

Note

Lithium chloride as an efficient catalyst for Friedlander synthesis of 1,8-naphthyridines via the use of microwave irradiation and pestle/mortar

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An efficient, practical and eco-friendly method of preparation of 1,8-naphthyridines **3** has been reported by Friedlander condensation between 2-aminonicotinaldehyde **1** and active methylene compounds **2** in the presence of lithium chloride in combination with microwave irradiation and also with a pestle and mortar.

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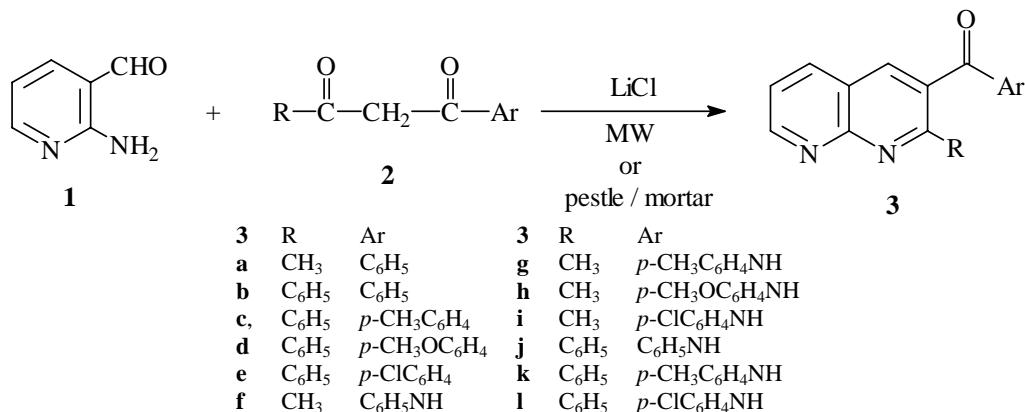
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1,8-Naphthyridines are usually the products of the Friedlander condensation between 2-aminonicotinaldehydes and carbonyl compound containing a reactive α -methylene group in the presence of base¹ or acid² catalysts. Owing to their scanty chemical literature and their real biological and pharmacological applications^{3,4}, these are of special interest. Because of certain limitations (harsh reaction conditions and longer reaction time) associated with the above methods, there exists a scope to develop a practical method for the synthesis

of 1,8-naphthyridines. Moreover, the use of microwave energy to accelerate organic reactions has been taking a new dimension currently and is a matter of increasing interest and offers several advantages⁵⁻⁷. Synthesis of molecules which normally require long reflux time periods can be achieved conveniently and very rapidly in a microwave oven. Solvent-free microwave assisted chemical reactions are gaining importance due to the advantages and environmentally friendly processes they offer, as compared to conventional reactions⁶. In recent years organic reactions in the solid state have been attracting the synthetic organic chemists because of their simplicity and synthetic value^{8,9}. Furthermore, the solid state reaction has many advantages namely, reduced pollution, low costs and simplicity in process and handling. The applications of lithium chloride to organic transformations have been investigated¹⁰⁻¹². To the best of our knowledge, there is no report on the use of LiCl in Friedlander condensation reaction.

In view of this and in continuation of our interest on microwave assisted organic transformations^{11,12} and solid state organic reactions^{13,14} we report herein an efficient, practical and enviro-friendly method for the preparation of 1,8-naphthyridines **3** (**Scheme I**).

The Friedlander condensation of 2-aminonicotinaldehyde **1** with active methylene compounds **2** in the presence of LiCl under microwave irradiation and also by grinding in a mortar afforded the corresponding 1,8-naphthyridines **3**. Both these methodologies are attractive as they are relatively non-toxic, economical, eco-friendly and highly effective.



Scheme I

Table I—1,8-Naphthyridines **3**

Compd	m.p. °C	lit, m.p. °C	MWI		Pestle/Mortar		Mol. formula
			Time (min)	Yield (%)	Time (min)	Yield (%)	
3a	143	143 ¹⁶	3	94	8	86	C ₁₆ H ₁₂ N ₂ O
3b	162	160 ¹⁶	5	92	10	84	C ₂₁ H ₁₄ N ₂ O
3c	161	160 ¹⁶	4	95	12	88	C ₂₂ H ₁₆ N ₂ O
3d	146	148 ¹⁶	5	90	15	82	C ₂₂ H ₁₆ N ₂ O ₂
3e	142	143 ¹⁶	4	96	10	90	C ₂₁ H ₁₃ N ₂ OCl
3f	215	215 ¹⁵	5	98	7	92	C ₁₆ H ₁₃ N ₃ O
3g	172	170 ¹⁵	6	94	12	87	C ₁₇ H ₁₅ N ₃ O
3h	149	150 ¹⁵	6	90	15	83	C ₁₇ H ₁₅ N ₃ O ₂
3i	207	205 ¹⁵	5	95	10	88	C ₁₆ H ₁₂ N ₃ OCl
3j	280	280 ¹⁷	5	88	12	84	C ₂₁ H ₁₅ N ₃ O
3k	277	278 ¹⁷	6	90	15	87	C ₂₂ H ₁₇ N ₃ O
3l	200	201 ¹⁷	5	93	14	88	C ₂₁ H ₁₄ N ₃ OCl

The two non-conventional methods are fairly general, clean, rapid and efficient. The high yield transformations did not form any undesirable by-products. The process is environmentally benign. The purity of the products is high. The experimental procedures are very simple. The microwave procedure is slightly superior to the solid state method in terms of reduced time period and better yields. The results of both the studies are summarized in **Table I**. All the compounds prepared were characterized by spectroscopic data and finally by comparison with authentic samples¹⁵⁻¹⁷.

In conclusion, we have utilized non-conventional methodologies for the Friedlander synthesis of 1,8-naphthyridines using LiCl in conjunction to microwave irradiation and pestle/mortar. Both the methods are attractive due to their simplicity, ease of workability, enhanced yields, reduced reaction time period and practical applicability.

Experimental Section

Melting points were determined in open capillary tubes using Cintex apparatus and are uncorrected. The purity of the compounds was checked on TLC. IR (KBr) spectra were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer; ¹H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard; and mass spectra on a Jeol JMS D-300 spectrometer. The reactions were carried out in a BPL 800 G domestic microwave oven.

Typical procedure utilizing microwave irradiation. LiCl (0.01 mole) was added to a mixture

of 2-aminonicotinaldehyde **1** (0.01 mole) and appropriate active methylene compound **2** (0.01 mole) and mixed thoroughly. The reaction mixture was irradiated in a microwave oven at 700 W for the specific period of time as indicated in **Table I**, the completion of the reaction was monitored by TLC. The reaction mixture was allowed to attain room temperature and digested with water. The resulting precipitate was filtered, washed with water and recrystallized from appropriate solvent to give **3** (**Table I**).

Typical procedure using pestle/mortar. A mixture of **1** (0.01 mole) active methylene compound **2** (0.01 mole) and LiCl (0.01 mole) was ground by pestle and mortar at room temperature for the specific time indicated in **Table I**. On completion of the reaction as monitored by TLC, the mixture was treated with water. The reaction was worked-up as described in the above method.

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