Int. J. Chem. Sci.: 9(2), 2011, 565-572
ISSN 0972-768X
www.sadgurupublications.com

FACILE SYNTHESIS OF SOME NEW DIHYDROPYRAZOLE DERIVATIVES FROM 3-(SUBSTITUTED)-N-PHENYL-2-ENAMIDES UNDER THE FRAMEWORK OF GREEN CHEMISTRY

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ABSTRACT

The present work reports MW assisted synthesis of dihydropyrazoles (5a-5e) by cyclocondensation of 3-(substituted)-N-phenyl-2-enamide (3a-3e) with the hydrazide derivatives of benzotriazole (4) in presence of glacial acetic acid (GAA). The synthesized compounds have been characterized by their IR, ^{1}H NMR and Mass spectral studies.

Key words: Pyrazole, Hydrazide, Benzotriazole, Microwave.

INTRODUCTION

Development of microwave technique has helped immensely in developing newer synthetic protocol towards eco-friendly mode[1-3]. The microwave assisted organic reactions occurs more rapidly, safely and with higher chemical yields render the microwave method superior to conventional method[4]. The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. This is mainly due to the ease of preparation and the important biological activity exhibited by this nucleus. The pyrazole nucleus has been proven to be fertile source of medicinal agents such as antibecterial[5], antifungal[l6], anti-tubercular[7], antiamoebic[8-10], anesthetic[11,12], analgesic[13] and antiparasitic[14,15] properties.

Looking to such a wide scope of pyrazoles as target molecules in medicinal chemistry, some new dihydropyrazole derivatives were synthesized under framework of green chemistry. The present work gives an environmentally benign synthesis of

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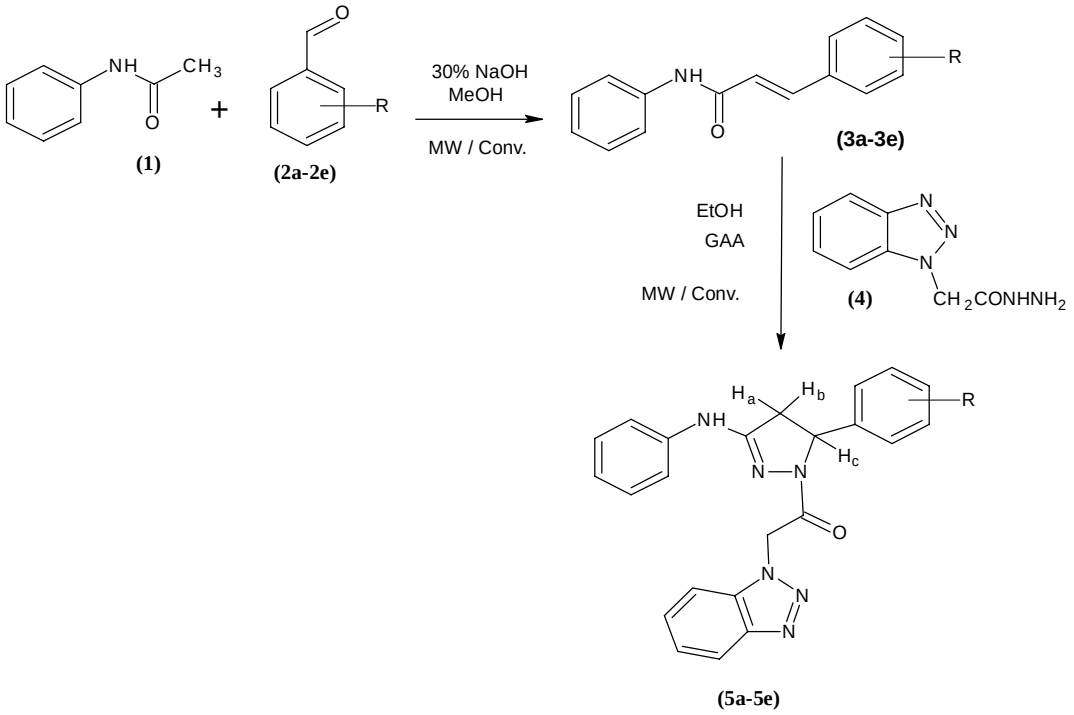
dihydropyrazole derivatives **(5a-5e)** from substituted N-phenylprop-2-enamide **(3a-3e)** with the hydrazide derivatives of benzotriazole **(4)** under acetic condition in ethanol solvent (Reaction Scheme). A comparative study in terms of yield and reaction period is shown in Table 1.



Scheme

R = (a) H; (b) 3-OH; (c) 4-OCH_3; (d) 4-Br; (e) 3-NO_2

Table (1) Physical and Analytical data of compounds (3a-3e and 5a-5e)

Compd.	m.p. (^oC)	Conv. (hrs) (% yield)	MWI min. (% yield)	Mol. formula (M.W.)	Elemental analysis Calculated (Found) (%)		
					C	H	N
3a	150	6 (45)	4 (80)	$C_{15}H_{13}NO$ (223)	80.69 (80.62)	5.87 (5.84)	6.27 (6.24)
3b	126	6 (52)	4 (76)	$C_{15}H_{13}NO_2$ (239)	75.30 (75.22)	5.48 (5.44)	5.85 (5.80)

Cont…

Compd.	m.p. (^oC)	Conv. (hrs) (% yield)	MWI min. (% yield)	Mol. formula (M.W.)	Elemental analysis Calculated (Found) (%)		
					C	H	N
3c	105	6 (50)	4 (80)	$C_{16}H_{15}NO_2$ (253)	75.87 (75.81)	5.97 (5.86)	5.53 (5.48)
3d	92	6 (54)	4 (74)	$C_{15}H_{12}BrNO$ (302)	59.62 (59.50)	4.00 (3.92)	4.64 (4.60)
3e	110	6(50)	4 (78)	$C_{15}H_{12}N_2O_3$ (268)	67.16 (67.10)	4.51 (4.46)	10.44 (10.38)
5a	186	9 (46)	7 (86)	$C_{23}H_{20}N_6O$ (396)	69.68 (69.62)	5.08 (5.02)	21.20 (21.16)
5b	198	9 (42)	8(81)	$C_{23}H_{20}N_6O_2$ (412)	66.98 (66.90)	4.89 (4.82)	20.38 (20.36)
5c	156	10 (56.3)	8 (88)	$C_{24}H_{22}N_6O_2$ (426)	67.59 (67.52)	5.20 (5.12)	19.71 (19.64)
5d	206	10 (54.5)	8(80)	$C_{23}H_{19}BrN_6O$ (475)	58.12 (58.06)	4.03 (4.00)	17.68 (17.62)
5e	140	9 (60.10)	7 (83.4)	$C_{23}H_{19}N_7O_3$ (441)	62.58 (62.50)	4.34 (4.28)	22.21 (22.18)

EXPERIMENTAL

All the reactions were carried out in a domestic microwave oven (Kenstar Microwave Model No. OM-26 EGO). The progress of the reaction was monitored by thin layer chromatography using silica gel-G coated glass plates. Benzene and methanol in 8 : 2 ratios has been used as eluent. The melting points of the newly synthesized compounds were determined in an open capillary and were uncorrected. The IR spectra were recorded on Perkin-Elmer IR spectrometer. The ^1H NMR spectra were recorded on Bruker AC 400 (400 MHz) NMR spectrometer using DMSO as solvent and TMS as internal standard. All chemical shift values are expressed in the δ (ppm) scale. Mass spectra of the compounds were recorded on a JEOL-DX 300 Mass Spectrometer at 70 eV.

N,3-diphenylprop-2-enamide (3a)

Conventional method: N,3-diphenylprop-2-enamide **(3a)** was prepared by reacting a mixture of acetinalide **(1)** (0.01 mol), benzaldehyde **(2a)** (0.01 mol), aqueous NaOH (30% ,

10 mL) and methanol (50 mL). The reaction mixture was stirred for 10 hrs. at room temperature using magnetic stirrer. Then, it was refluxed for 6-8 hrs. on water bath.

After the completion of reaction (monitored by TLC) an excess of solvent was removed by distillation and the resultant viscous mass was poured into ice water (150 mL) mass with vigorous stirring and left over night for complete precipitation. The resultant solid product was filtered, washed with cold water, dried and recrystallized from ethanol.

MW irradiation method: To prepare N,3-diphenylprop-2-enamide **(3a)** the reactant acetanilide **(1)** (0.01 mol), benzaldehyde **(2a)** (0.01 mol) were dissolved in methanol (50 mL) with drop wise addition of 30% aqueous NaOH (10 mL) under vigorous stirring. The reaction mixture was stirred for 1 hrs. at room temperature, then it was irradiated for 3-5 minutes under microwave giving 30 seconds pulses.

After completion of reaction (monitored by TLC) the reaction mixture was poured into ice water (150 mL) with vigorous stirring and left overnight for complete precipitation. The resultant solid was filtered, dried and recrystallized from ethanol.

N,3-diphenylprop-2-enamide (3a)

IR (KBr) cm^{-1}: 3308 (NH), 3010 (C-H str., Ar-H), 1660 (C=O), 1596 (C=C); ^1H NMR (DMSO) δ, ppm: 6.40-7.0 (m, 10H, Ar), 5.90 (d, 1H, CH vinyl), 5.67 (d, 1H, CH vinyl), 4.90 (s, 1H, NH); Mass: m/z 223.

3-(3-hydroxypenyl)-N-phenylprop-2-enamide (3b)

IR (KBr) cm^{-1}: 3462 (OH), 3310 (NH), 3012 (C-H str., Ar-H), 1661 (C=O), 1598 (C=C); ^1H NMR (DMSO) δ, ppm: 6.50-7.20 (m, 9H, Ar), 6.08 (d, 1H, CH vinyl), 5.82 (d, 1H, CH vinyl), 5.12 (s, 1H, NH), 5.52 (s, 1H, OH); Mass: m/z 239.

3-(4-methoxypenyl)-N-phenylprop-2-enamide (3c)

IR (KBr) cm^{-1}: 3311 (NH), 3014 (C-H str., Ar-H), 1662 (C=O), 1599 (C=C); ^1H NMR (DMSO) δ, ppm: 6.20-7.30 (m, 9H, Ar), 6.10(d, 1H, CH vinyl), 5.92 (d, 1H, CH vinyl), 5.24 (s, 1H, NH), 3.5 (s, 3H, OCH_3); Mass: m/z 253.

3-(4-bromopenyl)-N-phenylprop-2-enamide (3d)

IR (KBr) cm^{-1}: 3312 (NH), 3016 (C-H str., Ar-H), 1664 (C=O), 1600 (C=C), 848 (Ar-Br); ^1H NMR (DMSO) δ, ppm: 6.40-7.35 (m, 9H, Ar), 6.20 (d, 1H, CH vinyl), 6.08 (d, 1H, CH vinyl), 5.80 (s, 1H, NH); Mass: m/z 302 $[M]^{+\cdot}$, 304 $[M+2]^{+\cdot}$.

3-(3-Nitropenyl)-N-phenylprop-2-enamide (3e)

IR (KBr) cm^{-1}: 3315 (NH), 3018 (C-H str., Ar-H), 1666 (C=O), 1602 (C=C), 1540, 1499 (NO_2); ^1H NMR (DMSO) δ, ppm: 6.35-7.40 (m, 9H, Ar), 6.30 (d, 1H, CH vinyl), 6.22 (d, 1H, CH vinyl), 5.95 (s, 1H, NH); Mass: m/z 268.

2-(1H-benzotriazole-1-yl)-1-[5-phenyl-3-(phenyl amino)-4,5-dihydro-1H-pyrazol-1-yl] ethanone (5a)

Conventional method: Compound **(5a)** was prepared by reacting a mixture of purified N-phenylprop-2-enamide **(3a)** (0.01 mol), hydrazide of benzotriazole **(4)** (0.01 mol), glacial acetic acid (1-2 mL) in ethanol (50mL) by refluxing for 9-10 hrs. on water bath.

After completion of reaction an excess of the solvent was removed by distillation and the resultant mass was poured into ice water (100 ml) with vigorous stirring. It was kept cool overnight. The resultant solid product was filtered, washed with cold water, dried and purified by recrystallization from ethanol.

MW irradiation method: To prepare **(5a)** the equimolar amount of reactant **(3a)** (0.01 mol), hydrazide of benzotriazole **(4)** (0.01 mol) were dissolved in ethanol (50 mL). Glacial acetic acid (GAA) (2 mL) added to the reaction mixture was exposed for 6-8 minutes under microwave irradiation giving intermittent 30 seconds pulses. The completion of reaction was monitored byTLC. After completion of reaction resultant mass was poured into ice cold water (100 mL) with vigorous stirring. It was kept cool overnight. The resultant solid product was filtered, washed with sufficient cold water, dried and purified by recystallization from absolute ethanol.

2-(1H-benzotriazole-1-yl)-1-[5-phenyl-3-(phenyl amino)-4,5-dihydro-1H-pyrazol-1-yl] ethanone (5a)

IR (KBr) cm^{-1}: 3342 (NH), 3016 (C-H str., Ar-H), 2950 (CH_2), 1810 (C=O), 1676(C=N); ^1H NMR (DMSO) δ, ppm: 6.82-7.50 (m, 14H, Ar), 6.2 (dd, 1H, H_c), 5.2 (s, 1H, NH), 4.46(dd, 1H, H_a), 3.42 (dd, 1H, H_b), 3.1 (s,2H, CH_2); Mass: m/z 396.

2-(1H-benzotriazole-1-yl)-1-[5-phenyl(3-hydroxyphenyl)-3-(phenylamino)-4,5-dihydro-1H-pyrazol-1-yl] ethanone (5b)

IR (KBr) cm^{-1}: 3460 (OH), 3344 (NH), 3017 (C-H str., Ar-H), 2952 (CH_2), 1811(C=O), 1677 (C=N); ^1H NMR (DMSO) δ, ppm: 6.40-7.80 (m, 13H, Ar), 6.35 (dd, 1H,

H_c), 5.35 (s, 1H, OH), 5.25 (s, 1H, NH), 4.48 (dd, 1H, H_a), 3.49 (dd, 1H, H_b), 3.18 (s, 2H, CH_2); Mass: m/z 412

2-(1H-benzotriazole-1-yl)-1-[5-phenyl(4-methooxyphenyl)-3-(phenylamino)-4,5-dihydro-1H-pyrazol-1-yl] ethanone (5c)

IR (KBr) cm^{-1}: 3345 (NH), 3018 (C-H str., Ar-H), 2954 (CH_2), 1812 (C=O), 1678 (C=N), 1225 (C-O-C); ^{1}H NMR (DMSO) δ, ppm: 6.50-7.86 (m, 13H, Ar), 6.36 (dd, 1H, H_c), 5.30 (s, 1H, NH), 4.50 (dd, 1H, H_a), 3.46 (dd, 1H, H_b), 3.60 (s, 3H, O-CH_3), 3.22 (s, 2H, CH_2); Mass: m/z 426.

2-(1H-benzotriazole-1-yl)-1-[5-phenyl(4-bromophenyl)-3-(phenylamino)-4,5-dihydro-1H-pyrazol-1-yl] ethanone (5d)

IR (KBr) cm^{-1}: 3346 (NH), 3020 (C-H str., Ar-H), 2960 (CH_2), 1814 (C=O), 1680 (C=N), 840 (Br); ^{1}H NMR (DMSO) δ, ppm: 6.60-7.88 (m, 13H, Ar), 6.38 (dd, 1H, H_c), 5.32 (s, 1H, NH), 4.52 (dd, 1H, H_a), 3.47 (dd, 1H, H_b), 3.23 (s, 2H, CH_2); Mass: m/z 475 $[M]^{+\cdot}$, 477 $[M+2]^{+\cdot}$.

2-(1H-benzotriazole-1-yl)-1-[5-phenyl(3-nitrophenyl)-3-(phenylamino)-4,5-dihydro-1H-pyrazol-1-yl] ethanone (5e)

IR (KBr) cm^{-1}: 3348 (NH), 3022 (C-H str., Ar-H), 2962 (CH_2), 1815 (C=O), 1683 (C=N),1606, 1415 (NO_2); ^{1}H NMR (DMSO) δ, ppm: 6.64-7.96 (m, 13H, Ar), 6.40 (dd, 1H, H_c), 5.33 (s, 1H, NH), 4.54 (dd, 1H, H_a), 3.48 (dd, 1H, H_b), 3.24 (s, 2H, CH_2); Mass: m/z 441.

RESULTS AND DISCUSSION

N,3-diphenyl-prop-2-enamide **(3a)** is the required starting material and was prepared by reacting acetanilide **(1)** with substituted benzaldehyde **(2a)**, using both conventional and microwave irradiation method in basic medium (30% NaOH) and methanol as solvent.

Compound **(3a)** showed IR peaks at 1660 (C=O), 3308(NH), 1596 (C=C), 3010 (C-H str., Ar-H) cm^{-1}. In ^{1}H NMR spectrum, characteristic peaks were observed at δ 5.67 (1H, d, CH vinyl), 5.90 (1H, d, CH vinyl), 4.90 (1H, s, NH). Similarly structures of compounds **(3b-3e)** were confirmed from their spectral data. Then compounds **(3a-3e)** were subjected to cyclization with compound 4 in ethanol under acetic medium to give compounds **(5a-5e)** respectively. The IR spectrum of compound **(5a)** showed bands at 3342 (NH), 1810 (C=O), 1646 (C=N), 2950 (CH_2) along with other bands at 932, 762, 668, 549 cm^{-1}. The

disappearance of IR peaks of CH=CH **(3a)** at 1596 cm^{-1} and appearance of IR peaks at 1646 cm^{-1}(C=N), 2950 (CH_2), 1810 (C=O) supports the formation of final product **(5a)**. ^{1}H NMR signals at δ 4.46 (1H, dd, H_a), 3.42 (1H, dd, H_b), 6. 2 (1H, t, H_c) and 5.2 (1H, s, NH), further confirmed the formation of product.

ACKNOWLEDGEMENT

We are thankful to Prof. Suresh C. Ameta for giving valuable suggestions during the progress of the work. Authors are also thankful to the Head, Department of Chemistry, M.L. Sukhadia University, Udaipur for providing laboratory facilities. Our thanks are also due to the Director, SAIF, CDRI, Lucknow, India for providing spectral and analytical data.

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Revised : 06.04.2011 *Accepted : 08.04.2011*