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Improved microwave-induced synthesis of indolyl chalcones

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ABSTRACT

Various indolyl chalcones have been synthesized in unsealed vessels in a domestic microwave oven. Considerable increase in the reaction rate has been observed with better yields.

Keywords: Indolyl chalcones, acetophenones, indole 3-carboxaldehyde, sodium hydroxide, microwave irradiation

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INTRODUCTION

The Claisen-schmidt condensation is the most important reaction for the synthesis of chalcones (1,3-diaryl-2-propen-1-ones) with an enone system between two aromatic rings constitute an important class of natural products which serves as precursors for the preparation of various flavonoids and exhibit interesting pharmacological activities.[1,2] Natural and synthetic chalcones have shown broad spectrum of biological activities such as antimalarial,[3] antifungul,[4] anti-inflammatory,[5] antituberculosis,[6] antileish-manicidal[7] and anticancer.[8] Recent development of anticancer agents involves structural modification of chalcones to improve their bioavailability and to study the role of various substituents on aryl or heteroaryl rings.[9] Indole-based chalcones such as **1** and **2** gained considerable interest due to cytotoxicity against all three cancer cell lines: epithelial (A-549), pancreatic carcinoma (PaCa-2) and androgen-independent human prostatic adenocarcinoma (Pc-3).[10] Selected indolyl chalcones and N-substituted chalcones showed good to excellent antibacterial and antifungal activities.[11] Compounds **1** and **2** (**Fig I**) are also used as an intermediate for synthesizing various indole-based heterocyclic compounds such as indolyl-isoxazoles, indolyl hydroxyl/amino/thiopyrimidines which showed anti-inflammatory, antibacterial and antioxidant agents.[12,13]

Based on the above observation, here we are reporting the synthesis of various indolyl chalcones by condensation of substituted acetophenones with indole 3-carboxaldehyde using sodium hydroxide under microwave irradiation.

MATERIALS AND METHODS

All reactions were run in dried glassware. Reagents were purchased (Spectrochem or SRL or Sigma-Aldrich) and used without further purification. Melting points were determined on a Kofler block and uncorrected. Reactions were irradiated in a domestic microwave oven (LG, MH-4048GW, 900 Watt). ^{1}H NMR spectrum were obtained in $CDCl_3$ on Bruker AV-300 (300 MHz) spectrometers using TMS as an internal standard. Analytical samples were dried in vacuo at room temperature. The carbon, hydrogen and nitrogen percentages in synthesized products were analyzed by Perkin-Elmer 2400 series II C, H, N analyzers. Thin layer chromatography was carried out on silica gel G.

General procedure for synthesis of indolyl chalcones under microwave irradiation
To a solution of acetophenones (1 mmol) and indole 3-carboxaldehyde (1 mmol) in aqueous ethanol (15 mL, 1:2 ratio) taken in a a borosil conical flask (100 mL), a catalytic quantity of sodium hydroxide (1-2 pellets) was added

and the reaction mixture was placed inside a domestic microwave oven for 30 sec to 2 minutes at 40% power input (LG, MH-4048GW, 900 Watt). The progress of the reaction was monitored by TLC. On completion of the reaction, the reaction mixture was cooled at room temperature and was poured into cold water (50 mL). The reaction product was extracted with diethyl ether (20 x 2 mL) and then dried over anhydrous sodium sulphate. The pure products were isolated after column chromatographic separation from the concentrate of the extract. All the indolyl chalcones **5** are known compounds[14] (**Table 1**) and they were characterized from their physical and spectral data.

Spectral data of selected compounds

Compound (**5a**): Yield: 85%, mp. 165-167 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (br. s, 1H, NH), 8.12 (d, J = 15.6 Hz, 1H, C=C-H), 8.07-8.9 (m, 3H), 7.62 (d, J = 15.9 Hz, 1H, C=C-H), 7.61 (d, J = 3 Hz, 1H), 7.56-7.44 (m, 4H), 7.34-7.30 (m, 2H). Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66%. Found C, 82.38; H, 5.19; N, 5.79%.

Compound (**5b**): Yield: 80%, mp. 170-172 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.79 (br. s, 1H, NH), 8.32 (d, J = 8.7 Hz, 2H), 8.10 (d, J = 15.9 Hz, 1H, C=C-H), 7.85 (d, J = 3 Hz, 1H), 7.63 (d, J = 15.9 Hz, 1H, C=C-H), 7.45 (d, J = 8.7 Hz, 2H), 7.34-7.32 (m, 4H), 3.90 (s, 3H, OMe). Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05%. Found C, 77.79; H, 5.31; N, 5.23%.

Compound (**5c**): Yield: 80%, mp. 168-170 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (br. s, 1H, NH), 8.11 (d, J = 15.6 Hz, 1H, C=C-H), 8.03 (m, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 15.9 Hz, 1H, C=C-H), 7.60 (d, J = 3 Hz, 1H), 7.47-7.44 (m, 1H), 7.32-7.30 (m, 4H), 2.44 (s, 3H, Me). Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36%. Found C, 82.65; H, 5.68; N, 5.21%.

Compound (**5d**): Yield: 90%, mp. 190-192 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (br. s, 1H, NH), 8.11 (d, J = 15.6 Hz, 1H, C=C-H), 8.00 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.54 (d, J = 15.6 Hz, 1H, C=C-H), 7.49 (d, J = 8.7 Hz, 2H), 7.45-7.43 (m, 2H), 7.36-7.31 (m, 2H). Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97%. Found C, 72.35; H, 4.35; N, 5.02%.

Compound (**5e**): Yield: 88%, mp. 192-193 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (br. s, 1H, NH), 8.11 (d, J = 15.6 Hz, 1H, C=C-H), 8.03-8.00 (m, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.53 (d, J = 15.6 Hz, 1H, C=C-H), 7.48-7.44 (m, 1H), 7.34-7.31 (m, 2H). Anal. Calcd. for $C_{17}H_{12}BrNO$: C, 62.60; H, 3.71; N, 4.29%. Found C, 62.46; H, 3.64; N, 4.31%.

RESULTS AND DISCUSSION

Microwave-assisted synthesis, in general, has a large impact on synthetic organic chemistry compared to traditional processing of organic synthesis. Microwave-enhanced organic synthesis saves significant time and very often improves yields. Most of the reported reactions have been carried out either in sealed vessels or in the solid phase, though a few reports of the use of unmodified domestic microwave ovens have appeared for carrying out organic synthesis in open vessels using organic solvents such as ethanol, *N*,*N*-dimethyl formamide, *o*-dichlorobenzene, 1,2-dichloroethane, 1,2-glycols etc. as energy transfer.

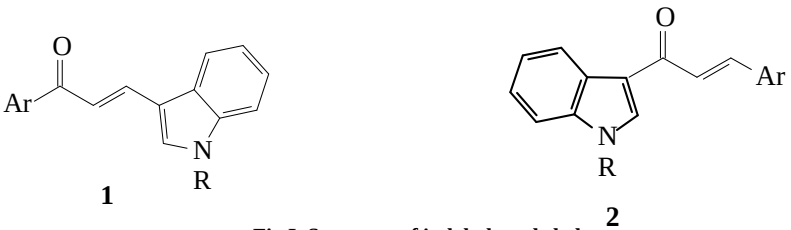
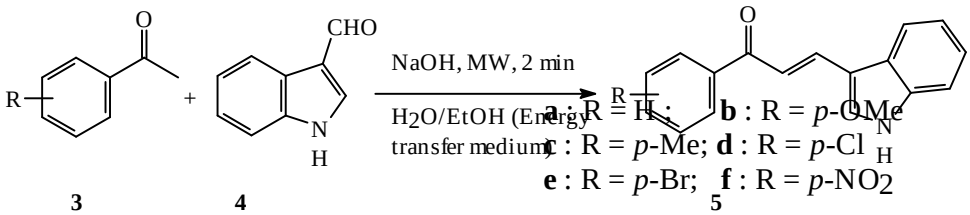


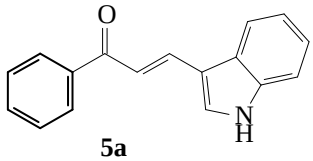
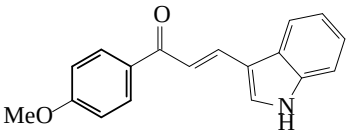
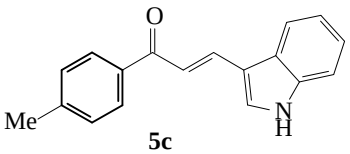
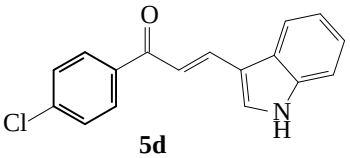
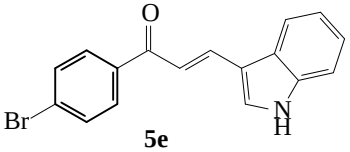
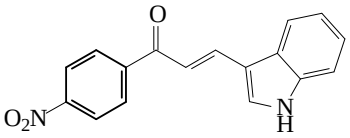
Fig I. Structure of indole-based chalcones



Scheme II. Synthesis of indolyl chalcones

In our attempts towards a non-traditional approach to the experimental set up of organic reactions, the concept of "Microwave-induced Organic Reactions Enhancement" (MORE) chemistry has been utilized for rapid and efficient synthesis of various indolyl chalcones (**5**) by condensation of substituted acetophenones (**3**) with indole 3-carboxaldehyde (**4**) in presence of sodium hydroxide in open borosil glass vessels under microwave irradiation using aqueous ethanol as energy transfer medium (**Scheme 1**). The results obtained demonstrate the versatility of the process as considerable reaction rate enhancement has been observed bringing down the reaction times from hours to minutes (2 min). The products obtained have improved yields (80-92%) (**Table 1**). In order to synthesize the indolyl chalcones (**5**), indole 3-carboxaldehyde (**4**) was treated with different acetophenones (**3**) under conventional heating method by using aqueous ethanol as a solvent in basic condition. It was found that the synthesis of **5** attempted by conventional method took a longer time (10-20 h) for completion of reaction with moderate yield (65-70%). The assigned molecular structures of all indolyl chalcones (**5**) were based on ^{1}H NMR spectral data, elemental analysis and reported melting points.

Table 1. Synthesis of indolyl chalcones under microwave irradiation[a]

Entry	Substrate (3)	Product (5)	Yield (%)[b]	M.p. (ºC) (Lit. Value)[c]
1	Acetophenone **3a**	 **5a**	85	165-167 (166)
2	4-Methoxy-acetophenone **3b**	 **5b**	80	170-172 (170)
3	4-Methyl-acetophenone **3c**	 **5c**	80	168-170 (171-172)
4	4-Chloro-acetophenone **3d**	 **5d**	90	190-192 (192-193)
5	4-Bromo-acetophenone **3e**	 **5e**	88	192-193 (194)
6	4-Nitro-acetophenone **3f**	 **5f**	92	226-228 (228-229)

*[a]All reactions were carried out with 1 mmol of compound **3** and 1 mmol of compound **4** in 2 min.*
[b]Yield of the isolated product after crystallisation from diethyl ether.
[c]Literature references of melting point.

CONCLUSION

In conclusion, we have developed an easier, facile, and practically convenient methodology for the synthesis of indolyl chalcones under microwave irradiation. The notable merits offered by this protocol are mild reaction condition, simple procedure, very short reaction time, and excellent yield of the product.

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