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Solvent-free improved syntheses of some substituted 1, 3-diaryl-propenones and 3,5-diaryl-6-carbethoxycyclohexenones under microwave irradiation and their antibacterial activity

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Microwave induced solvent-free solid phase syntheses of substituted 1,3-diarylpropenones (chalcones) **3a-f** using basic alumina and their subsequent rapid transformation to 3,5-diaryl-6-carbethoxycyclohexenones **4a-f** with ethyl acetoacetate in the presence of basic alumina and piperidine under solvent free condition using domestic microwave oven has been described. This process has advantages over conventional methods such as shorter reaction time, higher yields and environmental acceptability. All the synthesized compounds have been screened for their antibacterial activity.

Keywords: Microwave, Solvent-free syntheses, 3, 5-diaryl-6-carbethoxycyclohexenones, antibacterial activity

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The wide applicability of microwave activation[1-3] in chemical reactions is due to cleaner products, higher yield, shorter reaction time, operational simplicity and minimization of side reactions. In recent years the microwave (MW) heating under solvent free[4-10] reaction conditions on a inorganic solid support is a promising alternative to conventional methods as these reactions represent a clean, efficient, safe, economical and eco-friendly procedure.

1,3-Diarylpropenones (chalcones) have been popular substrates for the generation of variety of heterocyclic[11], carbocyclic[12,13] and flavonoids[14]. In addition to this the chemistry of chalcones[15-18] has assumed significance because some of these compounds and their cyclohexenone transformation products[19-21] possess a wide range of biological activities.

In view of the above and in continuation of our interest in the chemistry of chalcones[22-27] and use of microwave in various organic synthesis[3,28-30], we report herein environmentally benign solvent-free procedures in the presence of inorganic solid support for the synthesis of 1,3-diarylpropenones **3a-f** and their cyclohexenone derivatives **4a-f** under microwave irradiation (**Scheme I**).

1,3-Diarylpropenones required during the course of our present investigation were synthesized by condensing substituted acetophenones **1** and aromatic aldehydes **2** using basic alumina under solvent-free microwave irradiation in a modified Claisen-Schmidt condensation reaction. Microwave irradiation for 2-3 min of the substrates provided the condensation products in high yields (80%) whereas the conventional method required longer periods (7-8 hr) and with low yields (60%). The structures of chalcones **3a-f** were supported by elemental analysis and molecular ions. IR spectra exhibited the conjugated carbonyl at 1630 cm^{-1} and ^1H NMR showed trans-coupled doublets (J = 15 Hz) at 7.63 (H_α) and 7.82 (H_β) for vinylic hydrogens.

Cyclohexenone derivatives[31-33] have been prepared by conventional methods using acetone - ethanol as a solvent in the presence of basic medium. However, in the present work the synthesis of 3,5-diaryl-6-carbethoxycyclohexenones **4a-f** have been carried out by condensing chalcones **3** with ethyl acetoacetate in the presence of basic alumina and piperidine under microwave irradiation (4-6 min) without using any solvent in high yields (82-90 %) as compared to conventional methods (60-65 %).

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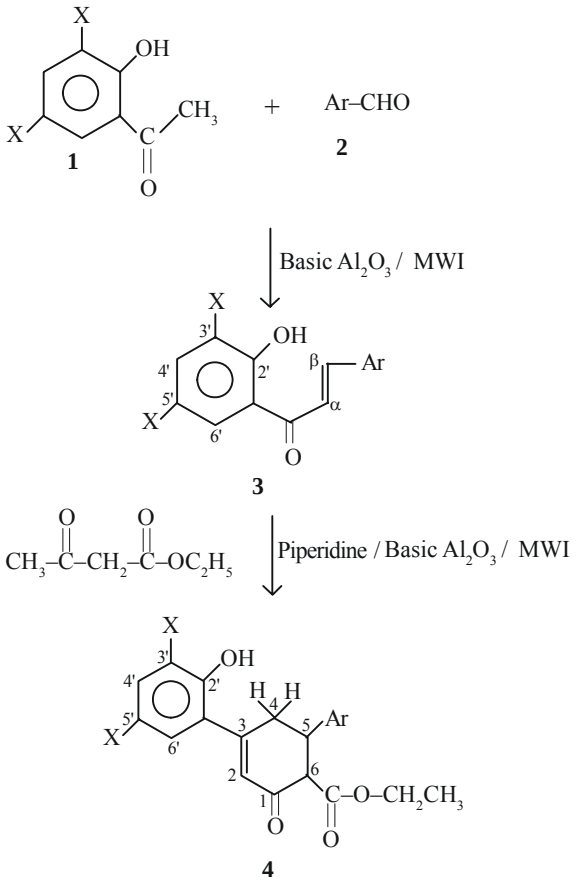

3a, 4a; X= H, Ar = C_6H_5-
3b,4b; X= H, Ar = 4-OCH_3.C_6H_4-
3c,4c; X= H, Ar = 4-Cl.C_6H_4-
3d,4d; X= H, Ar =3,4, 5-OCH_3.C_6H_2-
3e, 4e; X= H, Ar = 4-$N(CH_3)_2$.C_6H_4-
3f, 4f; X= I, Ar = 4-Cl.C_6H_4-

Scheme I

IR spectra of compound **4** showed absorption bands due to the conjugated carbonyl (1630) and ester carbonyl (1710-1750) in addition to other bands. ^{1}H NMR spectra of **4** indicated the presence of ethoxy carbonyl group, an olefinic proton at C_2, an allylic methylene group at C_4, a benzylic methine at C_5 and a methine proton at C_6. Mass spectral data of synthesized compounds **3** and **4** were in accordance with the proposed structures.

In conclusion for the synthesis of chalcones **3**, the modified Claisen-Schmidt condensation method using basic alumina and new microwave mediated synthesis of cyclohexenone derivatives **4** using basic alumina and piperidine under solvent-free conditions has several advantages as compared to conventional methods in terms of shorter reaction time, increased yield, purity of the products, environmentally benign and safe protocol.

Antibacterial activity

Synthesized compounds **3** and **4** were tested against gram +ve organisms *Staphylococcus aureus*, *Streptococcus fecalis* and gram –ve organisms *Escherichia coli*, *Proteus mirabilis*, using DMF as solvent at 200 µg / mL concentration by paper disc diffusion method. The zone of inhibition after 18 hr of incubation at 37 °C was compared with that of standard drugs Amicacin and Tobramycin.

The screening data indicated that compound **3b** showed excellent activity whereas, compounds **3c** and **3d** showed moderate activity against *S. aureus*. Compounds **3b** and **3c** displayed significant activity against *E. coli*. None of the compounds was found to exhibit any significant activity against *S. fecalis* and *P. mirabilis*.

Amongst the 3,5-diaryl-6-carbethoxycyclohexenones, **4b** and **4e** showed good activity against *S. aureus, S. fecalis* and *E. coli.* Weak to moderate activity has also been displayed by **4a, 4c** and **4d** against *S. fecalis*. Compounds **4** showed no significant activity against *P. mirabilis*.

Experimental Section

All melting points were determined in open capillaries on electrically heated metal blocks and are uncorrected. IR spectra (ν_{max} in cm^{-1}, KBr) were recorded on a Perkin-Elmer 16pc (FTIR) spectrophotometer; mass spectra were taken on a Jeol D-300 (EI) and VG-70S mass spectrometer; and ^{1}H NMR spectra in $CDCl_3$ and acetone-d_6 on a BrukerDRX-300 (300MHz, FTNMR) spectrometer (chemical shifts in δ, ppm downfield from TMS). The reactions were carried out in unmodified microwave oven (Kenstar, Output energy 1200 W, frequency 2450 MHz model no. M69706).

General procedure for the synthesis of 1, 3-diarylpropenones 3a-f. To a solution of substituted acetophenone (0.01 mole) and substituted aromatic aldehyde (0.01 mole) in ethanol (5 mL) taken in a 100 mL borosil flask, was added basic alumina (4 g). The mixture was uniformly mixed with glass rod and air dried to remove the solvent. Adsorbed material was irradiated inside a microwave oven for 2-3 min. at

medium power level (600 W). After the completion of reaction (monitored by TLC), the reaction mixture was cooled at room temperature and the product was extracted with ethanol (2 × 20 mL). Removal of the solvent and subsequent recrystallisation with ethanol resulted analytical samples of **3a-f**.

Characterization data of 1,3-diarylpropenones **3 a-f** are given in **Table I**.

3d: IR: 3438, 3045, 2938, 2834, 1634, 1576, 1498, 1446, 1374, 1263, 1199, 1020, 825, 760, 664 cm^{-1}; ^1H NMR: δ 3.9 (s, 9H, 3 × OCH_3), 6.8-7.1 (m, 6H, Ar-H), 7.3 (s, 1H, OH), 7.6-7.7 (d, 1H, = C- H_α), 7.8-7.9 (d, 1H, = C- H_β); MS: m/z (%) 311 (M^+, 4), 274 (2), 210 (2), 194 (3), 181 (8), 179 (10), 165 (12), 141 (20), 91 (20), 71 (30), 57 (100), 51 (38).

3e: IR: 3434, 3050, 2907, 1616, 1522, 1432, 1375, 1312, 1202, 1156, 985, 812, 763, 711 cm^{-1}; ^1H NMR: δ 3.0 [s, 6H, –N $(CH_3)_2$], 6.6-6.7, 6.9-7.0 (m, 8H, Ar-H), 7.3 (s, 1H, OH), 7.5-7.6 (d, 1H, = C- H_α), 7.7-7.8 (d, 1H, = C- H_β); MS: m/z (%) 267 (M^+, 2), 238 (2), 196 (1), 183 (1), 169 (2), 165 (2), 147 (4), 125 (5), 111 (45), 97 (20), 83 (28), 69 (42), 57 (100), 53 (18).

3f: IR: 3440, 3050, 2917, 1629, 1565, 1489, 1426, 1356, 1326, 1209, 1157, 1088, 1033, 986, 820, 716 cm^{-1}; MS: m/z (%) 510 (M^+, 100), 483 (9), 476 (21), 439 (5), 384 (55), 374 (29), 346 (6), 321 (5), 254 (40), 218 (16), 165 (76), 137 (42), 114 (10), 101 (50), 91 (30), 63 (20).

General procedure for the synthesis of 3,5-diaryl-6-carbethoxycyclohexenones 4a-f. A mixture of 3 (0.01 mole), ethyl acetoacetate (0.02 mole) and piperidine (0.02 mole) was dissolved in ethanol (10 mL) and taken in a 100 mL borosil flask. To this basic alumina (3.5 g) was added and the reactants properly mixed with the help of a glass rod. Adsorbed material was dried in air and irradiated inside the microwave oven at medium power level (600 W) intermittently at 0.5 min intervals. On completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and then product was extracted with ethanol (2 × 20 mL). The product separated after concentrating the solvent, was filtered and recrystallised to afford 4a-f. Their physical data are given in **Table I**.

4a: IR: 3500, 2940, 2880, 2840, 1730, 1630, 1590, 1570, 1460, 1370, 1310, 1300, 1240, 1200, 1170, 1150, 1120, 1100, 1080, 1030, 900, 860, 870, 750 cm^{-1}; ^1H NMR: δ 0.9-1.2 (t, 3H, O–CH_2–CH_3), 2.6 (m, 2H, 4-CH_2), 3.0-3.1 (distorted t, 1H, C_5-H), 3.6-3.8 (d, 1H, C_6-H), 3.9-4.0 (q, 2H, O–CH_2–CH_3), 6.4 (s, 1H, C_2-H), 6.8-7.7 (m, 9H, Ar-H).

Table I — Microwave induced syntheses of **3a-f** and **4a-f**

Compd†	m.p. °C	Colour *	Reaction time (min)	Yield (%)
3a	89 (lit.[34] 89)	Yellow	3	82
3b	92 (lit.[34] 93)	Orange	2	80
3c	149 (lit.[34] 150)	Pale Yellow	2.5	82
3d	142	Yellow	3	77
3e	160	Red	2.5	79
3f	180	Yellow	3	79
4a	155	Cream	4	76
4b	165	Cream	5	82
4c	178	Orange	4	90
4d	155	Cream	6	87
4e	150	Cream	5	91
4f	172	Yellow	6	82

† All the compounds gave satisfactory elemental analyses
* Solvent for recrystallisation was ethanol.

4b: IR: 3340, 2920, 2860, 1720, 1620, 1580, 1500, 1450, 1360, 1320, 1220, 1140, 1020, 900, 880, 800, 710, 680, 600 cm^{-1}; ^1H NMR: δ 1.0-1.2 (t, 3H, O–CH_2–CH_3), 1.6 (m, 2H, C_2-H), 2.2 (m, 2H, 4-CH_2), 2.9-3.0 (distorted t, 1H, C_5-H), 3.5-3.6 (d, 1H, C_6-H), 3.7-4.1 (q, 2H, OCH_2CH_3), 6.3-7.2 (m, 9H, Ar-H); MS:m/z (%) 366 (M^+, 55.2), 293 (100), 367 (14.9), 321 (9.4), 319 (11.9), 318 (20.7), 294 (21.9), 292 (20.3), 289 (9.5), 213 (13.1), 161 (26.2), 134 (12.1), 133 (14.1), 132 (24.5), 131 (30.5), 121 (51.5).

4c: IR: 3340, 2950, 2875 1710, 1610, 1550, 1450, 1360, 1320, 1290, 1240, 1210, 1140, 1020, 980, 950, 830, 740, 710, 700, 670 cm^{-1}; ^1H NMR: δ 1.0-1.2 (t, 3H, O – CH_2 – CH_3), 2.3 (m, 2H, C_4-H), 3.01-3.04 (distorted t, 1H, C_5-H), 3.7-3.8 (d, 1H, C_6-H), 4.0-4.2 (q, 2H, OCH_2CH_3), 6.7-7.2 (m, 9H, Ar-H); MS: m/z (%) 371 (M^+, 85), 352 (4), 341 (3), 327 (6), 324 (25), 297 (100), 289 (25), 279 (7), 266 (6), 259 (15), 244 (12), 231 (7), 213 (27), 202 (6), 187 (10), 165 (26), 157 (4), 131 (45), 115 (14), 101 (13), 91 (8), 83 (8), 77 (14).

4d: IR: 3319, 2940, 2840, 1736, 1640, 1594, 1504, 1451, 1352, 1319, 1269, 1239, 1123, 1037, 1007, 855, 755, 662 cm^{-1}; MS: m/z (%) 426 (M^+, 100), 410 (2), 397 (1), 380 (52), 365 (6), 353 (82), 338 (12), 322 (7), 311 (7), 293 (6), 280 (5), 266 (15), 251 (10), 234 (4), 213 (15), 194 (8), 181 (38), 168 (16), 153 (8), 131 (17), 115 (6), 91 (6), 77 (8).

4e: IR: 3310, 2977, 2794, 1740, 1596, 1522, 1447, 1353, 1309, 1238, 1206, 1164, 1114, 1039, 944, 885, 814, 763, 679 cm^{-1}; ^1H NMR: δ 1.06-1.1 (t, 3H, O–CH_2–CH_3), 2.90-2.92 (m, 2H, C_4-H), 3.0-3.1 (t, 6H, N$(CH_3)_2$), 3.2-3.3 (distorted t, 1H, C_5-H), 3.4-3.5 (d, 1H, C_6-H), 3.9-4.0 (q, 2H, OCH_2–CH_3); MS: m/z (%) 379 (M^+, 100), 333 (55), 306 (57), 289 (9), 277 (10), 264 (9), 256 (5), 246 (2), 219 (50), 202 (6), 183 (8), 174 (14), 158 (7), 147 (24), 134 (32), 121 (23), 103 (7), 91 (13), 77 (19).

4f: IR: 3448, 2948, 2855, 1733, 1640, 1588, 1488, 1448, 1381, 1295, 1248, 1200, 1165, 1037, 954, 824, 668 cm^{-1}.

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