Asian Journal of Chemistry; Vol. 25, No. 11 (2013), 6427-6433

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.15070

Microwave Enhanced Green Synthesis of 2-Pyrazolines, Isoxazolines and Cyclohexenones

ABDULLAH S. AL-BOGAMI[1,*], HAMAD Z. ALKHATHLAN[2] and TAMER S. SALEH[1]

[1]Department of Chemistry, Faculty of Science, King Abdulaziz University, North Jeddah, P.O. Box 80203, Jeddah 21589, Saudi Arabia
[2]Department of Chemistry, Faculty of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia

*Corresponding author: Fax: +966 2 6400376; Tel: +966 5 54433416; E-mail: chem_org@hotmail.com

(*Received*: 31 December 2012; *Accepted*: 11 May 2013) AJC-13486

Hydroxy chalcones undergo simple cyclizations with phenylhydrazine to afford 2-pyrazolines under microwave irradiation in the presence of glacial AcOH as cyclizing agent, also undergo simple cyclizations with hydroxylamine to afford 2-isoxazolines under microwave irradiation in the presence of KOH, and new cyclohexenone derivatives. Some valuable intermediates in the synthesis of fused heterocycles, have been prepared through K_2CO_3 which activate the cyclocondensation of hydroxychalcones with ethyl acetoacetate. The obtained results indicate that the microwave irradiation give shorter reaction times and cleaner reactions for synthesis of biologically important compounds.

Key Words: 2-Pyrazolines, 2-Isoxazolines, Cyclohexenone, Hydroxy Chalcone, Microwave Irradiation.

INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones.

Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed. In which chalcones are used to synthesize several derivatives like pyrazolines, isoxazoles, pyridine, pyrimidine, and many fused heterocyclic ring, also used for synthesis of cyclohexnone systems[1-4].

Numerous pyrazoline type compounds and isoxazoles have been found to possess useful bioactivity, *e.g.*, antimicrobial[5], central nervous system[6] and immunosuppressive[7]. Among the various pyrazoline isomers, 2-pyrazolines and 3,4-disubstituted isoxazoles appear to be the most frequently investigated compounds. As a consequence, a large number of 2-pyrazolines and 3,4-disubstituted isoxazoles have been described in the chemical literature, using different synthetic methods for their preparation. A popular procedure is based on the reaction of α,β-unsaturated carbonyl compounds with hydrazines and hydroxyl amine respectively[8-20]. However, there are always some problems due to long reaction time, low yield or environmental concerns.

A careful survey of literature reveals that cyclohexenone moiety constitutes an important structural feature in several biologically active heterocyclic compounds[21,22].

One of the most important reported methods for the synthesis of cyclohexenone that chalcones react with acetoacetic acid ester to give ethoxycarbonyl cyclohexenone derivatives presumably through Micheal addition followed by condensation of the terminal methyl group with the carbonyl function of the adduct. Although several chalcones underwent this reaction but suffer from by products, low yield and longer reaction time[23].

Microwave has increasingly been used in organic synthesis in last three decades. Compared with traditional methods, this method is more convenient and easily controlled. A large number of microwave reactions can be carried out in higher yield, shorter reaction time or milder conditions[24].

From all of the facts stated above and in continuation of our interest in utilizing green chemistry tools in synthesis of heterocyclic compounds[25-28], herein we wish to report a study the possibility of the reaction of different hydroxy chalcones with phenylhydrazines, hydroxylamines and ethyl acetoacetate under microwave irradiation as a green protocol.

EXPERIMENTAL

Melting points are uncorrected and were determined on Gallenkamp-melting point apparatus. NMR spectra were recorded on JEOL ECP 400 (400 MHz) in $CDCl_3$ and expressed as δ in ppm. Mass spectra were recorded on Shimadzu QP-5050A GC/MS system. Microwave experiments were carried out using CEM MARS synthator™ microwave apparatus. TLC was performed on (TLC plates silica gel $60F_{245}$ pre-coated 20 × 20 cm layer thickness 0.25 mm).

Microwave experiments were carried out using CEM MARS synthator™ microwave apparatus with temperature control for microwave experiments using IR sensor.

Synthesis of pyrazoline derivatives: Phenylhydrazine reagent (3 mmol) was added dropwise to a stirring solution of the chalcones **1a-j** (1 mmol) in glacial AcOH (10 mL). The mixtures in open vessel subjected to microwave heating (300 W) for suitable time 7-12 min. The progress of the reaction was monitored by TLC upon completion of the reaction, the reaction mixture after cooling poured into crushed ice water (30 mL) and the reaction mixture was left to stay at 2-3 ºC overnight. The separated solid was collected by filtration and recrystallized from absolute.

3-(2'-Hydroxyphenyl)-1,5-diphenyl-2-pyrazoline (3a)[29]: m.p. 160-162 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (dd, *J* = 16.88, 7.32 Hz, 1H) 3.99 (dd, *J* = 16.81, 12.44Hz, 1H), 5.23 (1H, dd, *J* = 12.50, 7.32 Hz, 1H), 6.95-7.36 (m, 14H, Ar' H), 10.8 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 44.07, 63.45, 113.43, 116.42, 116.70, 119.47, 120.02, 125.99, 127.23, 127.96, 129.21, 129.37, 130.52, 141.99, 144.11, 149.68. 157.28. MS: *m/z* 314.

5-(4'-Chlorophenyl)-3-(2''-hydroxy-6''methoxyphenyl)-1-phenyl-2-pyrazoline (3b)[29]: m.p. 158-159 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (dd, *J* = 18.00, 7.32 Hz, 1H), 3.76 (s, 3H, OMe), 4.18 (dd, *J* = 18.32, 12.4Hz, 1H), 5.11 (1H, dd, *J* = 12.50, 8.08 Hz, 1H), 7.17-7.81 (m, 12H, Ar' H), 11.83 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 48.09, 55.54, 62.72, 101.77, 106.35, 110.11, 113.35, 119.99, 127.48, 129.24, 119.45, 130.67, 133.48, 141.08, 144.10, 149.78, 158.57, 159.23. MS: m/z 378.

5-(4'-Chlorophenyl)-3-(2''-hydroxyphenyl)-1-phenyl-2-pyrazoline (3c)[29]: m.p. 138-140 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24 (dd, *J* = 17.50, 7.32 Hz, 1H), 4.02 (dd, *J* = 16.84, 12.5Hz, 1H), 5.22 (1H, dd, *J* = 12.50, 8.08 Hz, 1H), 6.92-7.34 (m, 13H, Ar' H), 11.22 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 43.97, 62.85, 113.48, 116.23, 116.77, 119.53, 120.29, 125.11, 127.23, 127.44, 129.04, 129.27, 129.58, 130.69, 133.75, 140.47, 143.92, 149.73, 157.28. MS: m/z 348.

3-(2'-Hydroxyphenyl)-5-(3'',4'',5''-trimethoxyphenyl)-1-phenyl-2-pyrazoline (3d): m.p. 97-99 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (dd, *J* = 16.88, 8.80 Hz, 1H), 3.82 (s, 9H, OMe), 3.98 (dd, *J* = 18.0, 12.44 Hz, 1H), 5.12 (1H, dd, *J* = 12.44, 8.80 Hz, 1H), 6.65-7.25 (m, 11H, Ar' H), 11.83 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 44.25, 56.28, 60.95, 102.49, 113.62, 116.33, 116.74, 119.51, 120.33, 127.28, 129.21, 129.29, 129.68, 130.56, 137.38, 137.86, 144.57, 150.03, 154.03,157.32,. MS: *m/z* 404.

5-(3',5'-Dichloro-2'-hydroxyphenyl)-5-(3'',4'',5''-trimethoxyphenyl)-1-phenyl-2-pyrazoline (3e): m.p. 153-155 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (dd, *J* = 16.88, 7.32 Hz, 1H), 3.81 (s, 9H, OMe), 4.07 (dd, *J* = 17.60, 12.44Hz, 1H), 5.57 (1H, dd, *J* = 12.50, 7.32 Hz, 1H), 6.48-7.22 (m, 9H, Ar' H), 11.44 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 43.78, 56.28, 60.95, 102.40, 113.71, 118.37, 120.97, 122.22, 124.14, 125.08, 129.32, 129.69, 137.04, 137.59, 143.61, 147.91, 151.58, 154.11 MS: *m/z* 472.

5-(2',4'-Dichlorophenyl)-3-(2''-hydroxy-5''-methylphenyl)-1-phenyl-2-pyrazoline (3f)[29]: m.p. 146-148 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H, Me), 3.30 (dd, *J* = 17.60, 8.80 Hz, 1H), 4.17 (dd, *J* = 17.60, 12.50 Hz, 1H), 5.65 (1H, dd, *J* = 12.00, 7.00 Hz, 1H), 6.82-7.48 (m, 11H, Ar' H), 10.24 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 20.13, 40.29, 59.76, 113.10, 116.53, 116.67, 119.98, 128.68, 128.85, 129.91, 130.10, 131.81, 132.77, 133.53, 138.22, 143.76, 150.82, 154.62. MS: *m/z* 396.

5-(2',4'-Dichlorophenyl)-3-(2''-hydroxy-5''-methoxyphenyl)-1-phenyl-2-pyrazoline (3g)[29]: m.p. 120-122 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12 (dd, *J* = 16.88, 7.32 Hz, 1H), 3.76 (s, 3H, OMe), 4.06 (dd, *J* = 17.60, 12.50Hz, 1H), 5.59 (1H, dd, *J* = 12.50, 7.36 Hz, 1H), 6.86-7.49 (m, 11H, Ar' H), 10.26 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 42.33, 56.01, 59.81, 112.00, 113.17, 116.65, 117.32, 120.40, 128.18, 128.40, 129.42, 129.80, 137.34, 143.39, 149.80, 151.43, 152.60. MS: *m/z* 412.

5-(5'-Bromo-2'hydroxyphenyl)-5-(2'',4''-dichlorophenyl)-1-phenyl-2-pyrazoline (3h)[29]: m.p. 128-129 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.14 (dd, *J* = 17.60, 7.32 Hz, 1H), 4.08 (dd, *J* = 16.84, 12.50 Hz, 1H), 5.59 (1H, dd, *J* = 12.50, 7.36 Hz, 1H), 6.87-7.26 (m, 11H, Ar' H), 10.64 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 42.12, 49.92, 111.28, 113.23, 117.97, 118.57, 120.72, 128.19, 128.26, 129.47, 129.55, 130.05, 133.22, 134.49, 137.00, 143.09, 148.72, 156.22. MS: *m/z* 462.

5-(3',5'-Dichloro-2'-hydroxyphenyl)-5-(2'',4''-dichlorophenyl)-1-phenyl-2-pyrazoline (3i)[29]: m.p. 203-204 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.14 (dd, *J* = 17.60, 7.36 Hz, 1H), 4.07 (dd, *J* = 16.80, 12.50Hz, 1H), 5.65 (1H, dd, *J* = 12.50, 7.32 Hz, 1H), 6.87-7.49 (m, 10H, Ar' H), 11.82 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 42.00, 60.14, 113.32, 118.14, 121.09, 122.35, 124.21, 125.11, 128.24, 129.53, 130.13, 130.22, 134.64, 136.68, 142.70, 148.11, 151.57. MS: *m/z* 452.

5-(5'-Chloro-2'-hydroxyphenyl)-5-(2'',4''-dichlorophenyl)-1-phenyl-2-pyrazoline (3j)[29]: m.p. 129-131 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (dd, *J* = 16.90, 7.32 Hz, 1H), 4.07 (dd, *J* = 17.60, 12.44 Hz, 1H), 5.58 (1H, dd, *J* = 12.50, 7.32 Hz, 1H), 6.85-7.24 (m, 11H, Ar' H), 11.62 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 42.12, 59.91, 113.23, 117.36, 118.11, 120.71, 124.28, 126.28, 128.19, 128.27, 129.47, 130.05, 130.36, 132.55, 134.48, 137.02, 143.12, 148.83, 155.74. MS: *m/z* 417.

Synthesis of isoxazoline derivatives: To a mixture of 2-hydroxychalcone (0.29 mmol) and hydroxylamine hydrochloride (1.45 mmol) in absolute ethanol (5 mL) a three drops of KOH solution (10 g in 20 mL of water) was added. The reaction mixture was subjected to microwave irradiation (300 W) for 6-10 min. as monitored by TLC. Then pour the reaction mixture on ice-water mixture, the resulting precipitate was washed with distilled water and dried. The resulting crude was crystallized from absolute ethanol to obtained white crystalline product.

3-(2'-Hydroxy phenyl)-5-(3'',4'',5''-trimethoxyphe-nyl)-2-isoxazoline (7a)[30]: m.p. 129-130 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (dd, *J* = 16.16, 8.08 Hz, 1H), 3.87 (s, 9H, 3OMe), 3.95 (dd, *J* = 19.6, 11.00 Hz, 1H), 5.67 (1H, dd, *J* = 11.60, 8.08 Hz, 1H), 6.65 (s, 2H, Ar' H), 6.92-7.28 (m, 4H, Ar' H), 9.81 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 43.53, 56.10, 60.96, 81.68, 101.70, 117.06, 118.57, 122.41, 132.62, 135.27, 153.76, 156.08, 158.38. MS: *m/z* 329.

3-(5'-Chloro-2'-hydroxyphenyl)-5-(3'',4'',5''-trimethoxyphenyl)-2-isoxazoline (7b)[30]: m.p. 144-145 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.44 (dd, *J* = 16.90, 8.08 Hz, 1H), 3.89 (s, 9H, 3OMe), 3.91 (dd, *J* = 17.6, 11.60 Hz, 1H), 5.69 (1H, dd, *J* = 11.60, 8.80 Hz, 1H), 6.59 (s, 2H, Ar'H), 6.89-7.48 (m, 3H, Ar' H), 9.61 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 43.19, 56.21, 60.15, 81.95, 102.73, 115.06, 118.57, 124.33, 127.78, 131.62, 135.27, 153.76, 156.08, 157.51. MS: *m/z* 363.

3-(3',5'-dichloro-2'-hydroxyphenyl)-5-(3'',4'',5''-trimethoxyphenyl)-1-phenyl--2-isoxazoline (7c)[30]: m.p. 133-136 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (dd, *J* = 16.77, 8.08 Hz, 1H), 3.90 (s, 9H, 3OMe), 3.92 (dd, *J* = 17.8, 7.04 Hz, 1H), 5.67 (1H, dd, *J* = 11.20, 8.80 Hz, 1H), 6.54 (s, 2H, Ar'H), 7.19 (s, 1H, Ar'H), 7.48 (s, 1H, Ar' H), 10.01 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 43.66, 56.1, 61.35, 81.70, 103.25, 121.22, 126.47, 128.55, 134.56, 134.91, 137.84, 149.87, 152.58, 156.99. MS: *m/z* 398.

3-(5'-Chloro-2'-hydroxyphenyl)-5-(2'',4''-dichlorophenyl)-2-isoxazoline (7d)[30]: m.p. 112-116 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.29 (dd, *J* = 16.84, 6.60 Hz, 1H), 3.99 (dd, *J* = 16.9, 11.76 Hz, 1H), 5.98 (1H, dd, *J* = 11.00, 7.32 Hz, 1H), 6.95-7.38 (m, 6H, Ar' H), 9.98 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 43.10, 81.70, 116.25, 119.21, 125.56, 126.13, 129.56, 131.57, 133.56, 133.87, 134.16, 136.78, 156.22, 158.20. MS: *m/z* 342.

Synthesis of cyclohexenone derivatives: Hydroxy chalcone analogue **8** (2.2 mmol) and ethyl acetoacetate **2** (2.9 mmol) were mixed in dichloromethane (5 mL) then K_2CO_3 (6.6 mmol) was added the evaporate under vaccum the solvent, the remaiang residue was taken and subjected to microwave irradiation for 6 min. as monitered by TLC. The reaction mixture was then taken in dichloromethane to get ride of K_2CO_3 then the reaction product separated as a solid after evaporation of dichloromethane under vacuum, which was filtered off and recrystallized from absolute ethanol.

Ethyl 4-(2'-hydroxyphenyl)-2-oxo-6-phenyl-cyclohex-3-en-1-carboxylate (10a): Yield: 85 %, m.p. 152-154 ºC, IR (KBr, ν_{max}, cm^{-1}): 1660 (C=O ketone), 1740 (C=O ester), 3310 (OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, 3H, *J* = 6.8 Hz, Me Ester), 3.05 (d, *J* = 5.88 Hz, 1H, H6), 3.15 (1H, dd, J_{trans} = 5.60 Hz, J_{cis} =17.4 Hz, H1) 3.81-3.83 (m, 1H, H5), 4.08 (q, *J* = 6.8 Hz, CH_2 Ester), 6.74 (s, 1H, H_{vinyl}), 7.21-7.31 (m, 9H, Ar' H), 7.77 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 13.99, 37.72, 44.61, 59.83, 61.09, 116.91, 120.70, 126.75, 127.39, 127.49, 128.64, 128.83, 131.13, 141.10, 153.97, 159.33, 169.59, 195.43. MS: *m/z* 336. Anal. calcd. for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C 74.76, H 6.08.

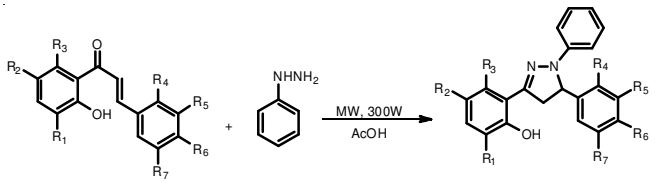
Ethyl 4-(2'-hydroxyphenyl)-2-oxo-6-(4'-chlorophenyl)-cyclohex-3-en-1-carboxylate (10b): Yield: 91 %, m.p. 173-175 ºC, IR (KBr, ν_{max}, cm^{-1}): 1667 (C=O ketone), 1740 (C=O ester), 3322 (OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, 3H, *J* = 6.9 Hz, Me Ester), 3.03 (d, *J* = 6.60 Hz, 1H, H6), 3.11 (1H, dd, J_{trans}= 6.30 Hz, J_{cis} =17.4 Hz, H1) 3.78-3.81 (m, 1H, H5), 4.08 (q, *J* = 6.9 Hz, CH_2 Ester), 6.70 (s, 1H, H_{vinyl}), 6.73 -7.31 (m, 8H, Ar' H), 7.98 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 14.09, 37.53, 43.96, 59.66, 61.32, 76.78, 77.10, 116.92, 120.77, 126.66, 128.70, 128.78, 129.04, 131.31, 133.28, 139.58, 154.10, 159.28, 169.46, 195.20. MS: *m/z* 370. Anal. calcd. for $C_{21}H_{19}ClO_4$: C, 68.02; H, 5.16. Found: C 68.25, H 5.01.

Ethyl-4-(2'-hydroxyphenyl)-2-oxo-6-(3',4',5'-trimethoxyphenyl)-cyclohex-3-en-1-carboxylate (10c): Yield: 77 %, m.p. 84-85 ºC, IR (KBr, ν_{max}, cm^{-1}): 1662 (C=O ketone), 1743 (C=O ester), 3312 (OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, 3H, *J* = 6.9 Hz, Me Ester), 3.04 (m, 1H, H6), 3.12 (1H, dd, J_{trans} = 3.30 Hz, J_{cis} =17.4 Hz, H1), 3.80-3.82 (m, 1H, H5), 3.86 (s, 9H, 3OMe), 4.08 (q, *J* = 6.9 Hz, CH_2 Ester), 6.56 (s, 2H, Ar'H), 6.72 (s, 1H, H_{vinyl}), 6.92-7.31 (m, 4H, Ar' H), 7.99 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 14.18, 37.73, 44.80, 55.49, 56.21, 60.93, 61.12, 102.47, 104.30, 106.74, 117.52, 124.83, 129.90, 137.07, 137.15, 153.39, 156.82, 158.77, 162.42, 169.66, 196.38. MS: *m/z* 426. Anal. calcd. for $C_{24}H_{26}O_7$: C, 67.59; H, 6.15. Found: C 67.84, H 5.95.

Ethyl 4-(2'-hydroxy-4'-methoxyphenyl)- 2-oxo-6-(3',4',5'-trimethoxyphenyl)-cyclohex-3-en-1-carboxylate (10d): Yield: 86 %, m.p. 172-174 ºC, IR (KBr, ν_{max}, cm^{-1}): 1660 (C=O ketone), 1741 (C=O ester), 3322 (OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, 3H, *J* = 6.8 Hz, Me Ester), 3.03 (m, 1H, H6), 3.11 (1H, dd, J_{trans} = 6.30 Hz, J_{cis} =17.4 Hz, H1) 3.75-3.83 (m, 1H, H5), 3.86 (s, 12H, 4OMe), 4.07 (q, *J* = 6.8 Hz, CH_2 Ester), 6.44 (s, 2H, Ar'H), 6.50 (s, 1H, H_{vinyl}), 6.99-7.31 (m, 3H, Ar' H), 8.01 (s, 1H, D_2O exchangable, OH). ^{13}C NMR: δ 14.12, 26.10, 34.98, 55.81, 56.10, 61.30, 63.78, 102.11, 103.55, 106.88, 107.64, 126.01, 127.58, 136.11, 142.30, 151.24, 152.11, 156.41, 161.00, 169.58, 197.11. MS: m/z 456. Anal. calcd. for $C_{25}H_{28}O_8$: C, 65.78; H, 6.18. Found: C 66.01, H 6.02.

RESULTS AND DISCUSSION

We report in our earlier paper that some Aldol reactions between 2-hydroxyacetophenone derivatives and benzaldehydes in the presence of KOH/MeOH to give chalcones[28], it has been found that undergo a rapid cyclization with phenylhydrazine in the presence of glacial AcOH under microwave irradiation at (300 W) to yield 2-pyrazolines in 4-12 min. The results of the study are summarized in Table-1.

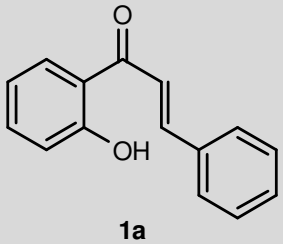
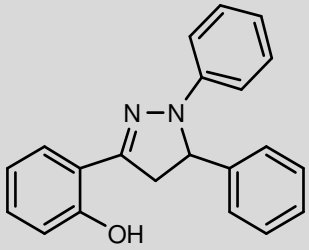
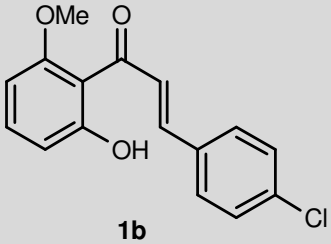
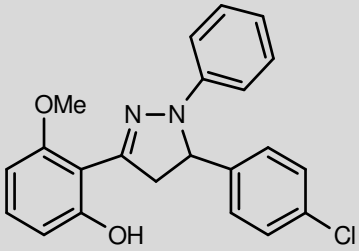
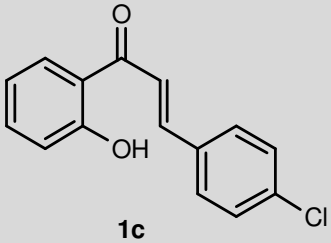
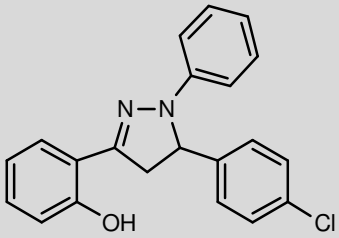
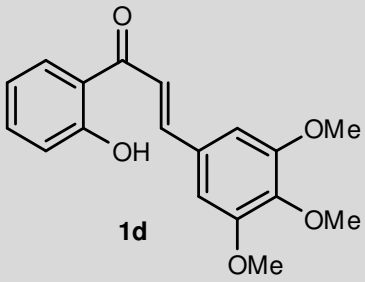
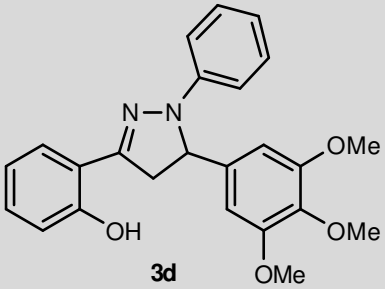
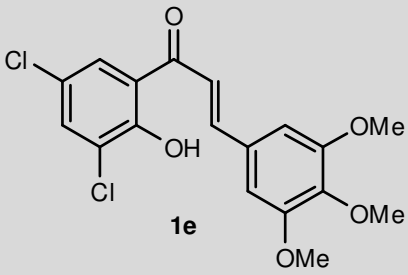
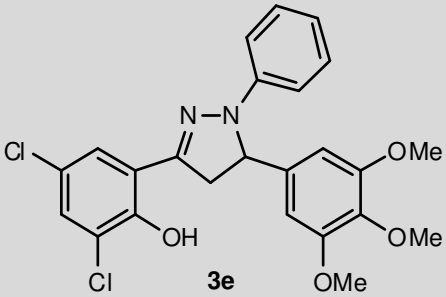
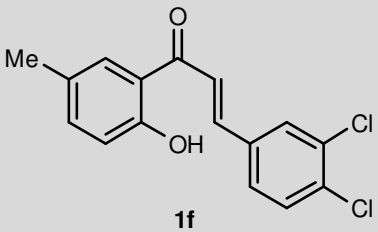
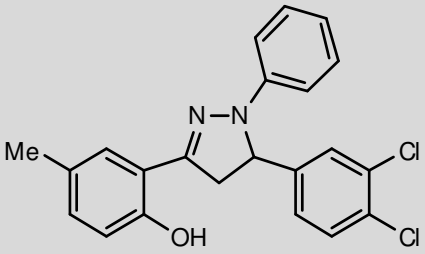


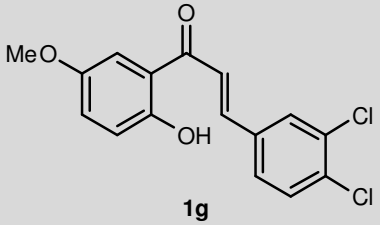
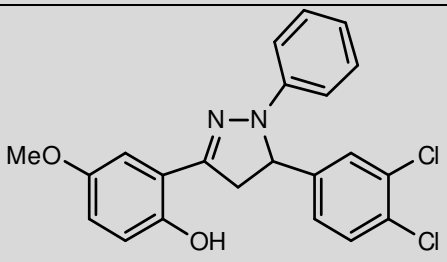
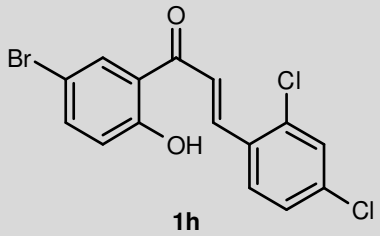
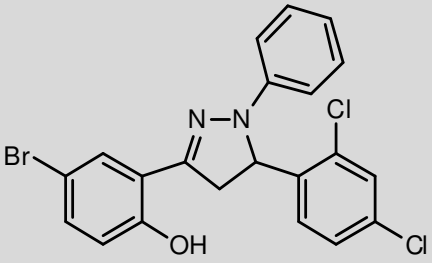
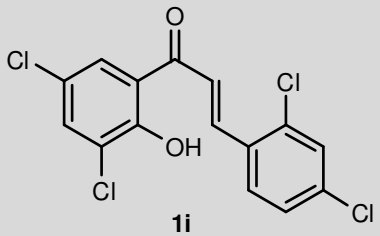
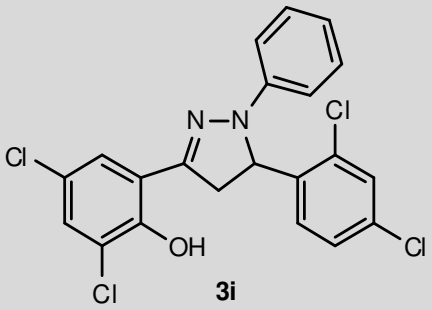
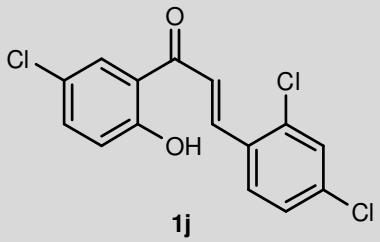
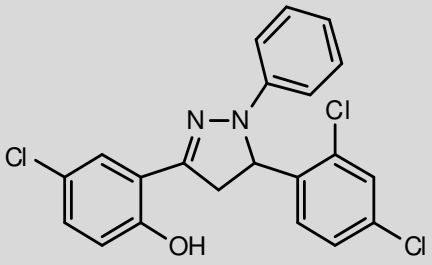
1,3	a	b	c	d	e	f	g	h	I	J
R_1	H	H	H	H	Cl	H	H	H	Cl	H
R_2	H	H	H	H	H	Me	H	Br	Cl	Cl
R_3	H	OMe	H	H	Cl	H	H	H	H	H
R_4	H	H	H	H	H	Cl	Cl	Cl	Cl	Cl
R_5	H	H	H	OMe	OMe	H	H	H	H	H
R_6	H	Cl	Cl	OMe	OMe	Cl	Cl	Cl	Cl	Cl
R_7	H	H	H	OMe	OMe	H	H	H	H	H

Scheme-I: Microwave assisted synthesis of 2-pyrazolines

The heterocyclic products were characterized on the basis of their ^{1}H NMR, ^{13}C NMR and MS spectral analysis (*cf.* experimental part).

TABLE-1
SYNTHESIS OF PYRAZOLINE FROM 2-HYDROXYCHALCONES

Entry	Substrate	Product	Yield (%)	Time (min)
1	 **1a**	 **3a**	90	5
2	 **1b**	 **3b**	88	9
3	 **1c**	 **3c**	82	4
4	 **1d**	 **3d**	94	8
5	 **1e**	 **3e**	91	9
6	 **1f**	 **3f**	84	10

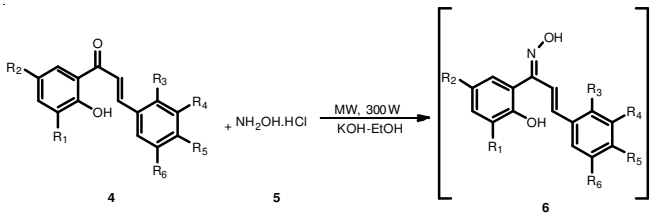
Entry	Substrate	Product	Yield (%)	Time (min)
7	 **1g**	 **3g**	90	12
8	 **1h**	 **3h**	87	8
9	 **1i**	 **3i**	83	9
10	 **1j**	 **3j**	81	10

On the other hand, the ring closure reaction of chalcone **a-d** and hydroxylamine hydrochloride (**5**) occurred under microwave irradiation in the presence of potassium hydroxide to afford the isoxazoline derivatives **6a-d** (**Scheme-II**).

A possible mechanism for this reaction, proposed based on our experimental results together with some literature data for the cyclization reaction of chalcone, is that it is realized in two steps; first nucleophilic attack of the carbonyl group by the NH_2 moiety occurs, which is followed by oxime formation (adduct 6) and then intramolecular cyclization lead to the five member ring products **7a-d** (**Scheme-II**).

The reactions were performed using α,β-unsaturated carbonyl compounds with diverse substituents. The results of the experiments are summarized in Table-2.

Also, the reaction of chalcones and their heterocyclic analogs with ethyl acetoacetate is known to lead to three structurally diverse types of compounds, depending on the experimental conditions employed: pyrylium salts[31], Michael addition

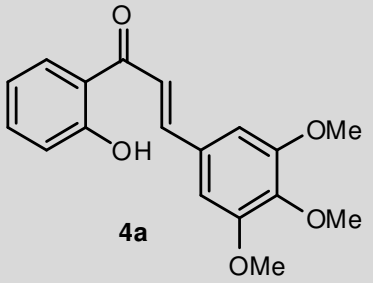
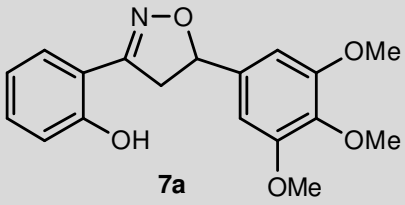
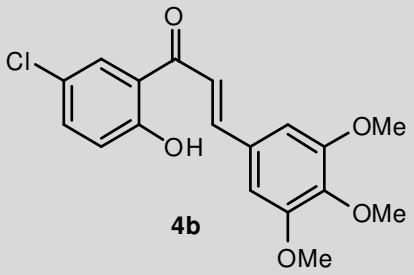
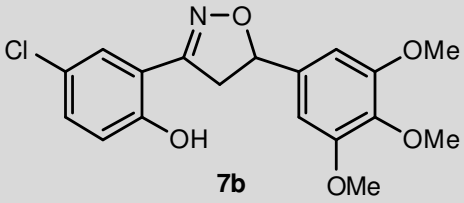
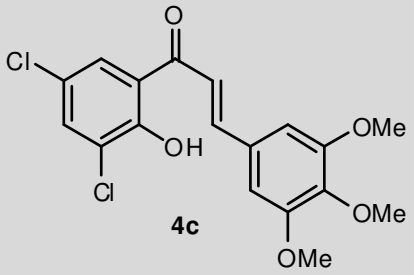
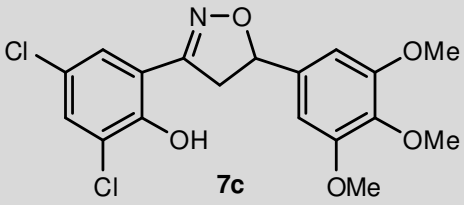
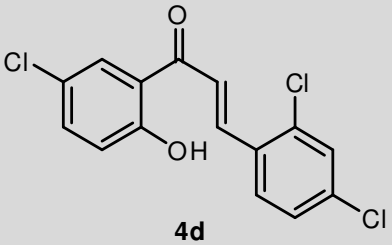
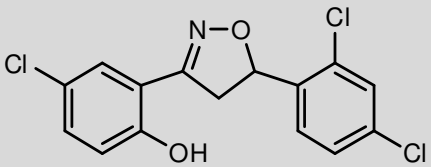


4,7	A	B	C	D
R_1	H	H	Cl	H
R_2	H	Cl	Cl	Cl
R_3	H	H	H	Cl
R_4	OMe	OMe	OMe	H
R_5	OMe	OMe	OMe	Cl
R_6	OMe	OMe	OMe	H

Scheme-II: Microwave assisted synthesis of isoxazolines

products[32] and cyclohexenone derivatives[33]. The catalyst plays a key role in directing the reaction to different end products.

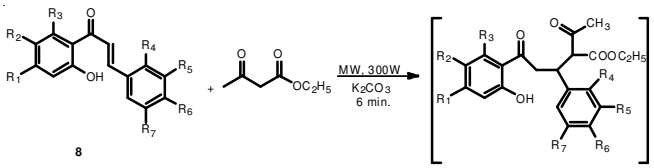
TABLE-2
SYNTHESIS OF ISOXAZOLINES FROM 2-HYDROXYCHALCONES

Entry	Substrate	Product	Yield (%)	Time (min)
1	 **4a**	 **7a**	82	6
2	 **4b**	 **7b**	88	8
3	 **4c**	 **7c**	80	9
4	 **4d**	 **7d**	77	10

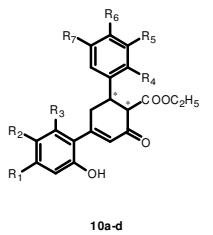
A strong Lewis acid such as boron trifluoride etherate generates pyrylium cations from the reaction of chalcones and acetoacetic acid esters, but basic catalysts would turn the intermediate.

Michael addition product into cyclohexenones through the intramolecular cyclocondensation of the methyl group originating from acetoacetic acid ester and the ketone function of the initial chalcone. Thus, in the presence of a base, chalcone analogs **8a-f** and ethyl acetoacetate produce cyclohexenones **10a-f** by means of an intermediate Michael adduct **9** in 6 min, as outlined in **Scheme-III**.

The cyclocondensation of ethyl acetoacetate with chalcones **8** leads to the generation of two chiral centers at C_1 and C_6 in the structure of cyclohexenones **10**. As the explored reaction is not stereoselective, both configuration of the chiral carbon atoms are expected to be noticed in the synthesized cyclohexenones **10**, which would result in a mixture of diastereomers. No attempt to separate the diastereomeric cyclohexenones **10** has been undertaken and the cyclocondensation



8,10	A	B	c	d
R_1	H	H	H	OMe
R_2	H	H	H	H
R_3	H	H	H	H
R_4	H	H	H	H
R_5	H	H	OMe	OMe
R_6	H	Cl	OMe	OMe
R_7	H	H	OMe	OMe


10a-d

Scheme-III: Microwave assisted synthesis of cyclohexenones

products have been characterized in the form of the mixture originated from the synthesis. Structural analysis of the newly

synthesized cyclohexenones **10** comprised IR and NMR investigations. The IR spectra of these compounds revealed a sharp strong absorption band above 1700 cm^{-1} that can be correlated with the presence of the ester function in the structure of cyclohexenones **10**. Furthermore, another sharp strong absorption band was noticed at approximately 1660 cm^{-1} and was assigned to the carbonyl group conjugated with a carbon-carbon double bond. In addition to a broad absorption band in region 3500-3200 cm^{-1} due to hydroxyl group. No other absorption band could be evidenced in the region of the IR spectrum associated with the stretching vibrations of the carbonyl group, thus excluding the intermediate Michael adduct having an extra carbonyl group. The ^1H NMR spectra substantiated the results of the IR analysis. The characteristic signals of an ethyl ester moiety (a triplet at chemical shift values of about 1 ppm and a quartet at δ values above 4 ppm) confirmed the presence of the ester group in the structure of cyclohexenones **10**. The proton at C_6 of the cyclohexenone skeleton usually appears as a multiplet immediately below 3 ppm, when the signals due to this proton shift to higher δ values and single with the peaks attributed to the proton at C_1. The latter proton's signals at about 3.15 ppm turn up as two pairs of doublets, on one hand as a result of the splitting due to the neighboring C_6 proton and owing to the possible *cis-trans* geometry on the other hand. The two diastereotopic protons at C_5 of the cyclohexenone ring are represented in the ^1H NMR spectra of compounds **10** as a multiplet at 3.6-3.8 ppm. The characteristic signal in the ^1H NMR spectra of compounds **10** is however the singlet of the vinylic proton in the position 3 of the cyclohexenone ring, that occurs at approximately 6.5 ppm and confirms that the intramolecular cyclocondensation subsequent to the Michael addition actually took place.

In conclusion, we develop a facile synthesis of pyrazoline, isoxazoline and cyclohexanone derivatives utilizing hydroxy chalcone derivatives under microwave irradiations which give high yield in short reaction time.

REFERENCES

1. M.A. El.Hashah, M. El-Kady, M.A. Saiyed and A.A. Elaswy, *Egypt. J. Chem.*, **27**, 715 (1985).
2. L.S. Crawley and W.J. Fanshawe, *J. Heterocycl. Chem.*, **14**, 531 (1977).
3. E.C. Taylor and R.W. Morrison, *J. Org. Chem.*, **32**, 2379 (1967).
4. P.S. Utale, P.B. Raghuvanshi and A.G. Doshi, *Asian J. Chem.*, **10**, 597 (1998).
5. K. Ramalingham, G.X. Thyvekikakath, K.D. Berlin, R.W. Chesnut, R.A. Brown, N.N. Durham, A.E. Ealick and D. van der Helm, *J. Med. Chem*., **20**, 847 (1977).
6. R.E. Brown and J. Shavrel, US Patent, 624,102 (1972); *Chem. Abstr.*, **76**, 59618 (1972).
7. J.G. Lombardino and I.G. Otterness, *J. Med. Chem*., **24**, 830 (1981).
8. L.C. Raiford and W.J. Peterson, *J. Org. Chem.*, **1**, 544 (1936).
9. L.C. Raiford and G.V. Gundy, *J. Org. Chem*., **3**, 265 (1938).
10. L.C. Raiford and R.H. Manley, *J. Org. Chem*., **5**, 590 (1940).
11. W. Ried and G. Dankert, *Chem. Ber*., **90**, 2707 (1957).
12. R.H. Wiley, C.H. Jarboe, F.N. Hayes, E. Hansbury, J.T. Nielsen, P.X. Callahan and M.C. Sellars, *J. Org. Chem*., **23**, 732 (1958).
13. A.E.A. Sammour, *Tetrahedron*, **20**, 1067 (1964).
14. I. Bhatnagar and M.V. George, *Tetrahedron*, **24**, 1293 (1968).
15. J.L. Aubagnac, J. Elguero and R. Jacquier, *Bull. Soc. Chim. Fr.*, 3292 (1969).
16. F.G. Weber, K. Brosche, C. Seedorf and A. Rinow, *Monatsh. Chem.*, **100**, 1924 (1969).
17. M.G. Joshi and K.N. Wadodkar, *Indian J. Chem*., **20B**, 1090 (1981).
18. T.C. Sharma, S.R. Pawar and N.J. Reddy, *Acta Chim. Hung*, **112**, 159 (1983).
19. D.N. Dhar and R. Raghunathan, *Indian J. Chem.*, **23B**, 1187 (1984).
20. V.D. Orlov, M.A. Aziz, N.O. Mchedlov-Petrosyan and P.K.D. Asoka, *Khim. Geterotsikl. Soedin.*, 1511 (1985).
21. V. Padmavathi, K. Sharmila, A. Somasekhar and D. Bhaskar, *Indian J. Chem*, **40B**, 11 (2001).
22. D.B. Reddy, A.S. Reddy and V. Padmavathi, *J. Chem. Res. (S)*, 784 (1998).
23. S. Samshuddin, B. Narayan, B.K. Sarojini, H.S. Yathirajan and R. Raghavendra, *Der Pharma Chemica*, **4**, 1445 (2012).
24. C. Chen, K.M. Wilcoxen, C.Q. Huang, J.R. McCarthy, T. Chen and D.E. Grigoriadis, *Bioorg. Med. Chem. Lett*., **14**, 3669 (2004).
25. A.S. Albogami, *Asian J .Chem.*, **23**, 3045 (2011).
26. A.S. Albogami, A.M. Almajid, M.A. Al-Saad, A.M. Mosa, S.A. Almazroa and H.Z. Alkhathlan, *Molecules*, **14**, 2147 (2009).
27. A.S. Albogami, *Synthetic Commun.*, **41**, 2952 (2011).
28. A.S. Albogami, U. Karama, A.A. Mousa, V. Khan, S.A. Al-mazroa and H.Z. Alkhathlan, *Oriental J. Chem.*, **28**, 619 (2012).
29. A. Lévai and J. Jekob, *Arkivoc*, **10**, 199 (2005).
30. L. Jurd, *Tetrahedron*, **31**, 2884 (1975).
31. W. Davey and J.R. Gwilt, *J. Chem. Soc*., 1015 (1957).
32. J.A. VanAllan and G.A. Reynolds, *J. Org. Chem.*, **33**, 1102 (1968).
33. A. Sammour, M.T. Elzimaity and A. Abdel-Maksoud, *J. Chem. U.A.R.*, **12**, 481 (1969).