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 onepot 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-3furonitriles 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 d₆-DMSO showed a broad singlet at 8.40 ppm due to NH₂ 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.

Scheme 1

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

Entry	α-Haloketone 1	2-Amino-3-furonitrile	Isolated yield/%	M.p./°Cb	
				Found	Lit. ^{ref}
а	Br	CN ONH ₂	80	200–201	200 ²³
b	H ₃ CO-Br	H ₃ CO NH ₂	75	213–215	214–215 ²⁴
c	H ₃ C	H ₃ C NH ₂	70	218–220	220-222 ²⁴
d	CI——Br	CI ONH2	85	224–225	24–226 ²⁴
е	Br———Br	Br CN	90	229–230	228–229 ²⁴
f	O ₂ N Br	ONH ₂	65	200–201	-
g	O Br	O ₂ N H ₃ C CN NH ₂	70	155–157	158 ²³
h	OCI	H ₃ C O NH ₂	60	154–156	156–158 ²⁵

^aThe products were characterised by comparison of their IR and ¹H NMR spectroscopic data and their melting points are compared with reported values.

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 ¹H 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)-3furonitriles (3a-h)

A mixture of phenacyl bromide derivatives (1a-h) (2 mmol), malononitrile (0.13 g, 2 mmol), SiO₂ (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 CHCl₃: CH₃OH 9:1), the reaction mixture was washed with chloroform (30 ml). The organic layer was washed with water (2 × 30 ml), dried over MgSO₄ 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, 23-2

2-Amino-5-(3-nitrophenyl)-3-furonitrile (3f): Compound 3f was obtained in 65% yield; yellow solid; m.p. 200-201°C; IR (KBr, $v_{\rm max}/{\rm cm^{-1}}$): 3400 (NH), 3320 (NH), 2200 (CN), 1650 (NH₂), 1530 (NO₂), 1350 (NO₂). ¹H NMR (DMSO-d⁶, 100 MHz) δ : 6.95 (s, 1H, Furan H), 7.55 (t, 1H, J = 8 Hz, ArH-H₅), 8.05 (td, 1H, $J_1 = 8$ Hz, $J_2 = 1.5 \text{ Hz}$, ArH-H₆), 8.15 (td, 1H, $J_1 = 8 \text{ Hz}$, $J_2 = 1.5 \text{ Hz}$, ArH-H₄), 8.25 (t, 1H, J = 1.5 Hz, ArH-H₂), 8.40 (br s, 2H, NH₂). 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 C₁₁H₇N₃O₃ (229): C, 57.65; H, 3.08; N, 18.33%.

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^bIn all cases the products melt with decomposition.