Al₂O₃ catalyzed Friedlander synthesis of 1, 8-naphthyridines in the solid state

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

Received 4 April 2007; accepted (revised) 18 July 2007

Al₂O₃ catalyzes efficiently the Friedlander condensation of 2-aminonicotinaldehyde 1 with various carbonyl compounds containing α-methylene group 2 in the solid state at room temperature to afford the corresponding 1,8-naphthyridines 3. The reaction proceeds efficiently at room temperature in good yields and in a state of high purity.

Keywords: Friedlander synthesis, 1,8-naphthyridines, Al₂O₃, 2-aminonicotinaldehyde, carbonyl compounds containing α-methylene group, solid state

Friedlander synthesis is an acid or base catalyzed condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone with the carbonyl compound containing a reactive α-methylene group. 2-Aminonicotinaldehyde condenses readily with active methylene compounds in the presence of basic Al₂O₃ to give 1,8-naphthyridine derivatives. However, these methods suffer from drawbacks such as long reaction times, high temperature and low yields. Therefore, it is important to develop a simple and environmentally safe, solvent free method to synthesize 1,8-naphthyridine derivatives.

Solid state reaction without using harmful organic solvents is of great interest especially in relation to environmental concerns today. So, the grinding method has increasingly been used in organic synthesis in recent years. Compared to traditional methods, many organic reactions occur more efficiently in the solid state than in solution and in some cases even more selectively. Furthermore, the solid state reaction has many advantages: reduction pollution, low costs and simplicity in process and handling.

In view of this and in continuation of our interest on solid state organic transformations, herein we wish to report basic Al₂O₃ catalyzed Friedlander condensation under solid state grinding conditions at room temperature.

The Friedlander condensation of 2-aminonicotinaldehyde 1 with various carbonyl compounds containing α-methylene group 2 in the presence of basic Al₂O₃ in the solid state at room temperature resulted in the formation of the corresponding 1,8-naphthyridines 3 (Scheme 1). Reactions are not time consuming and the yields of the products are good. The experimental procedure is very simple. The process is environmentally benign.

In a typical case, an equimolar mixture of 1, acetoacetanilide 2a (R = CH₃; Ar = C₆H₅NH) and basic Al₂O₃ was ground in a mortar by pestle at room temperature for 8 min. Work-up of the reaction mixture afforded 3a, a white powder (88%), m.p. 215°C (lit.(ref.10) m.p. 215°C). The generality of this facile condensation was established by condensing other active methylene compounds 2b-l with 1 in the presence of basic Al₂O₃ under solid state grinding conditions to get the corresponding 1,8-naphthyridines 3b-l. The results are summarized in Table I.

To the best of our knowledge, this is the first report on rapid Friedlander synthesis of 1,8-naphthyridines using basic Al₂O₃ as catalyst in the solid state at room temperature.

In conclusion, a simple and efficient procedure for the preparation of 1,8-naphthyridines using Al₂O₃ in the solid state at room temperature is demonstrated. The significant advantages of this procedure are: operational simplicity, mild reaction conditions, economic viability, high purity of the products and minimum environmental impact.

Experimental Section
Melting points were determined on a Cintex melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer and ¹H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard.

General procedure for the preparation of 1,8-naphthyridines 3. A mixture of 2-aminonicotinaldehyde 1 (0.01 mole) active methylene compound 2 (0.01 mole) and basic Al₂O₃ (0.01 mole)
was ground by pestle and mortar at room temperature for the period indicated in Table 1. After completion of the reaction (monitored by TLC), the reaction mixture was treated with methanol (30 mL), the alumina is filtered off, and the filtrate was treated with cold water. The solid separated was filtered and recrystallized from appropriate solvent to afford 3 (Table 1). The products were characterized by IR and ¹H NMR data and finally by comparison with authentic samples¹⁰⁻¹².

**IR and ¹H NMR spectral data for selected compounds**

3a: IR (KBr): 3248 (NH), 1679 (C=O), 1602 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆) : δ 2.92 (s, 3H, CH₃), 8.32 (m, 2H, C₄-H, C₅-H), 9.10 (m, 1H, C₇-H), 7.03-7.82 (m, 6H, Ar-H), 10.38 (s, 1H, NH).

3f: IR (KBr): 3200 (NH), 1655 (C=O), 1600 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆) : δ 8.10 (s, 1H, C₄-H), 8.65 (m, 1H, C₅-H), 7.86 (m, 1H, C₆-H), 9.16 (m, 1H, C₇-H), 6.97-7.78 (m, 10H, Ar-H), 10.25 (s, 1H, NH).

3k: IR (KBr): 1656 (C=O), 1600 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆) : δ 8.10 (s, 1H, C₄-H), 8.65 (m, 1H, C₅-H), 7.86 (m, 1H, C₆-H), 9.16 (m, 1H, C₇-H), 6.97-7.78 (m, 10H, Ar-H), 10.25 (s, 1H, NH).

3l: IR (KBr): 1654 (C=O), 1602 cm⁻¹ (C=N); ¹H NMR (DMSO-d₆) : δ 7.92 (s, 1H, C₄-H), 8.35 (m, 1H, C₅-H), 9.12 (m, 1H, C₇-H), 6.83-7.62 (m, 11H, Ar-H).
Acknowledgement
The authors are thankful to the Director, IICT, Hyderabad for providing $^1$H NMR spectra.

References