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ACID-MEDIATED CYCLIZATION OF 3-BENZOYL-2-CYANO-BUTYRONITRILE TO 2-AMINO-4-METHYL-5-PHENYLFURAN-3-CARBONITRILE

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Abstract - Cyclization of 3-benzoyl-2-cyanobutyronitrile to 2-amino-4-methyl-5-phenylfuran-3-carbonitrile was effected under acidic conditions, rather than the basic conditions previously reported. Since treatment with trifluoroacetic acid (TFA) at room temperature is very mild, 2-amino-4-methyl-5-phenylfuran-3-carbonitriles containing various functional groups can be accessed *via* this route.

Substituted 2-aminofuran-3-carbonitriles are useful intermediates in the synthesis of furo[2,3-*b*]-pyrimidines and furo[2,3-*b*]pyridines.[1] There have been many reports on the synthesis of 2-aminofuran-3-carbonitriles,[2] most of them involving the cyclization of phenacylmalononitrile, mediated by base. Synthesis of functionalized 2-aminofuran-3-carbonitriles, according to a previously reported procedure (Et_2NH, DMF),[3] was attempted without success. Various conditions were investigated to promote the required cyclization and it was discovered that cyclization could be accomplished by treatment with acid. In this communication, an improved method for the synthesis of 2-amino-4-methyl-5-phenylfuran-3-carbonitrile (**2a**) is reported and the scope of this reaction is discussed.

In order to promote the cyclization, activation of the nucleophilic species (ketone) or electrophilic species (nitrile) is required (Scheme 1). Most of the previously reported cyclizations were induced by activation of the ketone, which was converted to enol form under basic conditions (**A**). However the electrophilic cyano group was deactivated by deprotonation because the acidity of the α-proton of malononitrile moiety was higher than that of the carbonyl function. This deactivation obstructed the desired cyclization. It was assumed that activation of nitrile could be accomplished by protonation of the nitrogen in acidic media (**C**), and the carbonyl oxygen could then attack the highly activated nitrile group (**D**).

Dedicated to Professor L. A. Paquette on the occasion of his 70th birthday.

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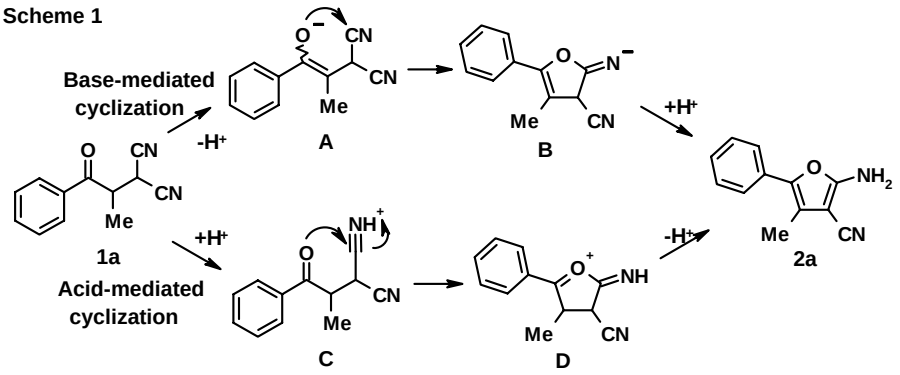
Scheme 1



3-Benzoyl-2-cyanobutyronitrile (**1a**) was treated with various acids (Table 1). It has been previously reported that when counter anions were highly nucleophilic, intermolecular attack of the counter anion on the nitrile was the predominant pathway to provide pyrrole derivatives (X=Cl, Br).[4] In the case of trifluoroacetic acid (TFA) and trifluoromethanesulfonic acid (TfOH), the desired compound (**2a**) was obtained in 77% and 52% yields respectively. Since the trifluoroacetate anion and trifluoromethane sulfonate anion are very weak nucleophiles, intramolecular attack by the carbonyl oxygen proceeded. When **1a** was treated with H_2SO_4 and AcOH respectively, the desired compound (**2a**) was not formed. Among the conditions examined, TFA gave the optimal results.

Scheme 2

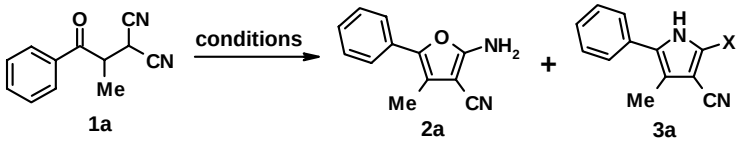


Table 1 Cyclization of 1a[a)]

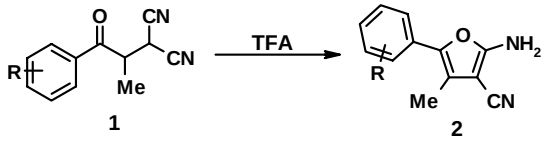
conditions	Yield	
	2a	3a
HCl, EtOH	—	49% (X=Cl)
HBr, AcOH	—	41% (X=Br)
TFA	77%	—
CF_3SO_3H [b)]	52%	—
H_2SO_4 [b)]	Decomposed	
AcOH [c)]	No reaction	

a) All reactions were carried out at room temperature unless otherwise noted.
b) Reactions were carried out at 0 ℃
c) up to 110 ℃

In order to investigate the scope of this reaction, the effect of substituents on the aromatic ring was examined (Table 2).[5] Whether electron withdrawing groups or electron donating groups were attached to the phenyl ring, the reactions proceeded at room temperature. Reaction time was dependent on the substituent on the phenyl ring (completion of the reaction was monitored by TLC or HPLC). Assuming that the reaction rate can be estimated by the reaction time, the order of reaction rate was OMe=OBn>H>Cl>CF_3>CO_2Me>SO_2Me. These results can be explained by examining the

nucleophilicity of the carbonyl oxygen. Electron donating groups increased the electron density of the carbonyl oxygen, and the reaction rate increased. In contrast, electron withdrawing groups decreased the reaction rate. In addition, a greater decrease in reaction rate was observed with electron withdrawing groups at the 4-position on the phenyl ring, than at the 3-position (Table 2 runs 5 and 6, 7 and 8). Therefore, these results indicate that cyclization occurs with the keto form, as opposed to the enol form (Scheme 1, **C**).

Scheme 3



1 **2**

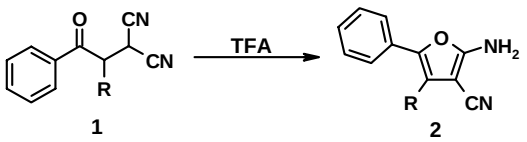
Table 2 Effect of substituents [a)]

run	R	Yield of 2
1	2-OMe	60%
2	2-OBn	70%
3	4-Cl	45%
4	4-CF_3	47%
5	3-CO_2Me	47%
6	4-CO_2Me	37%
7	3-SO_2Me [b)]	49%
8	4-SO_2Me [c)]	26%

a) All reactions were carried out at room temperature unless otherwise noted.
b) Reaction was carried out at room temperature for 24 h then at 50 °C for 4 h.
c) Starting material was recovered at 33% yield.

To expand the synthetic utility of this reaction, other substituents at the 4-position of furan ring were examined (Table 3). The reactions of compounds containing ethyl, isopropyl and phenyl groups were investigated in a similar manner, and furan (**2**), which contains an acetate group in the 4-position, was synthesized at 66% yield.

Scheme 4



1 **2**

Table 3 Synthesis of 2 having various substituents at 4-position [a)]

R	Yield of 2
Me	77%
Et	82%
i-Pr	51%
Ph	65%
CH_2CO_2Me	66%

a) All reactions were carried out at room temperature.

In conclusion, an improved synthetic route for the synthesis of 2-aminofuran-3-carbonitriles was identified. Acid-mediated cyclization is promoted using TFA and proceeds under mild reaction conditions, which provides access to many functionalized 2-aminofuran-3-carbonitriles.

General Procedure; 3-Benzoyl-2-cyanobutyronitrile (**1a**; 2.0 g, 10.1 mmol) was cooled in an ice-water bath while TFA (10 mL) was carefully added. The solution was stirred at rt for 1 h. Concentration, drying followed by crystallization (AcOEt-hexane) of the resulting solid afforded 1.54 g (77% yield) of 2-amino-4-methyl-5-phenylfuran-3-carbonitrile (**2a**).

REFERENCES AND NOTE

1. (a) T. I. Temnikova, Y. A. Sharanin, and V. S. Karavan, *Org. Khim.*, 1967, **3**, 681. (b) M. M. Ali, Y. A. Zahran, Y. A. Ammar, A. T. Mohamed, and A. T. Seleim, *Indian J. Heterocycl. Chem.*, 1995, **126**, 191. (c) C. C. Lockhart and J. W. Sowell, *J. Heterocycl. Chem.*, 1996, **33**, 659. (d) F. M. Abdelrazek and A. M. Salah, *Egypt. J. Chem.*, 1997, **40**, 105.
2. (a) A. O. Abderhamid, A. M. Negm, and I. M. Abbas, *J. Prakt. Chem.*, 1989, **331**, S.31. (b) J. G. Jun, *Bull. Korean Chem. Soc.*, 1996, **17**, 676. (c) X. Feng, J. C. Lancelot, H. Prunier, and S. Rault, *J. Heterocycl. Chem.*, 1996, **33**, 2007.
3. X. Feng, J. C. Lancelot, A. C. Gillard, H. Landelle, and S. Rault, *J. Heterocycl. Chem.*, 1998, **35**, 1313.
4. L. H. Foley, *Tetrahedron Lett.*, 1994, **35**, 5989.
5. Compound (**1**) having various functional groups was prepared as shown in the following scheme (Scheme 5). Bromination (Br_2, Et_2O) of corresponding ketone followed by substitution with malononitrile gave the compound (**1**).

Scheme 5