MICROWAVE-ASSISTED SYNTHESIS OF SUBSTITUTED PYRAZOLONES UNDER SOLVENT-FREE CONDITIONS

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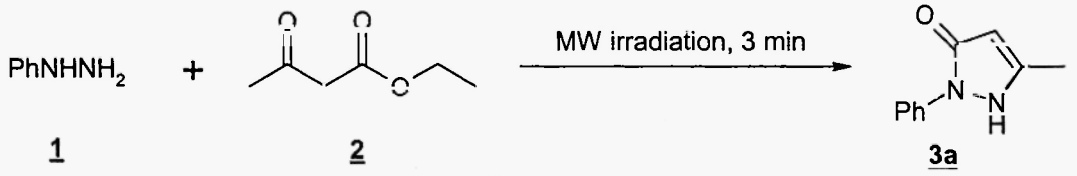
Abstract: Condensation of hydrazine derivatives with various ß-keto esters under solvent-free conditions using microwave irradiation leads to very rapid formation of pyrazolones with good to excellent yields.

Introduction

Pyrazolone derivatives are one of the important classes of organic compounds due to their biological activities (1) and pigment properties (2). They are also key organic intermediates for the preparation of various synthetic targets (3). A number of known methods have been documented in the literature for the synthesis of pyrazolones. Most of these methods are based on the reaction of a hydrazine derivative with a β-keto ester in a solvent under refluxing conditions (4). Recent developments include solid-phase synthesis of substituted pyrazolones from polymer-bounded β-keto esters (5) and a two-step reaction of benzoyl hydrazones with silyl enolates in the presence of catalytic amounts of $Sc(OTf)_3$ that result in formation of pyrazolone derivatives in low amounts after long reaction times (6).

There has been growing interests to apply microwave (MW) irradiations to enhance the scope of synthetic organic chemistry under solvent-free systems (7). In continuation of our recent investigations on organic manipulations using MW irradiation in solvent less systems (8) and because of our interests to develop the chemistry of heterocyclic compounds (9), we now report a simple and rapid method for preparation of pyrazolone derivatives using condensation reaction of hydrazine or phenyl hydrazine with various acetoacetate moieties under MW irradiation in short periods of time leading to formation of high to excellent yields of products (Scheme 1).

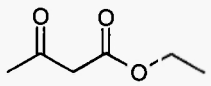
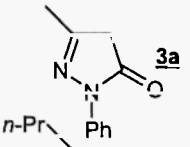
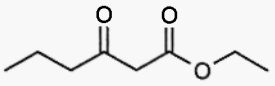
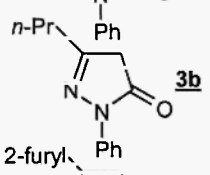
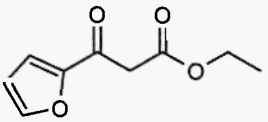
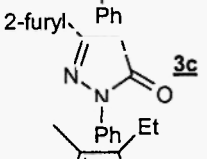
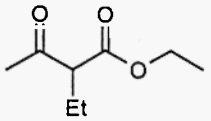
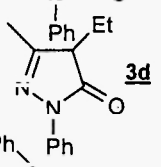
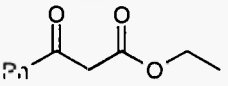
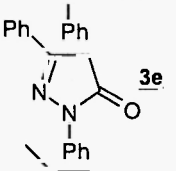
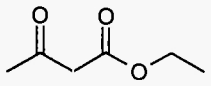
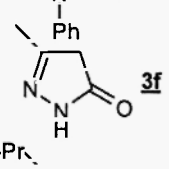
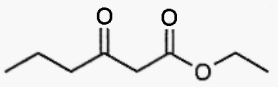
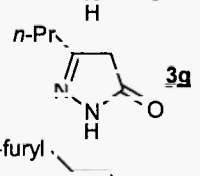
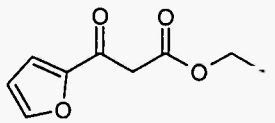
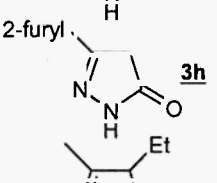
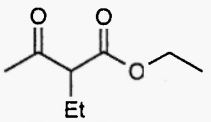
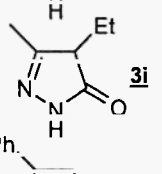
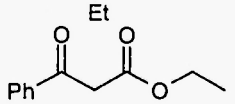
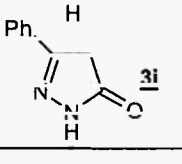


Scheme-1

Results and Discussions

When phenyl hydrazine (1) was treated with equimolar quantities of ethyl acetoacetate (2) under MW irradiation and without any solvent, complete coupling reaction took place in less than 3 minutes leading to formation of 2-Phenyl-5-methyl-2,4-dihydro-pyrazol-3-one (3a) via elimination of water and ethanol (Table 1, entry 1). The product was easily precipitated by aqueous work up. In contrast, the classical condensation gave a lower yield (38%) of 3a after several hours treatment of the mixture at elevated temperatures (140 °C). To examine a relatively large-scale synthesis, 100 mmole of phenylhydrazine and ethyl acetoacetate were irradiated in a conventional microwave oven for 3 minutes leading to isolation of more than 90% of 3a.

Table-1: MW Assisted Reactions of Hydrazines with β-Keto Esters

Entry	Substrate	Hydrazine	Product	Time (Sec)	Yield (%)[a]
1		C_6H_5 NH NH_2	 **3a**	180	91
2		C_6H_5 NH NH_2	 **3b**	165	94
3		C_6H_5 NH NH_2	 **3c**	150	91
4		C_6H_5 NH NH_2	 **3d**	180	91
5		C_6H_5 NH NH_2	 **3e**	120	93
6		NH_2 NH_2	 **3f**	30[b]	94
7		NH_2 NH_2	 **3g**	30[b]	87
8		NH_2 NH_2	 **3h**	15	86
9		NH_2 NH_2	 **3i**	30[b]	89
10		NH_2 NH_2	 **3i**	60	89

[a] isolated yields; [b] no irrdiation.

Other β-keto esters reacted in the same manner with phenyl hydrazine (entries 2-5) or hydrazine (entries 6-10) to obtain 86-94% of their respective pyrazolone derivatives in short time periods. In case of hydrazine, reactions completed much faster and even in some cases (entries 6, 7 and 9) there was no need for the use of MW irradiation. All reactions proceeded cleanly and resulted easily in precipitation of a single product.

Experimental

A conventional microwave oven (900 W) was used for the irradiation of the reaction mixture. All reported yields are isolated yields. Melting points were determined on Buchi melting point apparatus without any correction. IR spectra were recorded on a Bruker vector 22 Spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on FT-NMR Bruker Ac 80 as DMSO-d_6, and $CDCl_3$ solutions with TMS as internal reference. Mass spectra were recorded on Fisons 8000 Trio instrument at ionization potential of 70 eV.

General procedure for the preparation of pyrazolone derivatives

A mixture of phenyl hydrazine (2 mmole, 0.22 g) and ethyl acetoacetate (2 mmole, 0.24 g) were placed in a Pyrex test tube, and the mixture was exposed to MW irradiation for the time period specified in Table 1 by pulsed irradiation technique (1 minute irradiation with 30 seconds intervals). The reaction mixture was cooled to room temperature, poured into ice-water mixture (10 ml), and the precipitates were collected by filtration. The pure product was obtained by recrystallization of the precipitates using EtOH and H_2O. Structures of the products were verified by comparison of their IR, ^{1}H NMR, and MS spectra and their melting points with those reported in the literature.

Characterization Data

(**3a**): (91% yield), m.p. 127 °C (reported m.p. 126 °C (10a)); ^{1}H NMR (DMSO-d_6); δ 2.22 (s, 3H), 5.46 (s, 1H), 7.10-7.90 (m, 5H), 11.5 (br s, 1H); MS m/z (%), 174 (M^+, 100), 105 (55), 91 (94), 77 (92); IR (KBr, cm^{-1}) 2420, 1594,1530.

(**3b**): (94% yield), m.p. 110 °C (reported m.p. 110.5-111 °C (10a)); ^{1}H NMR (DMSO-d_6); 1.01 (t, 3H, *J*=7 Hz), 1.75 (m, 2H), 2.60 (t, 2H, *J*=7 Hz), 5.44 (s, 1H), 7.60-7.85 (m, 5H), 11.50 (br s, 1H); MS m/z (%), 202 (M^+, 100), 173 (59), 91 (99), 77 (97) ; IR (KBr, cm^{-1}) 2928, 1595,1540.

(**3c**): (91% yield), m.p. 182 °C (reported m.p. 236 °C (10b)); ^{1}H NMR (DMSO-d_6); 5.92 (s, 2H), 6.80-8.00 (m, 8H), 11.90 (br s, 1H); MS m/z (%), 226 (M^+, 52), 93 (100), 77 (68) ; IR (KBr, cm^{-1}) 2900, 1595,1557.

(**3d**): (91% yield), m.p. 108 °C (reported m.p. 108 °C (10a)); ^{1}H NMR ($CDCl_3$); 0.83 (t, 3H, *J*= 7.5 Hz), 1.85 (m, 2H), 2.06 (s, 3H), 3.14 (t, 1H, *J*=7.5 Hz), 7.10-7.92 (m, 5H); MS m/z (%), 202 (M^+, 63), 174 (23), 91 (42), 77 (100); IR (KBr, cm^{-1}) 2965, 1687,1496.

(**3e**): (93% yield), m.p. 88 °C (reported m.p. 90 °C (10a)); ^{1}H NMR ($CDCl_3$); 3.65 (s, 2H), 7.10-8.00 (m, 10H); MS m/z (%), 236 (M^+, 91), 194 (42), 103 (80), 91 (79), 77 (100) ; IR (KBr, cm^{-1}) 2965, 1705,1593.

(**3f**): (94% yield), m.p. 206 °C (reported m.p. 220 °C (10a)); ^{1}H NMR (DMSO-d_6); 2.19 (s, 3H), 5.30 (s, 1H), 9.50 (br s, 2H); MS m/z (%), 98 (M^+, 100), 67 (24), 41 (55), 39 (69) ; IR (KBr, cm^{-1}) 2738, 1623,1457.

(**3g**): (87% yield), m.p. 207 °C (reported m.p. 209 °C (10b)); ^{1}H NMR ($CDCl_3$); 0.96 (t, 3H, J=7.5 Hz), 1.57 (m, 2H), 2.50 (t, 2H, J=7.5 Hz), 5.32 (s, 1H), 10.50 (br s, 2H); MS m/z (%), 126 (M^+, 52), 111 (25), 98 (100); IR (KBr, cm^{-1}) 2735, 1620,1507.

(**3h**): (86% yield), m.p. 212 °C; ^{1}H NMR (DMSO-d_6); 5.73 (s, 1H), 6.64-7.75 (m, 3H), 11.20 (br s, 2H); MS m/z (%), 150 (M^+, 100), 121 (31), 93 (45) ; IR (KBr, cm^{-1}) 2598, 1608, 954.

(**3i**): (89% yield), m.p. 222 °C (reported m.p.90 °C (10a)); ^{1}H NMR (DMSO-d_6); 1.12 (t, 3H, *J*=7 Hz), 2.11 (s, 3H), 2.42 (q, 2H, *J*=7 Hz), 10.30 (br, 2H); MS m/z (%), 126 (M^+, 76), 111 (90), 98 (42), 42 (100); IR (KBr, cm^{-1}) 2965, 1616,1404.

(**3j**): (89% yield), m.p. 226 °C (reported m.p. 220 °C (10a)); ^{1}H NMR (DMSO-d_6); 6.00 (s, 1H), 7.33-7.92 (m, 5H), 11.00 (br,2H); MS m/z (%), 160 (M^+, 100), 103 (50), 102 (49), 77 (50) ; IR (KBr, cm^{-1}) 2600, 1598,1508.

Conclusions

We have reported a rapid and efficient method for the preparation of substituted pyrazolones by condensation of hydrazine derivatives with various β-keto esters under MW irradiation and solvent-free conditions.

Acknowledgements

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