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Microwave accelerated Gewald reaction: synthesis of 2-aminothiophenes☆

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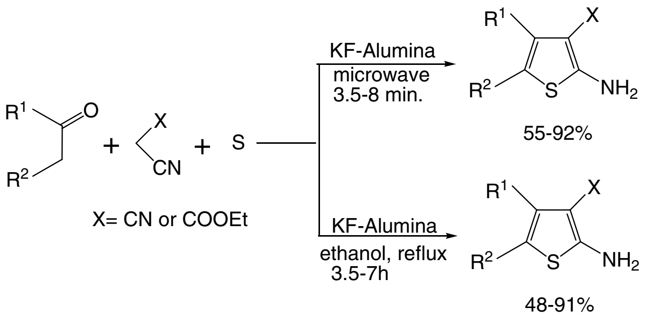
Abstract—Microwave-promoted synthesis of 2-aminothiophenes by multicomponent reactions of a ketone with an active nitrile and elemental sulfur under KF-alumina catalysis is described.

Substituted 2-aminothiophenes are important intermediates in the synthesis of a variety of agrochemicals, dyes and pharmacologically active compounds.[1] The most convergent and well-established classical approach for the preparation of 2-aminothiophenes is Gewald's method,[2] which involves multicomponent condensation of a ketone with an activated nitrile and elemental sulfur in the presence of morpholine as a catalyst.

Heterogeneous organic reactions using reagents immobilized on porous solid supports have often been proved to be advantageous over conventional solution phase reactions because of good dispersion of active reagent sites, better selectivity and easier work-up. One such reagent is KF immobilized on alumina (or KF-alumina).[3] The application of KF-alumina to a wide range of organic reactions has provided more convenient and efficient methods in organic syntheses.[4] Its benefits arise from the strongly basic nature of KF/Al_2O_3, which has allowed it to replace organic bases in a number of reactions.[5]

The high efficacy and ease of product isolation prompted us to investigate the Gewald reaction but replacing the organic base with KF-alumina and using microwave irradiation for heating (Scheme 1).



Scheme 1.

In the present study, a variety of ketones were reacted with ethyl cyanoacetate (or malononitrile) and elemental sulfur in the presence of KF-alumina as catalyst. This reaction was studied both under microwave irradiation as well as conventional heating conditions by refluxing in ethanol (Table 1). In both the cases, the reaction proceeded well producing 2-aminothiophene derivatives in moderate to good yields.

The general procedure is as follows: cyclohexanone (0.98 g, 1.0 mmol), ethyl cyanoacetate (1.13 g, 1.0 mmol), sulfur (0.32 g, 1.0 mmol), KF-alumina (1:1 w/w, 0.2 g) and 1.5 ml of dry ethanol were mixed and placed in a 10 ml pressure tube. The mixture was subjected to microwave irradiation (CEM Discover, 100 W, 250 psi, 100 °C) for 3.5 min and then diluted with dichloromethane (5 ml) and filtered. The solid was rinsed/triturated with dichloromethane (2 × 2.5 ml)

Keywords: 2-Aminothiophene; KF-alumina catalysis; Microwave-assisted synthesis.

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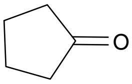
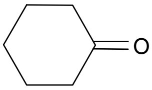
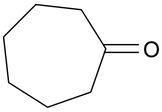
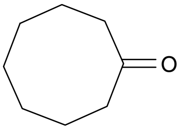
Table 1.

Entry	Ketone		X	Reaction conditions		Melting point (°C)
	R^{1}	R^{2}		Microwave[a] Yield (%) (Reaction time, min)	Conventional[a] Yield (%) (Reaction time, h)	
1			COOEt	56 (6.0)	52 (7.0)	91[b]
2			CN	57 (8.0)	55 (5.5)	151
3			COOEt	91 (6.0)	89 (3.5)	115[b]
4			CN	92 (6.0)	91 (3.5)	147[b]
5			COOEt	85 (6.0)	75 (3.5)	89
6			CN	86 (6.0)	81 (3.5)	126
7			COOEt	58 (7.0)	55 (4.0)	81
8			CN	62 (5.5)	60 (4.0)	110
9	CH_3	CH_3	CH_3	57 (3.5)	53 (4.0)	92[b]
10	CH_3	CH_3	CH_3	61 (3.5)	56 (4.0)	142[b]
11	CH_3	COOEt	COOEt	58 (3.5)	50 (4.0)	108[b]
12	CH_3	COOEt	CN	58 (3.5)	55 (4.0)	151
13	Ph	H	COOEt	61 (7.5)	55 (4.0)	98[b]
14	Ph	H	CN	66 (7.5)	61 (4.0)	142
15	H	CH_3	COOEt	62 (6.0)	55 (4.0)	46[b]
16	H	Et	COOEt	55 (6.0)	48 (4.0)	73[b]

[a] Isolated yields. All the products gave satisfactory ^{1}H NMR, mass and IR spectra.

[b] These values were identical with the literature report.[2]

and the combined extracts were concentrated and purified by normal chromatography to afford the corresponding 2-aminothiophene as a pale yellow solid (2.04 g, 91%, mp 115 °C). The product gave satisfactory IR, ^{1}H NMR and mass spectral data. In the case of conventional heating, the reactants, as above in 15 ml ethanol, were heated at reflux for 6 h. When the reaction was complete (TLC), ethanol was removed by evaporation and the reaction mixture was diluted with 10 ml of dichloromethane and filtered. After evaporation of the solvent, the mixture was purified by normal column chromatography to give the desired product in 89% yield (mp 115 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.4 (t, $J = 7.5$, Hz, 3H), 1.8 (m, 4H), 2.5 (m, 2H), 2.7 (m, 2H), 4.25 (q, $J = 7.0$, Hz, 2H), 5.95 (br s, 1H); exact mass $C_{11}H_{15}NO_2SNa$ (+Na): 248.0730 (calcd: 248.0721).

In conclusion, the present study is the first application of KF-alumina as a base for the preparation of 2-aminothiophenes by microwave accelerated multi-component condensation. This method offers an efficient and convenient modification to the Gewald reaction as it could be carried out with very short reaction times under microwave irradiation. Alternatively, the present reaction also proceeds well under conventional heating by refluxing in ethanol.

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References and notes

1. Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocycl. Chem.* **1999**, *36*, 333–345.
2. Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber.* **1966**, *99*, 94–100.
3. Clark, J. H. *Chem. Rev.* **1980**, *80*, 429–452; Apsimon, J. W.; Hooper, J. W.; Laishes, B. A. *Can. J. Chem.* **1970**, *48*, 3064–3075; Villemin, D.; Ricard, M. *Tetrahedron Lett.* **1984**, *25*, 1059–1060.
4. Blass, B. E. *Tetrahedron* **2002**, *58*, 9301–9320.
5. For some recent work see: Kabalka, G. W.; Wang, L.; Namboodiri, V.; Pagni, R. M. *Tetrahedron Lett.* **2000**, *41*, 5151–5154; Yadav, V. K.; Babu, K. G.; Mittal, M. *Tetrahedron* **2001**, *57*, 7047–7051; Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 108–110; Blass, B. E.; Harris, C. L.; Portlock, D. E. *Tetrahedron Lett.* **2001**, *42*, 1611–1613; Rissafi, B.; El Louzi, A.; Loupy, A.; Petit, A.; Soufiaoui, M.; Tétouani, S. F. *Eur. J. Org. Chem.* **2002**, 2518–2523; Basu, B.; Das, P.; Bhuiyan, M. D. H.; Jha, S. *Tetrahedron Lett.* **2003**, *44*, 3817–3820; Chhibber, M. *Synlett* **2004**, 197–198; Yang, L.; Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2005**, *46*, 3279–3282.