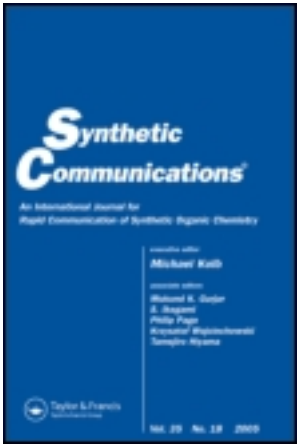


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Ring Closure Reactions of Chalcones Using Microwave Technology

Mazaahir Kidwai [a] & Preeti Misra [a]

[a] Department of Chemistry, University of Delhi, Delhi, 110007, India

Version of record first published: 17 Sep 2007.

To cite this article: Mazaahir Kidwai & Preeti Misra (1999): Ring Closure Reactions of Chalcones Using Microwave Technology, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:18, 3237-3250

To link to this article: http://dx.doi.org/10.1080/00397919908085949

SYNTHETIC COMMUNICATIONS, 29(18), 3237-3250 (1999)

RING CLOSURE REACTIONS OF CHALCONES USING MICROWAVE TECHNOLOGY

Mazaahir Kidwai* and Preeti Misra

Department of Chemistry, University of Delhi
Delhi-110007, India

Abstract : The synthesis of heterocyclic compounds containing pyrimidine, pyrazoline, isoxazoline and cyclohexenone ring from chalcone derivatives containing anisole and 3'4'-methylenedioxy phenyl ring under 'dry conditions' using microwaves and by conventional methods are described.

Chalcone derivatives are associated with diverse biological activities viz. antibacterial[1], anticonvulsant[2], antimicrobial[3], cytotoxic.[2] They serve as key intermediates for the synthesis of dyestuff[5], cosmetic ingredients[6] and as starting material for the synthesis of streptonigrin ring C.[7] Chalcones are also used for the synthesis of various biodynamic heterocycles[8-12] viz. pyrimidine[13], pyrazoline[14] and isoxazoline[15] derivatives.

Microwave irradiation (MWI) using commercial domestic ovens has been recently used to accelerate organic reactions, the high heating

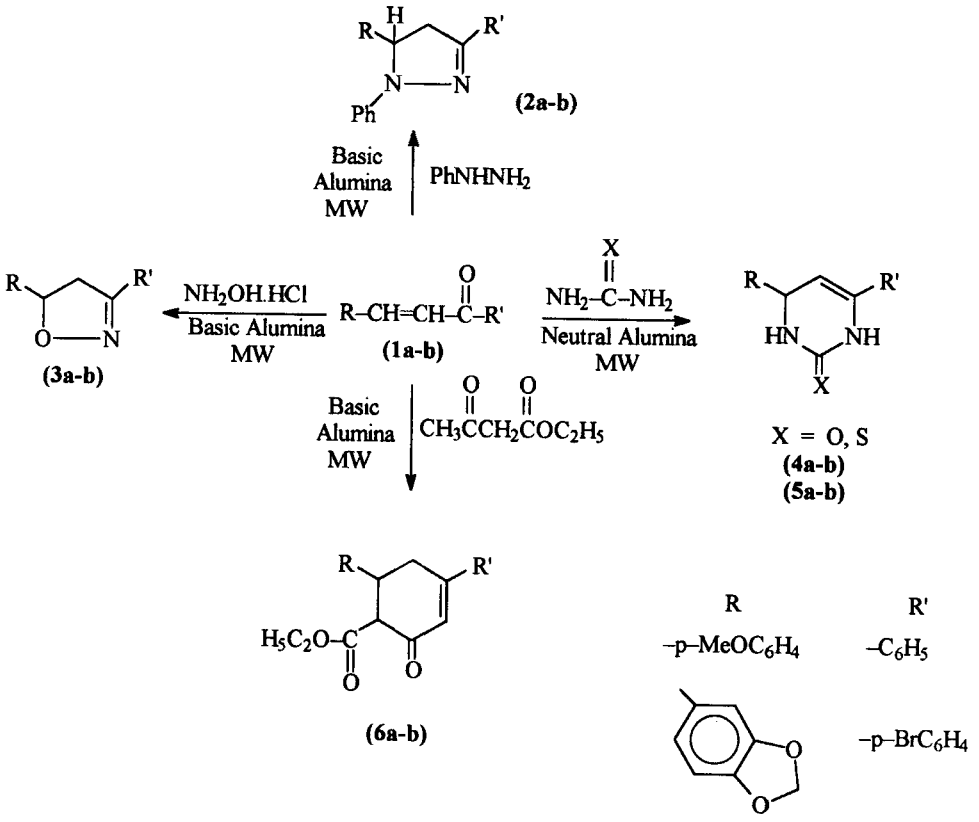
* To whom correspondence should be addressed.

efficiency giving remarkable rate enhancement and dramatic reduction of reaction times.[16-19] The timeliness of this topic and great impact caused by these procedures are evidenced by its recent inclusion in various journals.[20] Nevertheless, these procedures are seriously limited because the use of solvents in microwave ovens give rise to elevated temperature and consequently high pressure, thus leading in some cases to dangerous situation.

In order to avoid the experimental difficulties, arising from the utilization of homogeneous solutions and with the development of microwave oven reactions in dry media[21], also the importance of chalcones we have described here a novel way to induce ring closure reactions of chalcones by microwave irradiation coupled to the use of reagents supported on solid inorganic materials in the absence of any solvent.

Anisaldehyde or piperonal were condensed with acetophenone or p-bromoacetophenone to obtain the corresponding chalcones **1a-b**. The structure of these products were established from their physical and spectral data. The IR spectrum of **1a-b** showed absorption bands in the region 1650-1660 cm^{-1} (C=O). The H-NMR further support for their structure and showed multiplet in the region δ 6.7-8.25 due to olefinic and aromatic protons.

1,3,5-triaryl-pyrazoline **2a-b** were obtained by the cyclisation of chalcones **1a-b** with phenylhydrazine. The IR spectra of these



Scheme 1

compounds showed absorption band in the region 1650-1670 cm^{-1} (C=N). Its H-NMR spectra showed doublet at δ 2.7-2.85 due to 4-CH_2 protons and triplet at δ 2.95-3.72 due to 5-CH proton in addition to a multiplet for aromatic protons.

Adsorption of chalcones on neutral alumina with hydrochloride, 3,5-diarylisoxazoline **3a-b** were obtained under microwave irradiation.

The IR spectrum of **3a-b** exhibit absorption band at 1645-1660 cm^{-1} due to C=N group while its H-NMR spectra showed doublet at δ 2.4-2.7 due to 4-CH_2 and triplet at δ 2.8-3.3 due to 5-CH proton.

Treatment of chalcones with urea under dry conditions using basic alumina produced corresponding 4,6-diaryl-3,4-dihydropyrimidinone **4a-b**, while on treatment with thiourea produced corresponding 4,6-diaryl-3,4-dihydro-pyrimidine thione **5a-b**. The structure of these products were established from their physical and spectral data.

Cyclisation of chalcones with ethylacetoacetate yield corresponding ethyl-2,6-diaryl-cyclohexen-2-one-carboxylate **6a-b**. The structure of these products were characterised on the basis of its spectral datas.

This is the first report on the reaction of chalcones on a solid support using microwave irradiation. In short, the salient feature of our interest is coupling microwaves with solvent-free technique keeping modernisation and simplification of classical procedures, avoiding volatile and toxic organic solvents, corrosive mineral acids, which make it a clean, efficient and cheap technology to obtain various useful heterocyclic compounds for organic synthesis. In our approach on solid support less reaction time and better yield of products are found as compared with the organic solvent usage Table 1.

Table 1 : Physical data of compds. (2-6)

Compd. No.	Yield (%)			Reaction Period (h/min.)		
	Method A	Method B	Method C	Method A (h)	Method B (min.)	Method C (min.)
2a	68	78	82	2	3	1.5
2b	48	72	80	2.5	2.5	1.5
3a	47	60	63	3	3.5	2
3b	58	66	67	3	3	2.5
4a	72	69	69	5	3	2
4b	65	75	80	4.5	4	3
5a	63	76	78	4.5	6	4
5b	59	82	85	4.5	6	4.5
6a	71	77	82	3	2	1
6b	55	69	75	3.5	3	1.5

EXPERIMENTAL SECTION

Melting points were recorded on an Electrothermal apparatus and are uncorrected. IR (KBr) spectra were obtained on a Perkin-Elmer FTIR-1710 spectrophotometer. H-NMR spectra were recorded on a Perkin-Elmer R-32 instrument using TMS as internal reference. MWI were carried out in Padmini Essentia oven, Model Brownie at 2450 MHz. Elemental analysis were performed on a Heracus CHN-Rapid Analyser. The purities of the compounds were checked on silica gel coated Al plates (Merck).

Chalcones-(General Procedure) : To a hot solution of acetophenone/ 4-bromoacetophenone (0.1 mol) and anisaldehyde/piperonal (0.1 mol) in ethanol (25 ml), a potassium hydroxide solution (0.12 mol) in water (5 ml) was added gradually with shaking and kept at room temperature for 24h. It was diluted with water and acidified with dil. HCl. The precipitate was filtered and washed with chilled water and product recrystallized from methanol as pale yellow needles.

3-(4'-methoxy)-1-phenyl-2-propen-1-one (1a) : m.p. 210-11°C. H-NMR ($CDCl_3$) δ 3.6 (s, 3H, $-OCH_3$), 6.8-8.2 (11H, m, Ar-H + CH=CH); 1R (KBr) ν 1660 (C=O), 1585, 1560, 1480 (C=C) cm^{-1}. Anal. calcd. for $C_{16}H_{14}O_2$ (238): C, 80.5; H, 5.88. Found : C, 80.6; H, 5.88.

3-(3',4'-methylenedioxyphenyl)-1-(4'-bromophenyl)-2-propen-1-one (1b) : m.p. 140-42°C. H-NMR ($CDCl_3$) δ 6.0 (s, 2H, $-OCH_2O$), 7.2-8.5

(m, 9H, ArH + CH=CH). IR (KBr) ν 1650 (C=O), 1600, 1580, 1410 (C=C), 1250, 1040 (C-O-C) cm^{-1}. Anal. Calcd. for $C_{16}H_{11}O_3$ Br (331): C, 58.00; H, 3.32. Found: C, 57.75; H, 3.25.

Synthesis of 5-(4'-methoxyphenyl/3'4'-methylenedioxyphenyl)-3-(Phenyl/4'-bromophenyl)-1-phenyl-4-pyrazoline (2a-b) :

Method A : Phenyl hydrazine (0.013 mol) was added to **1a** or **1b** (0.01 mol) in acetic acid (15 ml) and the mixture was refluxed under constant stirring for 3 h. The reaction mix. was diluted with ice-cold water. The solid was collected washed with water and recrystallised from ethanol as pale yellow plates.

Method B : Phenyl hydrazine (0.013 mol) was added to compound **1a** or **1b** (0.01 mol) in acetic acid (15 ml) and the contents were subjected to microwave irradiation for an appropriate time and worked-up as described in method A.

Method C : Basic alumina[22] (18g) was added to the solution of phenylhydrazine (0.013 mol) and chalcones (**1a/1b** 0.01 mol) dissolved in dichloromethane (5 ml) at room temperature. The reaction mixture was thoroughly mixed and the adsorbed material was dried in air (beaker) and placed in an alumina bath[23] inside the microwave oven. Upon completion of the microwave reaction (1-2 min) as followed by TLC examination, the mixture was cooled to room temperature and then product was extracted into dichloromethane (4 x 15 ml). Removal of

the solvent under reduced pressure afforded the product which was purified by crystallisation from mixture of methanol-dichloromethane.

2a. m.p. 189-92°C. H-NMR ($CDCl_3$) δ 2.4 (d, 2H, J = 9.6Hz, 4-CH_2), 3.1 (t, 1H, J = 9.6 Hz, 5-CH), 6.8-7.7 (m, 14H, Ar-H), 3.7 (s, 3H, -OCH_3); IR(KBr) ν 1660 (C=O), 1605, 1575, 1540 (C=C); Anal. Calcd. for $C_{22}H_{20}N_2O$ (328): C, 80.48; H, 6.09. Found: C, 80.32; H, 6.10.

2b. m.p. 202-04°C. H-NMR ($CDCl_3$) δ 2.9 (d, 2H, J = 9.4Hz, 4-CH_2), 3.7 (t, 1H, J = 9.4 Hz, 5-CH), 5.9 (s, 2H, -OCH_2O-), 7.3-8.2 (m, 12H, Ar-H); IR(KBr) ν 1670 (C=N), 1605, 1590, 1520 (C=C), 1045 (C-O-C); Anal. Calcd. for $C_{22}H_{17}N_2O_2Br$ (421): C, 62.7; H, 4.03; N, 6.65. Found: C, 62.64; H, 4.12; N, 6.60.

Synthesis of 5-(4'-methoxyphenyl/3'4'-methylenedioxyphenyl)-3-(Phenyl/4'-bromophenyl)-isoxazoline (3a-b) :

Method A : Hydroxylamine hydrochloride (0.01 mol) in water (5ml) was added to a solution of compound (**1a/1b** 0.01 mol) in pyridine (10ml). The reaction mixture was refluxed for 3 h with constant stirring. The reaction mixture was cooled, acidified with dil. acetic acid and the deposit recrystallized from benzene as colourless crystals.

Method B : Hydroxylamine hydrochloride (0.01 mol) in water (5 ml) was added to a solution of compound (**1a/1b** 0.01 mol) in pyridine (10

ml). The reaction mix. was subjected to MWI for 3-4 min. and worked up as mentioned above.

Method C : To the solution of hydroxylamine and chalcones in CH_2Cl_2 basic alumina (18g) was added at room temperature. The reaction mix. was mixed and adsorbed material was dried and placed in an alumina bath inside the microwave oven and then irradiated for 2-2.5 min. On completion of the reaction the mix. was worked up as described in method C for preparation of compound **2a-b**.

3a. m.p. 148-51°C. H-NMR ($CDCl_3$) δ 2.4 (d, 2H, J = 9.8Hz, 4-CH_2), 4-CH_2), 2.9 (t, 1H, J = 9.8 Hz, 5-CH), 3.6 (s, 3H, -OCH_3), 6.4-8.1 (m, 9H, Ar-H); IR(KBr) ν 1645 (C=N), 1605, 1575, 1520 (C=C); Anal. Calcd. for $C_{16}H_{15}NO_2$ (253): C, 75.80; H, 5.92; N, 5.53. Found: C, 75.60; H, 5.73; N, 5.52.

3b. m.p. 174-75°C. H-NMR ($CDCl_3$) δ 2.5 (d, 2H, J = 9.8Hz, 4-CH_2), 2.8 (t, 1H, J = 9.8 Hz, 5-CH), 5.9 (s, 2H, -OCH_2O-), 7.1-7.8 (m, 7H, Ar-H); IR(KBr) ν 1660 (C=N), 1625, 1585, 1540 (C=C); Anal. Calcd. for $C_{16}H_{12}NO_3Br$ (346): C, 55.4; H, 3.47; N, 4.04. Found: C, 55.25; H, 3.52; N, 4.12.

Synthesis of 4-(4'-methoxyphenyl/3'4'-methylenedioxyphenyl)-6-(phenyl/4'-bromophenyl)-3,4-dihydropyrimidine-2(1H)-one (4a-b) :

Method A : A mix. of chalcone (**1a/1b** 0.005 mol) and urea (0.005 mol) in ethanol (5 ml) was added successively to a solution of sodium

ethoxide (0.002 mol) in absolute ethanol (10 ml). The reaction mixture was refluxed for 5 h. Reaction mixture was concentrated under reduced pressure and the solid obtained was filtered, washed with water and recrystallised from methanol.

Method B : All the contents were taken in Erlenmeyer flask and subjected to MWI for 3-4 min. and worked up similarly as in method A.

Method C : Neutral alumina[24] (18g) was added successively to a solution of chalcone (0.005 mol) and urea (0.005 mol) in ethanol (10 ml), reaction mixture was mixed-thoroughly and dried, adsorbed material was placed in an alumina bath inside the microwave oven and then irradiated for 2-3 min. and worked up as described above.

4a. m.p. 175-77°C. H-NMR ($CDCl_3$) δ 3.7 (s, 3H, $-OCH_3$), 6.5-6.7 (m, 2H, J=5.0Hz, 4-CH + 5-CH), 7.3-8.4 (m, 9H, Ar-H), 9.1 (bs, 2H, NH); IR(KBr) ν 3240 (NH), 1685(C=O), 1640 (C=N), 1590, 1550, 1480 (C=C); Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (280): C, 72.85; H, 5.71; N, 1.00. Found: C, 72.83; H, 5.72; N, 1.02.

4b. m.p. 195-96°C. H-NMR ($CDCl_3$) δ 5.8 (s, 2H, $-OCH_2O-$), 6.7-6.9 (m, 2H, J=5.2Hz, 4-CH + 5-CH), 7.3-7.7 (m, 7H, Ar-H), 8.7 (bs, 2H, NH); IR(KBr) ν 3350 (NH), 1685(C=O), 1650 (C=N), 1610, 1585, 1475 (C=C), 1240, 1020 (C-O-C); Anal. Calcd. for $C_{17}H_{13}N_2O_3Br$ (373): C, 54.69; H, 3.45; N, 7.50. Found: C, 54.73; H, 3.41; N, 7.55.

Synthesis of 4-(4'-methoxyphenyl/3'4'-methylenedioxyphenyl)-6-(phenyl/4'-bromophenyl)-3,4-dihydropyrimidine-2(1H)-thione (5a-b): Compound (**5a-b**) were prepared similarly as compound (**4a-b**) using thiourea instead of urea.

5a. m.p. 123-24°C. H-NMR ($CDCl_3$) δ 3.8 (s, 3H, $-OCH_3$), 6.3-6.6 (m, 2H, J=5.2Hz, 4-CH + 5-CH), 7.3-8.1 (m, 9H, Ar-H), 8.9 (bs, 2H, NH); IR(KBr) ν 3320 (NH), 1630 (C=N), 1585, 1550, 1490 (C=C); Anal. Calcd. for $C_{17}H_{16}N_2OS$ (296): C, 68.91; H, 5.40; N, 9.45. Found: C, 68.80; H, 5.39; N, 9.35.

5b. m.p. 99-100°C. H-NMR ($CDCl_3$) δ 5.9 (s, 2H, $-OCH_2O-$), 6.3-6.6 (m, 2H, J=5.1Hz, 4-CH + 5-CH), 7.4-8.2 (m, 7H, Ar-H), 8.9 (bs, 2H, NH); IR(KBr) ν 3320 (NH), 1650 (C=N), 1610, 1580, 1495 (C=C), 1230, 1020 (C-O-C); Anal. Calcd. for $C_{17}H_{13}N_2O_2SBr$ (389): C, 52.40; H, 3.34; N, 7.19. Found: C, 52.53; H, 3.28; N, 7.19.

Synthesis of ethyl-4-(phenyl/4'-bromophenyl)-6-(4'-methoxyphenyl/3'4'-methylenedioxyphenyl)-cyclohexen-2-one-carboxylate (6a-b) :

Method A : Compound (**1a/1b**, 0.005 mol) was added to a solution of Na (0.008 mol) in ethanol (20 ml) followed by ethylacetoacetate (0.008 mol) and more ethanol (25 ml). It was refluxed on a water bath at 90°C for 4 h and then diluted with ice-cold acidulated water, when a pale

yellow solid separated. This solid was crystallized from an acetone-chloroform mix. as yellow plates.

Method B : Chalcone (**1a/1b**) and ethylacetoacetate were taken in Erlenmeyer flask and dissolved in ethanol subjected to MWI for 2-3 min. worked up as earlier.

Method C : Basic alumina (18g) was added to the solution of ethylacetoacetate (0.08 mol) and chalcone (0.005 mol) in ethanol (20 ml) at room temperature, mixed thoroughly and dried, adsorbed material was placed in an alumina bath and subjected to MWI for 1-1.5 min. On completion of the reaction followed by TLC, the product was worked up as earlier.

6a. m.p. 193-95°C. H-NMR ($CDCl_3$) δ 1.1 (t, 3H, $-CH_2\underline{CH_3}$), 2.7 (d, 2H, 5-CH_2), 3.25 (q, 1H, 6-CH), 3.8 (s, 3H, $-OCH_3$), 4.1 (d, 1H, 1-CH), 4.4 (q, 2H, $-O\underline{CH_2}CH_3$), 6.3-7.9 (m, 10H, Ar-H + 3-CH); IR (KBr) ν 1740 (C=O), 1600, 1580, 1490 (C=C); Anal. Calcd. for $C_{22}H_{22}O_4$ (350); C, 75.42; H, 6.28. Found: C, 75.30; H, 6.32.

6b. m.p. 202-03°C. H-NMR ($CDCl_3$) δ 1.2 (t, 3H, $-CH_2\underline{CH_3}$), 2.9 (d, 2H, 5-CH_2), 3.3 (q, 1H, 6-CH), 3.9 (d, 1H, 1-CH), 4.2 (q, 2H, $-O\underline{CH_2}CH_3$), 5.9 (s, 2H, $-OCH_2O-$), 6.5-8.1 (m, 8H, Ar-H + 3-CH), IR (KBr) ν 1760 (C=O), 1605, 1560, 1485 (C=C); Anal. Calcd. for $C_{22}H_{18}O_5Br$ (442); C, 59.59; H, 4.29. Found: C, 59.64; H, 4.25.

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(Received in Japan 24 November 1998)