PTSA CATALYZED CLAISEN-SCHMIDT CONDENSATION IN SOLVENT-FREE CONDITIONS UNDER MICROWAVE IRRADIATION

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Abstract : Microwave assisted Claisen-Schmidt condensation of 2-(4-acetylphenyl-amino)-3-(2-chlorophenyl)-1,8-naphthyridine **3** with various aromatic aldehydes under solvent-free conditions to prepare 2-(4-cinnamoylphenyl-amino)-3-(2-chlorophenyl)-1,8-naphthyridines **4** (α, β-unsaturated ketones or chalkones) using *p*-toluenesulphonic acid (PTSA) as catalyst has been described.

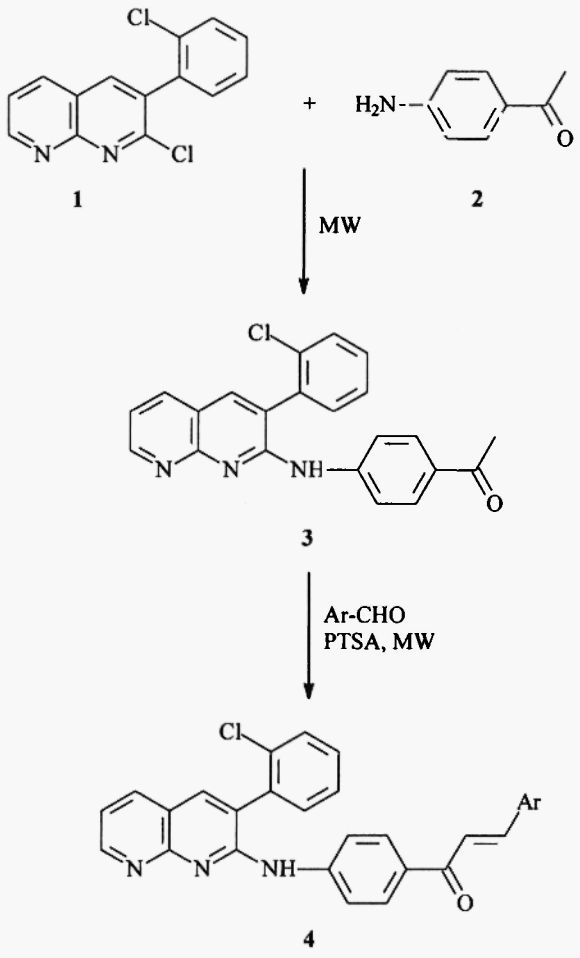
Introduction

In recent years, the solvent-free organic reaction and assisted by microwaves, in particular, have been gained special attention (1-3). One reason is that the use of microwave activation in organic synthesis can increase the purity of the resulting products, enhance the chemical yield and shorten the reaction time. The other reason is that solvent-free reaction avoids organic solvents during the reaction in organic synthesis leads to a clean, efficient and economical technology (4). It has many advantages such as high efficiency and selectivity, easy separation and purification, mild reaction conditions, and environmental acceptability. Chalkones, more generally α, β-unsaturated ketones are versatile intermediates as they can be readily converted into biologically interesting heterocycles (5,6). Moreover, chalcone derivatives are also used for their excellent second harmonic generation (SHG) properties (7). Some of the α, β-unsaturated ketones are used as sweeteners, sunscreen agents, photoresists, photographic emulsions and liquid crystal material (8). Further, the 1,8-naphthyridine ring system is an important pharmacophoric element in medicinal chemistry (9-10). In view of this and in continuation of our interest in microwave-assisted organic transformation (11-15), we report herein a convenient, practical and rapid microwave assisted Claisen-Schmidt condensation to prepare α, β-unsaturated ketones under solvent-free conditions using *p*-toluenesulphonic acid (PTSA) as catalyst.

Treatment of 2-chloro-3-(2-chlorophenyl)-1,8-naphthyridine **1** (16) with 4-aminoaceto-phenone **2** in the presence of catalytic amount of DMF without any solvent under microwave irradiation afforded 2-(4-acetylphenylamino)-3-(2-chlorophenyl)-1,8-naphthyridine **3** in 94% yield.

Claisen-Schmidt condensation of **3** with various aromatic aldehydes in the presence of PTSA in solvent-free conditions under microwave irradiation furnished the respective 2-(4-cinnamoylphenylamino)-3-(2-chlorophenyl)-1,8-naphthyridines **4** (**Scheme-I**). The reaction proceeds efficiently in excellent yields at ambient pressure within a few minutes. The transformation is very clean and rapid. The reaction conditions and work-up procedures are mild, simple and convenient. Furthermore, the products obtained are of high purity by this

procedure and in most cases no further purification was needed. The process is environmentally benign. The reaction did not proceed at all when performed without PTSA.



Scheme-1

In a typical case, equimolar quantities of **3**, benzaldehyde and PTSA were mixed together without any solvent in a 100 mL conical flask capped with a glass funnel and placed in a domestic microwave oven and irradiated at 400 W for 1.5 min. The reaction mixture was allowed to attain room temperature, treated with cold water and filtered off. After usual work-up 2-(4-cinnamoylphenylamino)-3-(2-chlorophenyl)-1,8-naphthyridine **4a** was obtained in 96% yield. The reaction is of general applicability and the different α, β-unsaturated ketones **4b-i** synthesized are given in **Table-2**. The spectral data of the compounds **4a-i** prepared are recorded in **Table-1**.

Interesting, this condensation reaction proceeds only to a minor extent (10-20% in 1.5-3.0 min) when conducted under conventional conditions in an oil-bath preheated to 120°C (temperature

measured at the end of exposure during microwave experiment) which confirms the rate increase during microwave heating.

The structure of compounds **3** and **4** were confirmed by their spectroscopic (IR and ^{1}H NMR) and analytical data.

In conclusion, we have reported a rapid and efficient synthesis of α,β-unsaturated ketones by using PTSA as catalyst under solvent-free microwave irradiation conditions. The advantages of this method are easily available and cheap catalyst, short reaction time, pure products and excellent yields.

Experimental

Melting points were determined using Cintex melting point apparatus and are uncorrected. Purity of compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr) (ν_{max}; cm^{-1}) were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ ppm) using TMS as internal standard. For microwave irradiation LG MG 556 P (2450 MHz) domestic microwave oven was used.

2-(4-Acetylphenylamino)-3-(2-chlorophenyl)-1,8-naphthyridine 3.

A mixture of **1** (0.01 mole), 4-aminoacetophenone **2** (0.01 mole) and DMF (5 drops) was thoroughly mixed and subjected to microwave irradiation at 400 W intermittently at 30 sec intervals for 3.5 min. On completion of reaction, as monitored by TLC, the reaction mixture was cooled and treated with chilled water. The solid that precipitated was filtered, washed with water and recrystallized from methanol to give **3**, Yield 94%, M.p. 262°C : IR (KBr) : 3325, 1660, 1596 cm^{-1}; ^{1}H NMR (DMSO-d_6) : δ 2.51 (s, 3H, $COCH_3$), 7.93 (m, 2H, C_4-H, C_6-H), 8.17 (m, 1H, C_5-H), 8.55 (m, 1H, C_7-H), 7.27-7.72 (m, 8H, Ar-H), 12.37 (s, 1H, NH); Anal. Calcd for $C_{22}H_{16}N_3OCl$: C, 70.68; H, 4.28; N, 11.24. Found : C, 70.84; H, 4.32; N, 11.30%.

General procedure for the synthesis of 2-(4-cinnamoylphenylamino)-3-(2-chlorophenyl)-1,8-naphthyridines 4 under microwave irradiation.

A mixture of **3** (0.01 mole), aromatic aldehyde (0.01 mole) and PTSA (0.01 mole) was mixed together without any solvent and exposed to microwave at 600 W intermittently at 30 sec intrnvals for the specified time (**Table 2**). After completion of the reaction as indicated by TLC, the reaction mixture was cooled and digested with cold water. The separated solid was filtered, washed with water and recrystallized from methanol to afford **4** (**Table 2**)

Table-1 : IR and ^{1}H NMR spectral data of 2-(4-cinnamoylphenylamino)-3-(2-chlorophenyl 1,8-naphthyridines **4**

Entry	Ar	IR (KBr) (cm^{-1})	^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6) (δ, ppm)
4a	C_6H_5	3420, 1652, 1605, 984	6.70 (d, 1H, *J*=15.6 Hz, olefinic C_α-H), 7.90 (m, 2H, C_4-H, C_5-H), 7.73 (m, 1H, C_6-H), 8.60 (m, 1H, C_7-H), 7.09-7.62 (m, 14H, olefinic, C_β-H, 13Ar-H), 11.79 (s, 1H, NH)
4b	4-$CH_3C_6H_4$	3410, 1650, 1602, 985	2.35 (s, 3H, CH_3), 6.65 (d, 1H, *J*=15.6 Hz, olefinic C_α-H), 7.88 (m, 2H, C_4-H, C_5-H), 7.71 (m, 1H, C_6-H), 8.58 (m, 1H, C_7-H), 7.08-7.56 (m, 13H, olefinic, C_β-H, , 12Ar-H), 11.75 (s, 1H, NH).
4c	4-$CH_3OC_6H_4$	3415, 1652, 1600, 985	3.78 (s, 3H, OCH_3), 6.62 (d, 1H, *J*=15.8 Hz, olefinic C_α-H), 6.89 (d, 1H, *J*=15.8 Hz, olefinic C_β-H), 7.89 (m, 2H, C_4-H, C_5-H), 7.60 (m, 1H, C_6-H), 8.54 (m, 1H, C_7-H), 6.80-7.43 (m, 12H, Ar-H), 11.92 (s, 1H, NH).
4d	2-ClC_6H_4	3435, 1648, 1602, 980	6.64 (d, 1H, *J*=15.6 Hz, olefinic C_α-H), 7.83 (m, 2H, C_4-H, C_5-H), 7.64 (m, 1H, C_6-H), 8.56 (m, 1H, C_7-H), 7.12-7.54 (m, 13H, olefinic C_β-H, 12Ar-H), 11.78 (s, 1H, NH).
4e	4-ClC_6H_4	3450, 1650, 1605, 984	6.60 (d, 1H, *J*=15.6 Hz, olefinic C_α-H), 7.81 (m, 2H, C_4-H, C_5-H), 7.52 (m, 1H, C_6-H), 8.51 (m, 1H, C_7-H), 7.04-7.42 (m, 13H, olefinic C_β-H, 12Ar-H), 11.89 (s, 1H, NH).
4f	3-$NO_2C_6H_4$	3420, 1652, 1600, 986	6.68 (d, 1H, *J*=15.6 Hz, olefinic C_α-H), 7.91 (m, 2H, C_4-H, C_5-H), 7.71 (m, 1H, C_6-H), 8.56 (m, 1H, C_7-H), 7.08-7.60 (m, 13H, olefinic C_β-H, 12Ar-H), 11.90 (s, 1H, NH).
4g	4-$NO_2C_6H_4$	3440, 1648, 1605, 982	6.72 (d, 1H, *J*=15.6 Hz, olefinic C_α-H), 7.87 (m, 2H, C_4-H, C_5-H), 7.74 (m, 1H, C_6-H), 8.52 (m, 1H, C_7-H), 7.11-7.64 (m, 13H, olefinic C_β-H, 12Ar-H), 11.86 (s, 1H, NH).
4h	3,4-$(OCH_3)_2$-C_6H_3	3425, 1650, 1594, 986	3.92 (s, 6H, 2 x OCH_3), 6.70 (d, 1H, *J*=15.8 Hz, olefinic C_α-H), 6.92 (d, 1H, *J*=15.6 Hz, olefinic C_β-H), 7.89 (m, 2H, C_4-H, C_5-H), 7.72 (m, 1H, C_6-H), 8.59 (m, 1H, C_7-H), 7.08-7.47 (m, 11H, Ar-H), 11.92 (s, 1H, NH).
4i	3,4-(O-CH_2-O)C_6H_3	3405, 1646, 1602, 982	6.05 (s, 2H, O-CH_2-O), 6.65 (d, 1H, *J*=15.8 Hz, olefinic C_α-H), 7.89 (m, 2H, C_4-H, C_5-H), 7.74 (m, 1H, C_6-H), 8.55 (m, 1H, C_7-H), 7.12-7.49 (m, 12H, olefinic C_β-H, 11Ar-H), 11.89 (s, 1H, NH).

Table-2 : Physical and analytical data of 2-(4-cinnamoylphenylamino)-3-(2-chlorophenyl)-1,8-naphthyridlnes **4**

Entry	Ar	Reaction Period (min)	M.p. °C	Yield (%)	Mol. formula	Found % (Calcd)		
						C	H	N
4a	C_6H_5	1.5	240	96	$C_{29}H_{20}N_3OCl$	75.57 (75.41	4.38 4.33	9.17 9.10)
4b	4-$CH_3C_6H_4$	2.0	252	98	$C_{30}H_{22}N_3OCl$	75.89 (75.71	4.67 4.63	8.89 8.83)
4c	4-$CH_3OC_6H_4$	2.5	245	94	$C_{30}H_{22}N_3O_2Cl$	73.43 (73.25	4.52 4.48	8.62 8.55)
4d	2-ClC_6H_4	3.0	278	95	$C_{29}H_{19}N_3OCl_2$	70.34 (70.16	3.88 3.83	8.53 8.47)
4e	4-ClC_6H_4	2.5	290	96	$C_{29}H_{19}N_3OCl_2$	70.32 (70.16	3.87 3.83	8.54 8.47)
4f	3-$NO_2C_6H_4$	2.0	272	92	$C_{29}H_{19}N_4O_3Cl$	68.90 (68.71	3.80 3.75	11.13 11.06)
4g	4-$NO_2C_6H_4$	1.5	294	95	$C_{29}H_{19}N_4O_3Cl$	68.91 (68.71	3.81 3.75	11.12 11.06)
4h	3,4-$(OCH_3)_2C_6H_3$	2.0	282	93	$C_{31}H_{24}N_3O_3Cl$	71.49 (71.33	4.64 4.60	8.13 8.05)
4i	3,4-(O-CH_2-O)C_6H_3	2.5	267	96	$C_{30}H_{20}N_3O_3Cl$	71.39 (71.22	3.92 3.96	8.37 8.31)

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