One-pot synthesis of substituted 2-amino-3-furonitriles

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Solvent-free reaction of substituted α-haloketones with malononitrile in the presence of diethylamine provides an efficient one-pot synthesis of 2-amino-5-aryl (alkyl)-3-furonitriles in high yield.

Keywords: 2-aminofuronitrile, furo[2,3-*d*]pyrimidine, heterocyclisation, phenacyl bromides

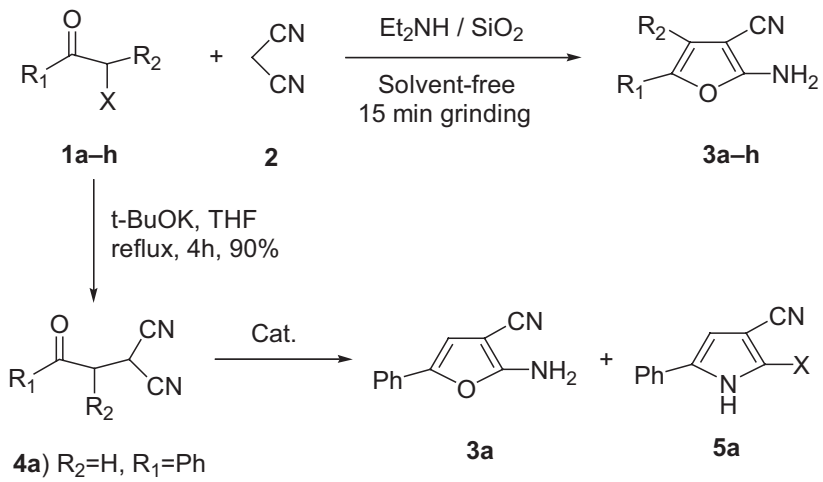
Substituted 2-amino-3-furonitriles are useful intermediates in the synthesis of furo[2,3-*b*]pyridines and furo[2,3-*d*] pyrimidines.[1-7] There have been many reports on the synthesis of polyheterocyclic compounds from these precursors which showed interesting biological activities.[8-13] In the most of the procedures,[8,9,14] a phenacylmalononitrile derivative was prepared from a phenacyl bromide, which then cyclised in the presence of an acid or a base. Acid-catalysed cyclisation of this intermediate gave predominantly a pyrrole derivative.[14,15] Another problem in the synthesis of furan derivatives, is a facile dimerisation of product by way of a Diels–Alder cycloaddition.[16,17] In pursuit of our work on the synthesis of polyheterocyclic systems,[18-22] we report a convenient one-pot synthesis of 2-amino-5-aryl (alkyl)-3-furonitriles (**3a–h**) under solvent-free conditions (Scheme 1).

Results and discussion

Reaction of phenacyl bromide (**1a**) and malononitrile in the presence of potassium *tert*-butoxide in THF gave exclusively the phenacylmalononitrile (**4a**) in 90% yield. Our attempts to convert the latter to furan (**3a**) under different conditions failed. In the case of trifluoroacetic acid (TFA) a mixture of furan and pyrrole derivatives was obtained. Heteropolyacid treatment in different solvents, reaction temperatures and long reaction times were also unsuccessful. We were then tried to find a straightforward procedure to prepare 2-amino-3-furonitriles from phenacyl bromide derivatives. Interestingly, grinding a mixture of phenacyl bromide derivatives (**1a–h**) and malononitrile in the presence of diethylamine furnished exclusively the 2-amino-5-aryl (alkyl)-3-furonitriles (**3a–h**) as shown in Scheme 1 and Table 1. In these reactions only furans were obtained in high yields without any byproduct formation such as pyrrole or furan-dimer. In the presence of other bases such as pyridine and triethylamine, the conversion decreased and a mixture of products was obtained.

The structures of new compounds were confirmed by spectral data. For example, the IR spectrum of **3f** was devoid of the stretching vibration bands at 1700 cm^{-1} for carbonyl absorption of the phenacyl bromide but instead showed new absorption bands at 3400, 3320 and 2200 cm^{-1} for amine and nitrile groups, respectively. The ^1H NMR spectra in d_6-DMSO showed a broad singlet at 8.40 ppm due to NH_2 group as well as characteristic signals corresponding to *m*-nitro-aryl group protons. The furan proton gave a singlet at 6.95 ppm. The Mass spectrum of the compound showed the molecular ion peak at *m/z* 229 corresponding to the (M^+). This compound gave a satisfactory elemental analysis data.

In conclusion, we have developed a facile method for the one pot synthesis of 2-amino-5-aryl (alkyl)-3-furonitriles through base-catalysed cyclocondensation of phenacyl bromide derivatives and malononitrile. Compared to the current syntheses of 2-amino-furan-3-carbonitriles, we have developed a simple and highly efficient method for one-pot synthesis of the title compounds under solvent-free conditions. The efficiency of the present work is apparent from high yields with the lack of side products.



Cat.:		
TFA, RT, 1 h	60 %	40 %
$H_3PW_{12}O_{40}$, EtOH, reflux, 5 h		No reaction
$H_3PW_{12}O_{40}$, Solvent-free, 30 min		No reaction
$H_3PW_{12}O_{40}$, MW,10 min		No reaction

Scheme 1

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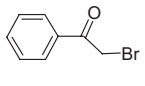
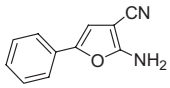
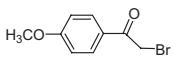
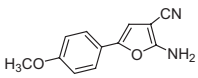
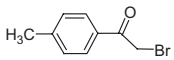
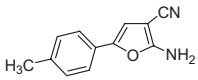
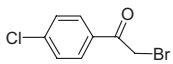
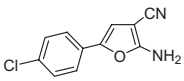
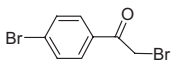
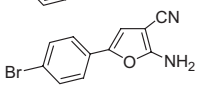
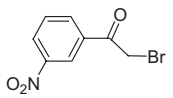
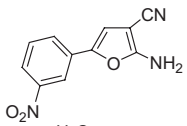
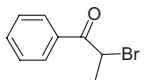
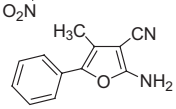
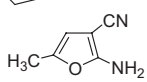
Table 1 Synthesis of 2-amino-3-furonitriles under solvent-free conditions[a]

Entry	α-Haloketone	2-Amino-3-furonitrile	Isolated yield/%	M.p./°C[b]	
	1	**3**		Found	Lit.[ref]
a			80	200–201	200[23]
b			75	213–215	214–215[24]
c			70	218–220	220–222[24]
d			85	224–225	24–226[24]
e			90	229–230	228–229[24]
f			65	200–201	–
g			70	155–157	158[23]
h			60	154–156	156–158[25]

[a]The products were characterised by comparison of their IR and ^{1}H NMR spectroscopic data and their melting points are compared with reported values.
[b]In all cases the products melt with decomposition.

Experimental

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analyses was obtained on a Thermo Finnigan Flash EA microanalyser.

General procedure for the synthesis of 2-amino-5-aryl(alkyl)-3-furonitriles (**3a–h**)

A mixture of phenacyl bromide derivatives (**1a–h**) (2 mmol), malononitrile (0.13 g, 2 mmol), SiO_2 (1.0 g) and diethylamine (0.44 g, 6 mmol) was ground in a mortar for 15 min. After the completion of the reaction (monitored by TLC $CHCl_3$:CH_3OH 9:1), the reaction mixture was washed with chloroform (30 ml). The organic layer was washed with water (2 × 30 ml), dried over $MgSO_4$ and evaporated. The crude product was recrystallised from ethanol to give compounds (**3a–h**) in 60–90% yields. The 2-amino-5-aryl(alkyl)-3-furonitriles **(3a–e** and **3g–h)** prepared are known compounds and were characterised by comparison of their physical and spectral data with those reported in the literature.[8-14, 23-25]

2-Amino-5-(3-nitrophenyl)-3-furonitrile (**3f**): Compound **3f** was obtained in 65% yield; yellow solid; m.p. 200–201 °C; IR (KBr, ν_{max}/cm^{-1}): 3400 (NH), 3320 (NH), 2200 (CN), 1650 (NH_2), 1530 (NO_2), 1350 (NO_2). ^{1}H NMR (DMSO-d^6, 100 MHz) δ: 6.95 (s, 1H, Furan H), 7.55 (t, 1H, J = 8 Hz, ArH–H_5), 8.05 (td, 1H, J_1 = 8 Hz, J_2 = 1.5 Hz, ArH–H_6), 8.15 (td, 1H, J_1 = 8 Hz, J_2 = 1.5 Hz, ArH–H_4), 8.25 (t, 1H, J = 1.5 Hz, ArH–H_2), 8.40 (br s, 2H, NH_2). MS: *m/z* 229 (M^+, 45), 194 (35), 183 (25), 125 (55), 107 (63), 93 (71), 77 (100), 65 (45). Found: C, 57.42; H, 2.97; N, 18.64. Calcd for $C_{11}H_7N_3O_3$ (229): C, 57.65; H, 3.08; N, 18.33%.

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