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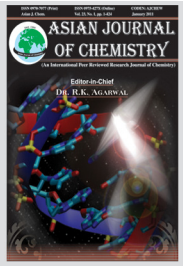

One Pot Synthesis and Antibacterial Activity of 3,5-Dibromo-2,4-dihydroxy Substituted Chalcones

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In an effort to develop antibacterial agents, a series of chalcones were prepared by Claisen-Schmidt condensation of appropriate acetophenones with appropriate aromatic aldehydes in the presence of basic alumina as solid support reagent under microwave irradiation. The synthesized compounds were characterized by their IR, ^{1}H NMR, mass spectral data and elemental analysis. The compounds have been screened for their antibacterial activity against *S. aureus*, *S. fecalis*, *E. coli* and *P. mirbilis*.

Key Words: Microwave, Solid-phase synthesis, Chalcone, Antibacterial activity.

INTRODUCTION

The combination of solid supported reagents and microwave irradiation can be used to carry out a wide range of reactions in short time and with high conversions and selectivity, without the need of solvent. Among the important tools the use of microwave irradiation (MWI) is attractive alternative for chemical application[1-4] and has become a widely accepted non-conventional energy source for performing organic synthesis[5-7].

The effect of microwave irradiation in chemical reactions is a combination of the thermal effect and non-thermal effect *i.e.* overheating, hot spots, selective heating and non-thermal effects of the highly polarizing field in addition to effects on the mobility and diffusion that may increase the probabilities of effective contacts.

Chalcones[8-10] having an α, β-unsaturated carbonyl compounds have been popular substrates for the generation of various heterocyclic compounds of therapeutic importance. The presence of enone functionality in chalcone moiety is the key factor for its biological activity as antimalarial[11], anticancer[12,13], antibacterial[13], antileishmanial[14], antiinflamatory [12,13], antineoplastic[15] and diuretic activities[15]. Further the importance of chalcones and analogous compounds in pharmaceutical[16] and biological field is well known.

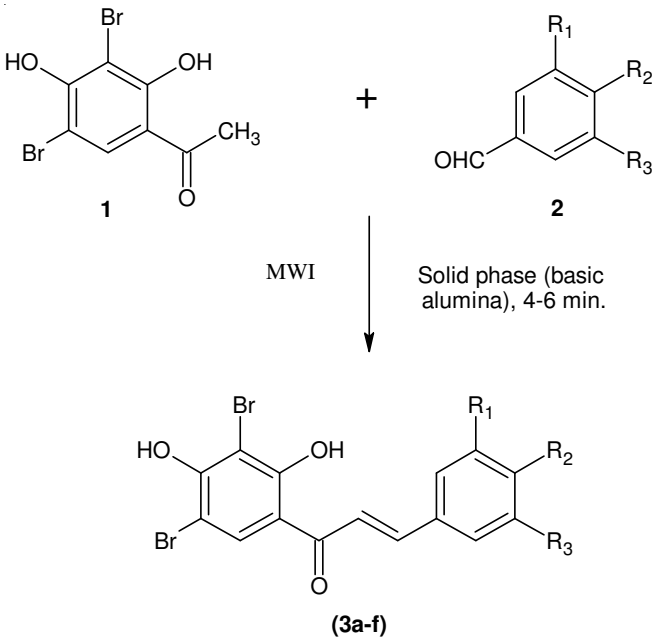
In the present communication we report the reaction of acetophenone with different aromatic aldehyde derivatives to form chalcones (**3a-f**). The structures of the various synthesized compounds were assigned on the basis of their elemental and spectral (IR, ^{1}H NMR and MASS) data. These compounds were also screened for their antibacterial activity.

EXPERIMENTAL

All melting points were determined in open capillaries on electrically heated metal blocks and are uncorrected, IR (KBr, ν_{max}, cm^{-1}) 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 on a Bruker DRX-300 (300 MHz, FTNMR) spectrometer [chemical shifts in δ (ppm) downfield from TMS using DMSO as solvent]. 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-(3,5-Dibromo-2,4-dihydroxyphenyl)-3 (substituted phenyl) propenone (3a-f): The equimolar amount (0.01mol) of the substituted acetophenones and substituted aromatic aldehydes was dissolved in ethanol (10 mL). The solution was adsorbed in basic alumina (4 gm) with constant stirring. Adsorbed material was mixed properly, dried in air and placed inside the microwave oven for 3-7 min. at medium power level (600 W). After the completion of the reaction (TLC) the mixture was cooled at room temperature and extracted with ethanol (3 x 15 mL). Removal of the solvent under reduced pressure yielded the product which on recrystallization with ethanol afforded the final product (**3a-f**) (**Scheme-I**).

Compound 3a: Orange crystals, m.p. 90 ºC (found: C, 43.95; H, 2.62. calcd. for $C_{18}H_{10}O_6Br_2$ (488.12): C, 44.29; H,3.30 %); IR (KBr, ν_{max}, cm^{-1}): 3365 (OH), 3030 (Ar-H), 1623 (conjugated C=O), 1561, 1473, 1412 (C=C/Ar), 1050, 969 (CH=CH, *trans*), 885, 780, 646 (substituted phenyl); ^{1}H



3a : $R_1 = R_2 = R_3 = OCH_3$

3b : $R_1 = R_3 = H$, $R_2 = OH$

3c : $R_1 = R_3 = H$, $R_2 = Cl$

3d : $R_3 = H$, $R_1 = R_2 = OCH_3$

3e : $R_1 = R_3 = H$, $R_2 = OCH_3$

3f : $R_2 = R_3 = H$, $R_1 = NO_2$

Scheme-I

NMR δ_H (DMSO, ppm) : 6.98-7.95 (m, Ar-H), 7.63 (d, 1H, α-H), 7.95 (d, 1H, β-H), 8.36 (s, 1H, phenolic OH), 13.38 (s, 1H, phenolic OH) ; MS : m/z (%) 438 (M^+, 96), 489 (M+1, 100), 391 (20), 311 (65), 307 (50), 295 (45).

Compound 3b : Pale yellow crystals, m.p. 170 ºC (Found :C, 42.78; H, 1.82. calcd. for $C_{15}H_{10}O_4Br_2$ (414.04): C, 43.51; H, 2.43 %); IR (KBr, ν_{max}, cm^{-1}): 3360 (OH), 3020 (Ar-H), 1629 (conjugated C=O), 1507, 1473, 1410 (C=C/Ar), 966 (CH=CH, *trans*), 887, 753, 644 (substituted phenyl); ^1H NMR δ_H (DMSO, ppm) : 6.92-8.20 (m, Ar-H), 7.55 (d, 1H, α-H), 7.86 (d, 1H, β-H), 8.33 (s, 1H, phenolic OH), 13.33 (s, 1H, phenolic OH); MS: m/z (%) 414 (M^+, 30), 412 (M-2, 25), 395 (40), 383 (35), 294 (42), 255 (36), 154 (100), 175 (44).

Compound 3c: Yellow crystals, m.p. 145 ºC (Found : C, 39.97; H, 1.56. calcd. for $C_{15}H_9O_3Br_2Cl$ (432.49) : C, 41.66; H, 2.10 %); IR (KBr, ν_{max}, cm^{-1}): 3450 (OH), 3050 (Ar-H), 1640 (conjugated C=O), 1588, 1480, 1420 (C=C, Ar), 1045 (CH=CH, *trans*), 875, 750, 680 (substituted phenyl); ^1H NMR δ_H (DMSO, ppm) : 7.53-8.0 (m, Ar-H), 7.56 (d, 1H, α-H), 7.89 (d, 1H, β-H), 8.69 (s, 1H, phenolic OH), 13.39 (s, 1H, phenolic OH); MS: m/z (%) 432 (M^+, 35), 431 (M-1, 20), 391 (22), 289 (30), 155 (15), 107 (28), 91 (20).

Compound 3d: Orange crystals, m.p. 130 ºC (Found : C, 42.87; H, 2.52. calcd. for $C_{17}H_{14}O_5Br_2$ (458.09) : C, 44.57; H, 3.08 %); IR (KBr, ν_{max}, cm^{-1}): 3216 (OH), 3045 (Ar-H), 1648 (conjugated C=O), 1510, 1479, 1439 (C=C/Ar), 1026, 947 (CH=CH, *trans*), 768, 739, 720, 631 (substituted phenyl); ^1H NMR δ_H (DMSO, ppm) : 7.12-8.05 (m, Ar-H), 7.52 (d, 1H, α-H), 7.87 (d, 1H, β-H), 8.39 (s, 1H, phenolic OH), 13.37 (s, 1H, phenolic OH); MS : m/z (%) 458 (M^+, 100), 457 (M-1, 70), 397 (40, 307 (52), 289 (45), 191 (20), 154 (90), 136 (80), 95 (38).

Compound 3e: Yellow crystals, m.p.140 ºC (Found : C, 43.65; H,1.76, calcd. for $C_{16}H_{12}O_4Br_2$ (428.07): C, 44.89; H, 2.83 %); IR (KBr, ν_{max}, cm^{-1}): 3420 (OH), 3040 (Ar-H), 1648 (conjugated C=O), 1510, 1479, 1439 (C=C/Ar), 1026, 947 (CH=CH, *trans*), 768, 739, 720, 631 (substituted phenyl); ^1H NMR δ_H (DMSO, ppm) : 6.94-8.0 (m, Ar-H), 7.53 (d, 1H, α-H), 7.84 (d, 1H, β-H,), 8.30 (s, 1H, phenolic OH), 13.35 (s, 1H, phenolic OH); MS: m/z (%) 428 (M^+, 52), 429 (M+1, 90), 307 (30), 154 (100), 121 (20), 107 (25), 89 (22).

Compound 3f: Brown crystals, m.p.178 ºC (Found : C, 39.86; H, 1.42. calcd. for $C_{15}H_9NO_5Br_2$ (443.04) : C, 40.66; H, 2.05 %); IR (KBr, ν_{max}, cm^{-1}): 3365 (OH), 3048 (Ar-H), 1621 (conjugated C=O), 1562, 1473, 1410 (C=C/Ar), 1094, 966 (CH=CH, *trans*), 887, 780, 644 (substituted phenyl); ^1H NMR δ_H (DMSO, ppm) : 6.83-7.1 (m, Ar-H), 7.62 (d, 1H, α-H), 7.92 (d, 1H, β-H), 8.49 (s, 1H, phenolic OH), 13.32 (s, 1H, phenolic OH); MS: m/z (%) 443 (M^+, 10), 445 (M+2, 30), 416 (15), 339 (20), 295 (40), 279 (22), 230 (17), 115 (12), 89 (23), 154 (60), 136 (45).

RESULTS AND DISCUSSION

Reaction of 3,5-dibromo-2,4-dihydroxy acetophenone (**1**) with aromatic aldehyde (**2**) were carried out in presence of basic alumina without solvent under microwave irradiation. The result shows the synthesis of chalcones (**3a-f**) in 89-95 % yield within 4-6 min.

In IR spectra characteristic absorptions in the region of 1650-1630 cm^{-1} is observed due to the conjugated carbonyl group (α,β-unsaturated carbonyl group). A characteristic absorption in the region 3400-3200 cm^{-1} (OH), 3050 (Ar-H), 1588, 1480, 1420 (C=C/Ar), 1050, 969 (CH=CH, *trans*) and 779, 752, 688 (substituted phenyl) also observed. The ^1H NMR spectra exhibited protons as two doublets around δ 6.8-7.3 due to α-proton and δ 7.9-8.2 due to β proton of α, β-unsaturated system. The aromatic protons of the ring (1) and (2) were observed around δ 6.7-7.9. The phenolic proton of the ring was observed around δ 8.30-8.69 and δ 13.32-13.38. Mass spectral studies of compounds **3a-f** revealed the presence of strong ions for M^+, M+2 that is isotopic peak due to the presence of bromine.

The title compounds were screened for their antibacterial activity using paper disc method and tested against gram +ve organisms. *S. aureous*, *S. fecalis* and gram-ve organisms *E. coli*, *P. mirabilis* using DMF as solvent at 200 µg/mL concentration. The zone of inhibition was recorded in mm after 18 h. of incubation at 37 ºC and the results were compared with that of standard drugs amicacin and tobramycin.

Amongst the compound **3e** showed excellent activity against gram +ve organisms. Compound **3f** showed moderate to excellent activity against gram +ve and gram -ve organisms. All **3a-f** compounds showed good activity against *E. coli* whereas other compounds showed good to moderate activity.

Conclusion :

Use of basic alumina as solid support eliminated the use of toxic solvents and bases used in classical reaction. A microwave irradiation reaction method reduces the reaction

time and improves the yield. The present methodology provides a convenient, facile, easy, economic and environmentally benign one-pot synthesis of bioactive chalcones.

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