An efficient Friedlander condensation using Zr(OH)₂CO₃.ZrO₂ as catalyst in the solid state

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A simple and efficient Friedlander condensation of 2-aminonicotinaldehyde 1 with various carbonyl compounds containing α-methylene group 2 under solid state conditions to prepare 1,8-naphthyridines 3 in very good yields using Zr(OH)₂CO₃.ZrO₂ as catalyst has been described.

Keywords: Friedlander condensation, 2-aminonicotinaldehyde, carbonyl compounds containing α-methylene group, 1,8-naphthyridines, Zr(OH)₂CO₃.ZrO₂, solid state

In recent years organic reactions in the solid state have been attracting the synthetic organic chemist because of their simplicity and synthetic value. 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: reduced pollution, low costs and simplicity in processing and handling.

Friedlander synthesis is an acid or base catalyzed condensation followed by a cyclodehydration between an aromatic 2-aminocetaldehyde or ketone with the carbonyl compound containing a reactive α-methylene group.

2-Aminonicotinaldehyde condenses readily with active methylene compounds in the presence of base catalysts to give 1,8-naphthyridines. However, most of these methods require high temperature, longer reaction times and give products in unsatisfactory yield. Therefore, the development of further convenient and efficient methods for the preparation of 1,8-naphthyridines is of practical importance. In view of this, and in continuation of the interest on solid state organic reactions, herein is reported a simple and efficient Friedlander condensation using Zr(OH)₂CO₃.ZrO₂ [Zirconium (IV) carbonate hydroxide oxide] under solid state grinding conditions at RT.

The Friedlander condensation of 2-aminonicotinaldehyde 1 with various carbonyl compounds containing α-methylene group 2 in the presence of Zr(OH)₂CO₃.ZrO₂ [Zirconium (IV) carbonate hydroxide oxide] in the solid state at RT afforded the corresponding 1,8-naphthyridines 3 in very good yields (Scheme I). The reaction is fairly general, facile and efficient and is devoid of by-products. The products that are obtained do not require purification. The process is environmentally benign. The experimental procedure is very simple.

In a typical case, an equimolar mixture of 1, acetoacetanilide 2 (R = CH₃, Ar = C₆H₅NH) and Zr(OH)₂CO₃.ZrO₂ was ground in a mortar by pestle at RT for 6 min. After work-up, 2-methyl-N-phenyl-1,8-naphthyridine-3-carboxamide 3a (R = CH₃, Ar = C₆H₅NH) was obtained in 90% yield. The reaction is of general applicability and the various 1,8-naphthyridines synthesized are given in Table I.

To the best of the knowledge, this is the first report on rapid Friedlander synthesis of 1,8-naphthyridines using Zr(OH)₂CO₃.ZrO₂ as catalyst in the solid state at RT.

In conclusion, a highly efficient and practical procedure has been developed for the synthesis of 1,8-naphthyridines using Zr(OH)₂CO₃.ZrO₂ in the solid state at RT. Moreover, mild reaction conditions, short reaction times, simple experimental work-up procedure, high yields and excellent purity of the products are noteworthy advantages of this environment friendly protocol.

Experimental Section

Melting points were measured on a cintex melting point apparatus and are uncorrected. The homogeneity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr, cm⁻¹) were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer and ¹H NMR spectra on Varian Gemini 200 MHz spectrometer using TMS as internal standard. The Zirconium (IV) carbonate hydroxide oxide [Zr(OH)₂CO₃.ZrO₂] was purchased from Aldrich Chemical Company.

General procedure for the synthesis of 1,8-naphthyridines 3. A mixture of 2-aminonicotinaldehyde 1 (0.01 mole), active methylene compound 2

Note

The Friedlander condensation of 2-aminonicotinaldehyde 1 with various carbonyl compounds containing α-methylene group 2 in the presence of Zr(OH)₂CO₃.ZrO₂ [Zirconium (IV) carbonate hydroxide oxide] in the solid state at RT afforded the corresponding 1,8-naphthyridines 3 in very good yields (Scheme I). The reaction is fairly general, facile and efficient and is devoid of by-products. The products that are obtained do not require purification. The process is environmentally benign. The experimental procedure is very simple.

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General procedure for the synthesis of 1,8-naphthyridines 3. A mixture of 2-aminonicotinaldehyde 1 (0.01 mole), active methylene compound 2
(0.01 mole) and Zr(OH)$_2$CO$_3$ZrO$_2$ (0.01 mole) was ground by pestle and mortar at RT for the period indicated in Table I. After completion of the reaction as monitored by TLC, the reaction mixture was treated with cold water. The solid separated was recrystallized from appropriate solvent to furnish 3. The products 3 were characterized by IR and $^1$H NMR and finally by comparison with authentic samples.

**Spectral data for selected compounds**

3a: IR (KBr): 3248 (NH), 1679 (C=O), 1602 cm$^{-1}$ (C=N); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.92 (s,3H,CH$_3$), 8.32 (m,2H, C$_6$-H, C$_7$-H), 9.10 (m, 1H, C$_7$-H). 7.03-7.82 (m, 6H, C$_o$-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-$d_6$): $\delta$ 8.10 (s, 1H, C$_7$-H), 8.65 (m, 1H, C$_7$-H), 7.86 (m, 1H, C$_o$-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-$d_6$): $\delta$ 2.73 (s, 3H, CH$_3$), 8.45 (m,2H, C$_7$-H, C$_5$-H), 7.93 (m, 1H, C$_o$-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-$d_6$): $\delta$ 7.92 (s, 1H, C$_4$-H), 8.35 (m, 1H, C$_7$-H), 9.12 (m, 1H, C$_7$-H), 6.83-7.62 (m, 11H, C$_o$-H, 10Ar-H).

### Table I — 1,8-Naphthyridines 3

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<th>Compd</th>
<th>R</th>
<th>Ar</th>
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<th>m.p. (°C)</th>
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**Scheme I**
References