–aldol–aldol (SAA) reactions for the synthesis of spiro bis-indanes; Ye et al.[12] reported a cascade Stetter–Aldol reaction for the synthesis of 4-hydroxytetralones. In both cases, the intermediates formed by the addition of aldehydes to Michael acceptors were used to attack another electrophile to complete the cascade reactions. We hypothesized the Stetter intermediates might attack electrophiles of Michael acceptors and cyclize to 2-aminofurans when α,β-unsaturated nitriles are used as Michael acceptors (Scheme 2).

2-Aminofurans and their derivatives are useful intermediates in the synthesis of several heterocyclic compounds, such as 4*H*-furo[2,3-*f*]-pyrrolo[1,2-*a*][1,4]diazepines[13] and isoindolinedinones.[14] Several approaches have been developed for the synthesis of 2-aminofurans, including the reaction of α-hydroxyketone with malononitrile[15] and the acid-catalyzed cyclization of phenacylmalononitriles.[16] In general, however, the previous methods using α-hydroxyketone and malononitrile are limited to the preparation of only a few compounds because cyclization to the corresponding hydroxypyrroles was likely to take place in many cases.[15] In order to access a variety of 2-aminofurans, the phenacylmalononitriles need to be synthesized beforehand, and this method often leads to low yields.[16] Therefore, more efficient methods are required to synthesize this motif from simple and readily available starting materials. We, herein, wish to develop an efficient cascade Stetter–γ-keto nitrile cyclization reaction from aromatic aldehydes **1** and acylidenemalononitriles **2** to generate 2-aminofuran-3-carbonitriles **3** catalyzed by NHCs (Scheme 2).



Scheme 2 Cascade Stetter–γ-keto nitrile cyclization of aromatic aldehydes and acylidenemalononitriles

To test the feasibility of our envisaged approach, we initially examined the reaction of benzaldehyde (**1a**) and 2-benzylidenemalononitrile (**2a**) catalyzed by NHC generated from thiazolium salt **4c** in the presence of the base *t*-BuOK in tetrahydrofuran (THF). We were delighted to obtain the desired product **3a** in 38% yield. A series of

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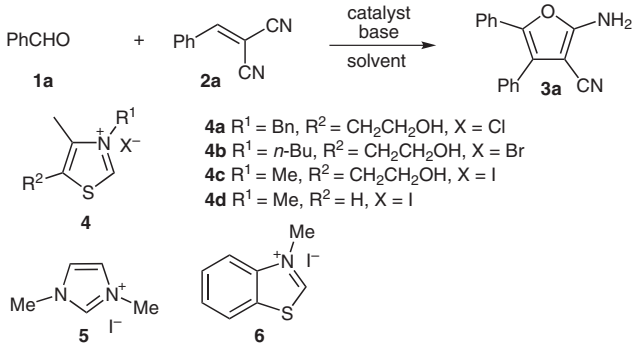
thiazolium salts **4a**–**d**, **6** and imidazolium salt **5** were then tested (Table 1, entries 1–6). The results showed that by using imidazolium **5** (Table 1, entry 5) as a precursor, the reaction did not give any observable product. A slightly lower yield of the desired product **3a** was isolated when thiazolium salt **4d** (Table 1, entry 4) was used in the reaction. However, the catalysts derived from thiazolium salts **4a** and **4b** (Table 1, entries 1 and 2) failed to give any product, despite the structural similarity of **4a**, **4b**, and **4c**. From the point of view of economy and yield, thiazolium salt **4c** was chosen to be the precatalyst for the further reactions. The catalyst loading was also investigated. When the amount of precatalyst **4c** was reduced to 40%, the reaction resulted in lower yield (Table 1, entry 7), but the employment of 60% **4c** did not increase the yield (Table 1, entry 8).

As summarized in Table 1, different solvents and bases were examined for the reaction. Among the bases tested (NaH, K_2CO_3, Et_3N, and DBU) in this reaction (Table 1, entries 9–12), *t*-BuOK was found to be optimal in terms of yield. Several polar solvents (MeOH, MeCN and EtOH) all led to good yields (Table 1, entries 13, 14, and 17) and the reaction in EtOH gave the best yield (65%). According to the above results, the optimal reaction conditions were obtained as follows: in the presence of thiazolium salt **4c** (50 mol%) and *t*-BuOK (100 mol%), the reactions were carried out in EtOH at room temperature.

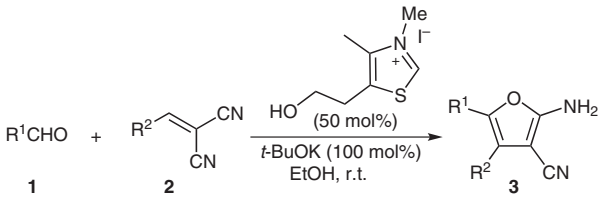
Table 1 Optimization of Reaction Conditions for the Formation of Representative Compound **3a**[a]



Entry	Precat. (mol%)	Base	Solvent	Yield (%)[b]
1	**4a** (50)	*t*-BuOK	THF	–[c]
2	**4b** (50)	*t*-BuOK	THF	–[c]
3	**4c** (50)	*t*-BuOK	THF	38
4	**4d** (50)	*t*-BuOK	THF	25
5	**5** (50)	*t*-BuOK	THF	–[c]
6	**6** (50)	*t*-BuOK	THF	–[c]
7	**4c** (40)	*t*-BuOK	THF	15
8	**4c** (60)	*t*-BuOK	THF	32
9	**4c** (50)	K_2CO_3	THF	trace
10	**4c** (50)	NaH	THF	20
11	**4c** (50)	Et_3N	THF	trace
12	**4c** (50)	DBU	THF	30
13	**4c** (50)	*t*-BuOK	MeOH	42
14	**4c** (50)	*t*-BuOK	MeCN	46
15	**4c** (50)	*t*-BuOK	CH_2Cl_2	–[c]
16	**4c** (50)	*t*-BuOK	Toluene	trace
17	**4c** (50)	*t*-BuOK	EtOH	65

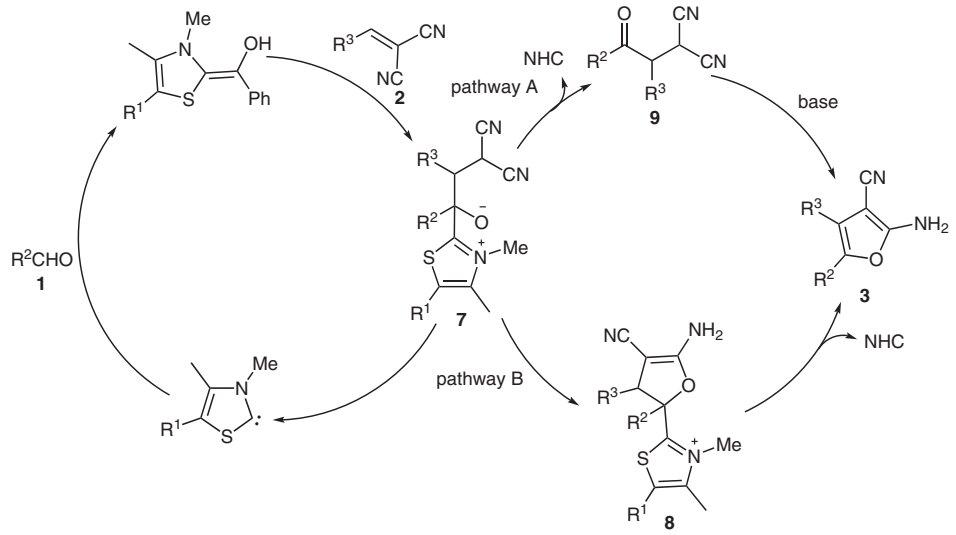
[a] Reaction conditions: benzaldehyde (1.0 mmol), 2-benzylidenemalononitrile (1.0 mmol), base (1.0 mmol), solvent (5.0 mL), r.t., 1 h.
[b] Isolated yield.
[c] No products were detected.

Table 2 Reaction of Aromatic Aldehydes with Acylidenemalononitriles to Generate 2-Aminofuran-3-carbonitriles[a]



Entry	R^1	R^2	Product **3**	Yield (%)[b]
1	Ph	Ph	**3a**	65[c]
2	4-$MeOC_6H_4$	Ph	**3b**	34[d]
3	2-Furyl	Ph	**3c**	68
4	4-FC_6H_4	Ph	**3d**	75
5	2-ClC_6H_4	Ph	**3e**	73
6	3-ClC_6H_4	Ph	**3f**	74
7	4-ClC_6H_4	Ph	**3g**	77
8	4-BrC_6H_4	Ph	**3h**	69
9	2,4-$Cl_2C_6H_3$	Ph	**3i**	80
10	4-CNC_6H_4	Ph	**3j**	82
11	Ph	4-$MeOC_6H_4$	**3k**	62[c]
12	4-ClC_6H_4	4-$MeOC_6H_4$	**3l**	75
13	2,4-$Cl_2C_6H_3$	4-$MeOC_6H_4$	**3m**	82
14	4-CNC_6H_4	4-$MeOC_6H_4$	**3n**	85
15	Ph	4-ClC_6H_4	**3o**	68[c]
16	4-ClC_6H_4	4-ClC_6H_4	**3p**	77
17	2,4-$Cl_2C_6H_3$	4-ClC_6H_4	**3q**	83
18	4-CNC_6H_4	4-ClC_6H_4	**3r**	85

[a] Reaction conditions: **1**/**2**/*t*-BuOK = 1:1:1 mmol, EtOH (5 mL), r.t., 0.5 h.
[b] Isolated yield.
[c] Reaction time: 1 h.
[d] Reaction time: 2 h.



Scheme 3 Two possible pathways to product **3**

With the optimal reaction conditions identified, we then examined the use of a variety of functionalized aldehydes **1** and acylidenemalononitriles **2** to assess the generality and scope of this reaction. The reactions of various aromatic aldehydes **1** (Table 2, entries 1–9) with 2-benzylidenemalononitrile (**2a**) were examined under the optimal conditions mentioned above. It was found that the use of aldehydes with electron-withdrawing substituents (Table 2, entries 4-10) usually led to good yields. On the other hand, aldehydes bearing electron-donating groups (Table 2, entry 2) gave low yield. It was interesting to find that 2-chlorobenzaldehyde (Table 2, entry 5) proved to be slightly less reactive than 4-chlorobenzaldehyde (Table 2, entry 7), which meant that steric factors did not affect the reactivity greatly.

Various acylidenemalononitriles **2** (Table 2, entries 11 and 15), which were easily prepared by Knoevenagel condensation,[17] bearing halogen or alkoxyl substituents in the *para* position of the phenyl ring were also tested in the reaction, and the results showed that the nature of the substituents did not affect the yields greatly.

On the basis of the above results, a tentative mechanism is depicted in Scheme 3. Aldehyde **1** reacts with carbene to give the Breslow intermediate, which attacks the acylidenemalononitrile **2** to afford the Stetter intermediate **7**. This intermediate then releases the NHC to generate the Stetter product **9**. Finally, the Stetter product **9** cyclizes to form the final product **3** in the presence of a base (Scheme 3, pathway A). Besides this mechanism, there may be an alternative pathway (Scheme 3, pathway B), starting from the Stetter intermediate **7** that generates the product **3** in a manner similar to that reported by Ye and co-workers.[12] In this pathway, intermediate **7** undergoes the cyclization reaction with NHC attached, followed by release of NHC to generate the final product **3**.

In conclusion, a cascade Stetter–γ-keto nitrile cyclization reaction of aromatic aldehydes and acylidenemalononitriles has been developed to synthesize 4,5-disubstituted 2-aminofuran-3-carbonitriles.[18] Aromatic and heteroaromatic aldehydes are successfully employed to afford 2-aminofuran-3-carbonitriles **3** in moderate to good yields by using an inexpensive catalyst under mild conditions.

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(18) General procedure for the synthesis of 4,5-disubstituted 2-aminofuran-3-carbonitriles **3**: A flame-dried, round-bottom flask was charged with thiazolium salt **4c** (0.5 mmol), aromatic aldehyde **1** (1.0 mmol), acylidenemalononitrile **2** (1.0 mmol), and EtOH (5 mL) under a positive pressure of nitrogen, followed by addition of *t*-BuOK (1.0 mmol). The resulting solution was stirred for 0.5–2 h at r.t. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether–EtOAc, 6:1) to afford the product **3**.