Indian Journal of Chemistry
Vol. 46B, October 2007, pp. 1721-1723

Note

Al_2O_3 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

Al_2O_3 catalyzes efficiently the Freidlander condensation of 2-aminonicotinaldehyde **1** with various carbonyl compounds containing α-methylene group **2** in the solid state 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, Al_2O_3, 2-aminonicotin-aldehyde, 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-Aminonicotinaldhyde condense readily with active methylene compounds in the presence of base[1] and acid[2] catalysts 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.[3-5]

In view of this and in continuation of our interest on solid state organic transformations,[6-9] herein we wish to report basic Al_2O_3 catalyzed Friedlander condensation under solid state grinding conditions at room temperature.

The Friedlander condensation of 2-aminonicotinal-dehyde **1** with various carbonyl compounds containing α-methylene group **2** in the presence of basic Al_2O_3 in the solid state at room temperature resulted in the formation of the corresponding 1, 8-naphthyridines **3 (Scheme I)**. 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 = CH_3; Ar = C_6H_5NH) and basic Al_2O_3 was ground in a mortar by pestle at room temperature for 8 min. Work-up of the reaction mixture afforded **3a**, a white power (88%), m.p. 215 (lit.(ref.10) m.p. 215^oC). The generality of this facile condensation was established by condensing other active methylene compounds **2b-l** with **1** in the presence of basic Al_2O_3 under solid state grinding conditions to get the corresponding 1, 8-naphthyridines **3b-l**. The results are summarized in **Table I**.

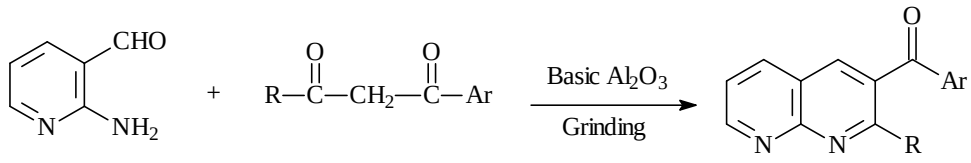
To the best of our knowledge, this is the first report on rapid Friedlander synthesis of 1,8-naphthyridines using basic Al_2O_3 as catalyst in the solid state at room temperature.

In conclusion, a simple and efficient procedure for the preparation of 1,8-naphthyridines using Al_2O_3 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 Al_2O_3 (0.01 mole)



1 **2** **3**

3	R	Ar	**3**	R	Ar
a	CH_3	C_6H_5NH	**g**	C_6H_5	p-$CH_3C_6H_4NH$
b	CH_3	p-$CH_3C_6H_4NH$	**h**	C_6H_5	p-$CH_3OC_6H_4NH$
c	CH_3	p-$CH_3OC_6H_4NH$	**i**	C_6H_5	o-ClC_6H_4NH
d	CH_3	o-ClC_6H_4NH	**j**	C_6H_5	p-ClC_6H_4NH
e	CH_3	p-ClC_6H_4NH	**k**	CH_3	C_6H_5
f	C_6H_5	C_6H_5NH	**l**	C_6H_5	C_6H_5

Scheme I

Table I — 1,8-Naphthyridines **3**

Compd	Reaction time (min)	Yield (%)	m.p. °C		Mol. formula
			Found	Reported	
3a	8	88	215	215(ref.10)	$C_{16}H_{13}N_3O$
3b	12	90	171	170(ref.10)	$C_{17}H_{15}N_3O$
3c	15	86	148	150(ref.10)	$C_{17}H_{15}N_3O_2$
3d	10	88	150	150(ref.10)	$C_{17}H_{12}N_3OCl$
3e	9	92	206	205(ref.10)	$C_{17}H_{12}N_3OCl$
3f	15	88	278	280(ref.12)	$C_{21}H_{15}N_3O$
3g	12	90	277	278(ref.12)	$C_{22}H_{17}N_3O$
3h	14	87	219	218(ref.12)	$C_{22}H_{17}N_3O_2$
3i	15	88	276	277(ref.12)	$C_{21}H_{14}N_3OCl$
3j	11	90	202	201(ref.12)	$C_{21}H_{14}N_3OCl$
3k	7	89	142	143(ref.11)	$C_{16}H_{12}N_2O$
3l	9	87	162	160(ref.11)	$C_{21}H_{14}N_2O$

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 I**). The products were characterized by IR and ^{1}H NMR data and finally by comparison with authentic samples[10-12].

IR and ^{1}H NMR spectral data for selected compounds

3a: IR (KBr): 3248 (NH), 1679 (C=O), 1602 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) : δ 2.92 (s, 3H, CH_3), 8.32 (m, 2H, C_4-H, C_5-H), 9.10 (m, 1H, C_7-H), 7.03-7.82 (m, 6H, C_6-H, 5Ar-H), 10.38 (s, 1H, NH).

3f: IR (KBr): 3200 (NH), 1655 (C=O), 1600 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) : δ 8.10 (s, 1H, C_4-H), 8.65 (m, 1H, C_5-H), 7.86 (m, 1H, C_6-H), 9.16 (m, 1H, C_7-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); ^{1}H NMR (DMSO-d_6) : δ 2.73 (s, 3H, CH_3), 8.45 (m, 2H, C_4-H, C_5-H), 7.93 (m, 1H, C_6-H), 9.00 (m, 1H, C_7-H), 6.98-7.52 (m, 5H, Ar-H).

3l: IR (KBr): 1654 (C=O), 1602 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) : δ 7.92 (s, 1H, C_4-H), 8.35 (m, 1H, C_5-H), 9.12 (m, 1H, C_7-H), 6.83-7.62 (m, 11H, C_6-H, 10Ar-H).

Acknowledgement

The authors are thankful to the Director, IICT, Hyderabad for providing ^{1}H NMR spectra.

References

1 Hawes E M & Wibberley D G, *J Chem Soc(C)*, **1966**, 315.
2 Thummel R P & Kohli D K, *J Heterocycl Chem*, 14, **1977**, 124.
3 Tanaka K & Toda F, *Chem Rev*, 100, **2000**, 1025.
4 Cave G W V, Raston C L & Scott J L, *Chem Commun*, **2001**, 2159.
5 Krchnak V & Holladay M W, *Chem Rev*, 102, **2002**, 61.
6 Mogilaiah K, Babu H R & Reddy N V, *Synth Commun*, 32, **2002,** 2377.
7 Mogilaiah K, Chowdary D S, Reddy P R & Reddy N V, *Synth Commun*, 33, **2003**, 127.
8 Mogilaiah K, Reddy N V & Reddy G R, *Synth Commun*, 33, **2003**, 3109.
9 Mogilaiah K & Reddy G R, *Oxidation Commun*, 27, **2004**, 668.
10 Reddy K R, Mogilaiah K & Sreenivasulu B, *J Indian Chem Soc*, 64, **1987**, 193.
11 Rao G R, Mogilaiah K, Reddy K R & Sreenivasulu B, *Indian J Chem*, 27B, **1988**, 200.
12 Rao G R, Mogilaiah K & Sreenivasulu B, *Indian J Chem*, 35B, **1996**, 339.