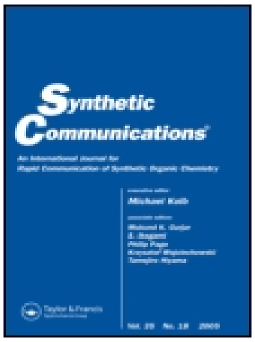

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: K. Mogilaiah & N. Vasudeva Reddy (2003) LiCl Catalyzed Claisen–Schmidt Condensation in Solvent-Free Conditions Using Microwaves, Synthetic Communications, 33:1, 73-78, DOI: 10.1081/SCC-120015561

To link to this article: http://dx.doi.org/10.1081/SCC-120015561

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 1, pp. 73–78, 2003

LiCl Catalyzed Claisen–Schmidt Condensation in Solvent-Free Conditions Using Microwaves

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ABSTRACT

Microwave assisted Claisen–Schmidt condensation of 2-(4-acetylphenyl-amino)-3-(4-methoxyphenyl)-1,8-naphthyridine **3** with various aromatic aldehydes under solvent-free conditions to prepare α,β-unsaturated ketones **4** using LiCl as catalyst has been described. The products are obtained in good yields and excellent purities.

In recent years the use of microwave irradiation in organic reactions is rapidly increasing because of the short reaction time, operational simplicity and formation of cleaner reaction products. It has been commonly employed as thermal energy source in various organic

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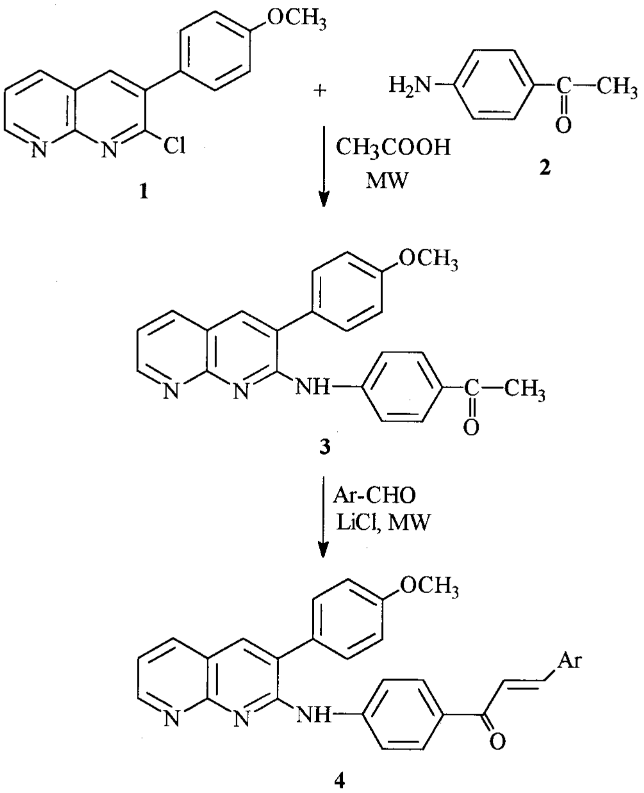
DOI: 10.1081/SCC-120015561
0039-7911 (Print); 1532-2432 (Online)
www.dekker.com

reactions.[1–3] The use of domestic microwave oven in this regard is now a well-established procedure in MORE[4] chemistry. It has been reported that the rate of a variety of organic reactions such as Michael addition,[5] Claisen rearrangement,[6] Fisher-indole synthesis,[7] Hantzsch synthesis,[8] Knoevenagel condensation[9] could be enhanced by microwave irradiation. Chalkones, more generally α,β-unsaturated ketones are widely recognized as versatile synthons for a variety of organic transformations.[10,11] Usually, the preparation of chalkones is



Ar = a, C_6H_5 f, o-HOC_6H_4
b, p-$CH_3C_6H_4$ g, p-$(CH_3)_2NC_6H_4$
c, p-$CH_3OC_6H_4$ h, m-$NO_2C_6H_4$
d, o-ClC_6H_4 i, 3,4-$(OCH_2O)C_6H_3$
e, p-ClC_6H_4

Scheme 1.

achieved with NaOH, KOH, or $Ba(OH)_2$ from benzaldehyde and methyl ketones.[12–14]

In view of this and in continuation of our interest on microwave assisted organic transformations,[15–17] we report here our results related to the preparation of α,β-unsaturated ketones, without solvent, catalyzed by LiCl under microwave irradiation, which to our knowledge, was not attempted up to now.

Interaction of 2-chloro-3-(4-methoxyphenyl)-1,8-naphthyridine **1**[18] with 4-aminoacetophenone **2** in glacial acetic acid under microwave irradiation yielded 2-(4-acetylphenylamino)-3-(4-methoxyphenyl)-1,8-naphthyridine **3** in 85% yield. Claisen–Schmidt condensation of **3** with various aromatic aldehydes in the presence of LiCl in solvent-free conditions under microwave irradiation afforded the respective 2-(4-cinnamoylphenylamino)-3-(4-methoxyphenyl)-1,8-naphthyridines **4**. The reaction is fairly general, facile, and efficient and devoid of any by-products. The reaction did not proceed at all when performed without LiCl. The optimum results were obtained when equimolar amounts of the substrates were reacted in the presence of LiCl under microwave irradiation. Furthermore, it is to be noted that highly pure products were obtained using this simple procedure and in most cases no further purification was needed. The reactions proceed efficiently in high yields at ambient pressure within a few minutes. The process in environmentally benign.

In conclusion, we have realized a very simple, fast and useful method for the preparation of various α,β-unsaturated ketones by simple mixing of the reactants without solvent and irradiation under microwaves. The other notable advantages offered by this protocol are the reduced reaction times, high purity, easy work-up, better yields of the products and inexpensive LiCl. Due to the simplicity and environmentally friendly conditions this methodology should find utility in organic synthesis.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes using Cintex apparatus and were uncorrected. IR spectra in KBr were recorded in a Perkin–Elmer spectrum BX series FT-IR spectrophotometer, ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard and mass spectra (EI) on a Jeol JMS D-300 spectrometer. Analytical TLC was performed on Merck 60F-254 silica gel plates.

2-(4-Acetylphenylamino)-3-(4-methoxyphenyl)-1,8-naphthyridine 3

A mixture of **1** (2.70 g, 0.01 mol) and 4-aminoacetophenone **2** (1.35 g, 0.01 mol) in glacial acetic acid (25 mL) was subjected to microwave irradiation at 450 watts for 4 min, the completion of the reaction was monitored by TLC and poured into ice cold water. The solid obtained was collected and washed with water. It was dried and recrystallized from methanol to give **3** (3.14 g, 85%) as a yellow compound, m.p. 240°C. IR (KBr) 3250, 1662, 1605 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.60 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 6.90–7.26 (m, 8H, Ar-H), 7.78 (m, 2H, C_4-H, C_6-H), 7.96 (m, 1H, C_5-H), 8.75 (m, 1H, C_7-H), 12.09 (s, 1H, NH); EIMS m/z 369 (M^+). Anal. Calcd for $C_{23}H_{19}N_3O_2$: C, 74.80; H, 5.15; N, 11.38. Found C, 74.99; H, 5.22; N, 11.49.

General Procedure for the Preparation of 2-(4-Cinnamoylphenylamino)-3-(4-methoxyphenyl)-1,8-naphthyridines 4

LiCl (0.01 mol) was added to a mixture of **3** (0.01 mol) and appropriate aromatic aldehyde (0.01 mol) and irradiated at 300 watts for 1.5–4.5 min, the completion of the reaction was monitored by TLC. The reaction mixture was allowed to attain room temperature and treated with water. The resulting precipitate was filtered, dried and recrystallized from methanol to afford **4**.

4a: Reaction time 2 min, yield 86%, m.p. 220°C. IR (KBr) 3280, 1640, 1607, 980 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3 + DMSO\text{-}d_6$ 200 MHz) δ 3.86 (s, 3H, OCH_3), 6.95 (d, $J = 15.6$ Hz, 1H, olefinic C_α-H), 7.45 (d, $J = 15.6$ Hz, olefinic C_β-H), 7.56–7.98 (m, 13H, Ar-H), 8.10 (m, 3H, C_4-H, C_5-H, C_6-H), 8.52 (m, 1H, C_7-H), 12.20 (s, 1H, NH); EIMS m/z 457 (M^+). Anal. Calcd for $C_{30}H_{23}N_3O_2$: C, 78.77; H, 5.03; N, 9.19. Found: C, 78.98; H, 5.10; N, 9.28.

4b: Reaction time 3 min, yield 83%, m.p. 245°C. IR (KBr) 3310, 1645, 1605, 970 $\mathrm{cm^{-1}}$; EIMS m/z 471 (M^+). Anal. Calcd for $C_{31}H_{25}N_3O_2$: C, 78.98; H, 5.31; N, 8.92. Found C, 78.83; H, 5.38; N, 8.83.

4c: Reaction time 1.5 min, yield 80%, m.p. 260°C. IR (KBr) 3250, 1640, 1605, 984 $\mathrm{cm^{-1}}$; EIMS m/z 487 (M^+) Anal. Calcd for $C_{31}H_{25}N_3O_3$: C, 76.39; H, 5.13; N, 8.62. Found: C, 76.60; H, 5.19; N, 8.75.

4d: Reaction time 4 min, yield 82%, m.p. 290°C; IR (KBr) 3240, 1640, 1606, 975 $\mathrm{cm^{-1}}$; EIMS m/z 491 (M^+). Anal. Calcd for $C_{30}H_{22}N_3O_2Cl$: C, 73.25; H, 4.48; N, 8.55. Found: C, 73.46; H, 4.55; N, 8.69.

4e: Reaction time 4.5 min, yield 84%, m.p. 205°C; IR (KBr) 3270, 1650, 1607, 980 cm^{-1}; EIMS *m*/*z* 491 (M^+). Anal. Calcd for $C_{30}H_{22}N_3O_2Cl$: C, 73.25; H, 4.48; N, 8.55. Found: C, 73.43; H, 4.57; N, 8.68.

4f: Reaction time 3 min, yield 81%, m.p. 270°C; IR (KBr) 3290, 1655, 1607, 978 cm^{-1}; EIMS *m*/*z* 473 (M^+). Anal. Calcd for $C_{30}H_{23}N_3O_3$: C, 76.11; H, 4.86; N, 8.88. Found: C, 76.30; H, 4.81; N, 8.98.

4g: Reaction time 3.5 min, yield 82%, m.p. 223°C; IR (KBr) 3210, 1640, 1600, 982 cm^{-1}; EIMS *m*/*z* 500 (M^+). Anal. Calcd for $C_{32}H_{28}N_4O_2$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.97; H, 5.67; N, 11.32.

4h: Reaction time 1.5 min, yield 85%, m.p. 255°C; IR (KBr) 3320, 1650, 1605, 970 cm^{-1}; EIMS *m*/*z* 502 (M^+). Anal. Calcd for $C_{30}H_{22}N_4O_4$: C, 71.71; H, 4.38; N, 11.16. Found: C, 71.52; H, 4.32; N, 11.28.

4i: Reaction time 3 min, yield 83%, m.p. 180°C; IR (KBr) 3280, 1645, 1606, 972 cm^{-1}; EIMS *m*/*z* 501 (M^+). Anal. Calcd for $C_{31}H_{23}H_3O_4$: C, 74.25; H, 4.59; N, 8.38. Found: C, 74.43; H, 4.53; N, 8.52.

ACKNOWLEDGMENT

One of the authors (NVR) is grateful to CSIR, New Delhi for the award of a senior research fellowship.

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Received in Japan November 5, 2001