Indian Journal of Chemistry
Vol. 45B, April 2006, pp. 1051-1053

# Note

## Microwave-assisted solvent-free Friedlander synthesis of 1,8-naphthyridines using ammonium acetate as catalyst

K Mogilaiah* & J Uma Rani

Department of Chemistry Kakatiya University,
Warangal 506 009, India
E-mail: mogilaiah_k@yahoo.co.in

*Received 3 January 2005; accepted (revised) 22 February 2005*

The microwave enhanced synthesis of 1,8-naphthyridines **3** is achieved rapidly and in good yield via the Friedlander condensation of 2-aminonicotinaldehyde **1** with carbonyl compounds containing α-methylene group **2** in the presence of ammonium acetate.

**Keywords**: Friedlander synthesis, 1,8-naphthyridines, microwave synthesis, ammonium acetate

**IPC: Int.Cl.[7] C 07 D**

1,8-Naphthyridine derivatives are of considerable interest because of their possible biological activities[1-3]. For these reasons their synthesis has always attracted the attention of synthetic organic chemists. Among the variety of strategies for the construction of 1,8-naphthyridine moiety, one of the most important methods is Friedlander condensation of 2-aminonicotinaldehyde with carbonyl compounds containing α-methylene group in the presence of an acid[4] or base[5] catalyst. This method has limitations such as harsh reaction conditions, longer reaction time period and tedious work-up. Therefore, it is important to develop a simple and environmentally safe solvent-free method to synthesize 1,8-naphthyridine derivatives. In recent years, considerable interest has emerged in microwave induced reactions[6,7] and solvent-free organic synthesis mediated by microwave irradiation[8,9] offers significant advantages. In view of this and in continuation of our ongoing programme to develop synthetic protocols utilizing inorganic reagents under microwave irradiation[10-13], herein, we report a novel solvent-free synthesis of 1,8-naphthyridines which utilizes the relatively benign reagent such as ammonium acetate and a clean energy source, microwave irradiation.

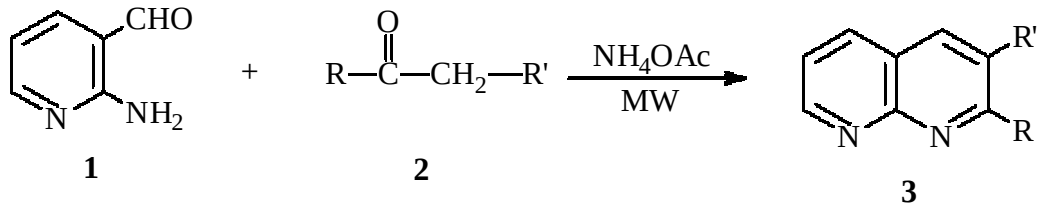
The Friedlander condensation of 2-aminonicotinaldehyde **1** with carbonyl compounds containing α-methylene group **2** in the presence of ammonium acetate under solvent-free condition and microwave irradiation afforded 1,8-naphthyridines **3** in good yield (80-92%) in a short reaction time period (2-5 min) (**Scheme I**).

That the effect may not be purely thermal is supported by the fact that, in the case of the microwave assisted reactions, the product yield (92%) was not attainable at 140°C when the same reaction was subjected to conventional heating in an oil-bath at the same temperature; only poor yield of the product (15%) was obtained with incomplete consumption of the starting material (compound **3a**, **Table I**). Further, we find that the microwave-assisted reactions are more efficient, convenient and cleaner.

The present high yielding protocol for the preparation of 1,8-naphthyridines provides a better alternative to the existing methods due to its shorter reaction time period, simpler reaction procedure and the formation of cleaner products that can be used for synthetic applications without further purification. All the compounds prepared were characterized by IR and $^1$H NMR spectroscopy and finally by comparison with authentic samples[5,14-17].

To our best knowledge, this is the first report on the use of ammonium acetate as catalyst in the Friedlander synthesis of 1,8-naphthyridines under solvent-free and microwave irradiation.

In conclusion, a simple, rapid and high yielding microwave-accelerated method for the Friedlander synthesis of 1,8-naphthyridines is developed under solvent-free conditions using ammonium acetate.




**1** **2** **3**

| **3** | R | R′ | **3** | R | R′ |
|---|---|---|---|---|---|
| **a** | $CH_3$ | $COCH_3$ | **g** | $CF_3$ | $COOC_2H_5$ |
| **b** | $CH_3$ | $COC_6H_5$ | **h** | OH | $COOC_2H_5$ |
| **c** | $C_6H_5$ | $COC_6H_5$ | **i** | $C_6H_5$ | $COOC_2H_5$ |
| **d** | $CH_3$ | $C_6H_5$ | **j** | $CH_3$ | $C_6H_5NHCO$ |
| **e** | H | $C_6H_5$ | **k** | $C_6H_5$ | $C_6H_5NHCO$ |
| **f** | $CH_3$ | $COOC_2H_5$ | | | |

**Scheme I**

**Table I** — Microwave-assisted preparation of 1,8-naphthyridines **3**

| Compd | Reaction time (min) | Yield (%) | m.p. °C | Lit. m.p. °C | Mol. formula |
|---|---|---|---|---|---|
| **3a** | 2 | 92 | 146 | 146-47[5] | $C_{11}H_{10}N_2O$ |
| **3b** | 2.5 | 84 | 143 | 143[15] | $C_{16}H_{12}N_2O$ |
| **3c** | 3 | 82 | 161 | 160[15] | $C_{21}H_{14}N_2O$ |
| **3d** | 5 | 80 | 129 | 128-29[15] | $C_{15}H_{12}N_2$ |
| **3e** | 5 | 86 | 126 | 126-27[5] | $C_{14}H_{10}N_2$ |
| **3f** | 3 | 90 | 86 | 85-6[5] | $C_{12}H_{12}N_2O_2$ |
| **3g** | 3.5 | 88 | 125 | 125[17] | $C_{12}H_9N_2O_2F_3$ |
| **3h** | 2.5 | 84 | 206 | 205-07[5] | $C_{11}H_{10}N_2O_3$ |
| **3i** | 3.5 | 86 | 104 | 104[16] | $C_{17}H_{14}N_2O_2$ |
| **3j** | 3 | 85 | 215 | 215[14] | $C_{16}H_{13}N_3O$ |
| **3k** | 3.5 | 83 | 279 | 280[16] | $C_{21}H_{15}N_3O$ |

## Experimental Section

Melting points were measured with a Cintex melting point apparatus and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer; and $^1H$ NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard. Analytical TLC was performed on Merk 60F-254 silica gel plates. Irradiation was carried out in domestic microwave oven (LG MG-556p, 2450 MHz).

**General procedure for the preparation of 1,8-naphthyridines 3**. A mixture of 2-aminonicotinaldehyde **1** (0.01 mole), the active methylene compound **2** (0.01 mole) and ammonium acetate (0.01 mole) was transferred into a 25 mL Erlenmeyer flask and irradiated in a domestic microwave oven (400 W) for the specific period of time as indicated in **Table I**. After completion of the reaction (monitored by TLC), the contents of the flask were cooled to room temperature and treated with cold water (50 mL). The precipitated solid was filtered, washed with water and recystallized from a suitable solvent to afford **3**.

## Acknowledgement

The authors are grateful to the Director, Indian Institute of Chemical Technology, Hyderabad, India for providing $^1H$ NMR spectra.

## References


1 Roma G, Braccio M D, Grossi G, Mattioli F & Ghia M, *Eur J Med Chem,* 35, **2000**, 1021.

2 Badawneh M, Ferrarini P L, Calderone V, Manera C, Martinotti E, Mori C, Saccomanni G & Testai L, *J Med Chem,* 36, **2001**, 925.

3 Leonard J T, Gangadhar R, Gnanasam S K, Ramachandran S, Saravanam M & Sridhar S K, *Biol Pharm Bull,* 25, **2002**, 798.

4 Thummel R P & Kohli D K, *J Heterocyclic Chem,* 14, **1977,** 685.

5 Hawes E M & Wibberley D G, *J Chem Soc (C),* **1966**, 315.

6 Caddick S, *Tetrahedron,* 51, **1995,** 10403.

7 Lidstrom P, Tierney J, Wathey B & Westman J, *Tetrahedron,* 57, **2001**, 9225.

8 Loupy A, Petit A, Hamelin J, Taxier-Boullet F, Jacquau P & Mathe D, *Synthesis,* **1998**, 1213.

9 Varma R S, *J Heterocyclic Chem,* 36, **1999**, 1565.

10 Mogilaiah K & Reddy N V, *Synth Commun,* 33, **2003**, 73.

11 Mogilaiah K & Reddy N V, *Synth Commun*, 33, **2003**, 1067.

12 Mogilaiah K, Prashanthi M, Reddy G R, Reddy Ch S & Reddy N V, *Synth Commun,* 33, **2003**, 2309.

13 Mogilaiah K & Reddy G R, *Synth Commun,* 34, **2004**, 205.

14 Reddy K R, Mogilaiah K & Sreenivasulu B, *J Indian Chem Soc,* 64, **1987,** 193.

15 Rao G R, Mogilaiah K & Sreenivasulu B, *Indian J Chem,* 27B, **1988**, 200.

16 Rao G R, Mogilaiah K & Sreenivasulu B, *Indian J Chem,* 35B, **1996**, 339.

17 Mogilaiah K, Rao R B & Reddy K N, *Indian J Chem,* 38B, **1999**, 818.