Journal of Chemistry and Chemical Sciences, *Vol.6(10), 893-901, October 2016* *ISSN 2229-760X (Print)*
(An International Research Journal), *www.chemistry-journal.org* *ISSN 2319-7625 (Online)*

Synthesis and Characterization of Novel Trisubstituted N-(2-methoxy-4-nitrophenyl)-1-phenyl-5-aryl-1 H-pyrazol-3-Amine Derivatives

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(Received on: October 9, 2016)

ABSTRACT

A series of novel trisubstituted pyrazole *N*-(2-methoxy-4-nitrophenyl)-1-phenyl-5-aryl-1*H*-pyrazol-3-amine derivatives have been synthesized by the reaction of substituted various novel cinnamamides with phenyl hydrazine. Various cinnamamide were prepared by condensation of appropriate 2-methoxy-4-nitroacetanilide with substituted aldehydes in the presence of sodium hydroxide in ethanol solvent under reflux. We are demonstrating the convenient process for synthesis novel trisubstituted *N*-(2-methoxy-4-nitrophenyl)-1-phenyl-5-aryl-1*H*-pyrazol-3-amine derivatives in high yield.

Keywords: Pyrazole derivatives, 2-methoxy-4-nitroacetanilide, Cinnamamide, Trisubstituted.

1. INTRODUCTION

Pyrazoles are well known five member heterocyclic compounds and several procedures for its synthesis have been extensively studied. Such studies have been stimulated by various promising applications, especially in the case of tri substituted pyrazole derivatives[1,2]. In fact, certain substituted pyrazoles are used as antitumor[3], antibacterial and antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal agents[4–12]. Some of these compounds have also anti-inflammatory[13], anti-diabetic[14], and anesthetic[15] and anticancer[16] properties.

Moreover, β-unsaturated ketones are convenient intermediate compounds for the synthesis of pyrazole heterocycles often exhibiting biological activity. Pyrazoles and chalcones played a crucial part in the development building blocks for both natural and

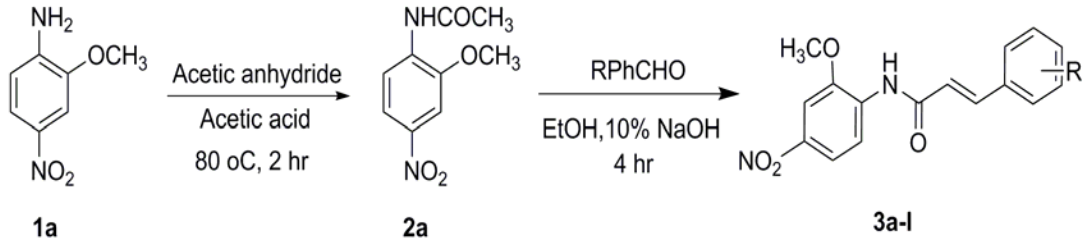
synthetic biological active compounds[17-22]. Keeping in view the importance of these biological activities, it was considered of interest to synthesize some new trisubstituted pyrazole derivatives.

Our group is involved in the development of various synthetic methodologies for the synthesis of novel heterocyclic derivatives[23-27]. In this context, recently we have reported a water mediated synthesis of highly Functionalized Pyrazolone derivatives using TEAB[28]. Earlier we have developed a library of trisubstituted pyrazoles and isoxazoles derivatives using ketene S,S-acetals as building block in aqueous medium[29]. These continue efforts in the field of heterocyclic synthesis motivated us to synthesize some novel trisubstituted pyrazoles using *N*-(2-methoxy-4-nitrophenyl)-3-phenylacrylamide for biological interest. In the present work we wish to report novel *N*-(2-methoxy-4-nitrophenyl)-1-phenyl-5-aryl-1*H*-pyrazol-3-amine.

2. RESULTS AND DISCUSSION

A series of trisubstituted pyrazole derivatives have been synthesized by the reaction of substituted various cinnamamides 3a-l with phenyl hydrazine. The starting materials, cinnamamide were prepared by claisen-schmidt condensation of appropriate acetanilide 2a with substituted aldehydes in the presence of sodium hydroxide in ethanol solvent. The newly synthesized derivatives were characterized using spectroscopy and element analysis.

Initially, a solution containing 2-methoxy-4-nitroaninline (0.03 mole), acetic anhydride (0.03 mole), and acetic acid (20 ml) as a solvent was prepared. This reaction mixture was refluxed at 80 ºC with stirring for 2 hr (Scheme 1). The reaction was being monitored by TLC. After completion of the reaction, the reaction mixture was poured onto crushed ice with vigorous stirring. The separated crude *N*(2-methoxy,4-nitro)acetanilide[30] 2a was then isolated through filtration.

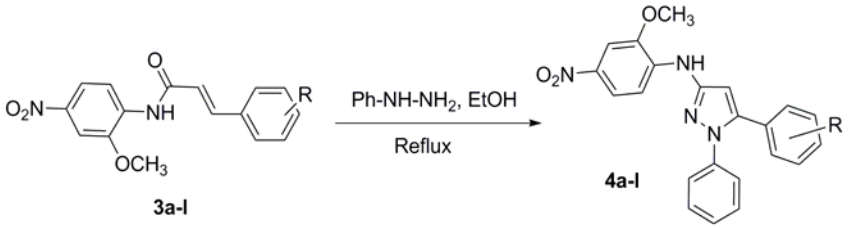


Scheme 1. General Synthesis of Cinnamamide derivatives 3a-l using *N*(2-methyl,4-nitro)acetanilide.

Further the reaction of *N*(2-methoxy,4-nitro)acetanilide (6 mmole) and benzaldehyde (6 mmole) was investigated in various solvent using catalytic amount of sodium hydroxide and found that ethanol works well as solvent and gives high yield of 3a. All the cinnamamides were prepared by using ethanol (10 ml) as solvent. The reactions were being monitored by TLC. After completion of the reaction, the reactions poured into the crushed ice with vigorous stirring so precipitate out of product. Experimental data is given in Table 1.

Table 1. Physical properties of cinnamamide derivatives

Entry	R	% Yield
3a	H	93
3b	4-methoxy	88
3c	4-fluoro	92
3d	2-chloro	89
3e	4-hydroxy	82
3f	2-hydroxy	87
3g	N,N'-dimethyl	91
3h	4-Nitro	85
3i	4-Methyl	82
3j	2-Methoxy	81
3k	2-Nitro	91
3l	4-Bromo	93



Scheme 2. Synthesis of *N*-(2-methoxy-4-nitrophenyl)-1-phenyl-5-aryl-1*H*-pyrazol-3-amine derivatives 4a-l using 3a-l and Phenyl hydrazine.

The condensation reaction of cinnamamide derivative 3a and phenyl hydrazine in various solvent was observed in reflux condition with stirring (Scheme 2). Among the various solvent ethanol found as suitable solvent for synthesis desired *N*-(2-methoxy-4-nitrophenyl)-1,5-diphenyl-1*H*-pyrazole-3-amine 4a derivative. The reaction was being monitored by TLC. The above optimized condition used for the synthesis of novel pyrazole derivatives. Experimental data is given in Table 2.

Table 2. Physical property of trisubstituted pyrazole derivatives 4a-l.

Entry	R	Time hr	% yield	Melting range ºC
4a	H	6.2	92	132-134
4b	4-methoxy	6.5	81	156 -158
4c	4-fluoro	6.5	85	138 -140
4d	2-chloro	7.0	92	142 -144
4e	4-hydroxy	6.8	87	170 -172
4f	2-hydroxy	8.0	97	128 -130
4g	N-N'-dimethyl	7.5	89	175 -177
4h	4-Nitro	7.8	78	210 212
4i	4-Methyl	6.5	89	168 -170
4j	2-Methoxy	6.0	94	184-186
4k	2-Nitro	8.0	92	189 -191
4l	4-bromo	7.2	89	174 -176

3. EXPERIMENTAL

3.1 Material and methods

Melting points were determined in open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS (diffuse reflectance spectroscopy) probe. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AVANCE II spectrometer. Chemical shifts are expressed in δppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-Agilent mass spectrometer. Elemental analysis was carried out using EuroEA elemental analyzer. Solvents were evaporated with a D-Lab rotary evaporator.

3.2. Characterization Data of the Compound

N-(2-methoxy-4-nitrophenyl)cinnamamide: Creamish solid, IR(KBr): C-H(3020 cm^{-1}), C=C(1550 cm^{-1}), C-C(1478 cm^{-1}), N-O(1410 cm^{-1}), C-N(1390 cm^{-1}); ^{1}H NMR: -OCH_3, 3H, at 3.84 *δ*ppm, 1H at 7.49 *δ*ppm (d, *J*=8.56), 1H at 8.09 *δ*ppm (d, *J*=7.52), Ar-H, 8H at 7.88 to 8.54 *δ*ppm, NH at 9.01 *δ*ppm, ^{13}C NMR: 52.4, 112.2, 118.09, 119.1, 122.4, 125.7, 127.5, 131.8, 132.7, 132.8, 135.5, 136.2, 146.7, 152.7, 162.7, 188.2 *δ*ppm; MS(m/z): 298, Elem. Anal. $C_{16}H_{14}N_2O_4$ Calcu: C, 64.42; H, 4.73; N, 9.39%. Found: C, 64.38; H, 4.62; N, 4.32%.

3.3. General synthesis of Pyrazole derivatives 4a-l using Cinnamamide 3a-l and Phenyl hydrazine.

A mixture of cinnamamide derivatives 3a-l (3.3 mmole) and phenyl hydrazine (3.3 mmole) was added to ethanol (10 ml) and refluxed with stirring for given period of time (Table 2). The reaction was being monitored by TLC. After completion of the reaction, the solvent was evaporated under vaccuo. The separated pyrazole derivatives were 4a-l washed with cold water and dried.

3.3.1. Characterization Data of the Compound

***N*-(2-methoxy-4-nitrophenyl)-1,5-diphenyl-1H-pyrazole-3-amine (4a)** : Lemon yellow solid, Rf :0.35 (Hexane-EtOAc); IR(KBr): N-H (3448 cm^{-1}), C-H(3020 cm^{-1}), C=C(1551 cm^{-1}), C-C(1532 cm^{-1}), N-O(1415 cm^{-1}), C-N(1390 cm^{-1}); ^{1}H NMR: -OCH_3, 3H, at 3.81 *δ*ppm, -NH, 1H at 5.49 *δ*ppm, Ar-H, 14 H at 6.88 to 8.54 *δ*ppm, ^{13}C NMR: 53.4, 92.3, 115.2, 118.09, 119.1, 128.4, 131.7, 132.5, 132.8, 135.8, 135.9, 137.8, 141.6, 142.7, 142.8, 145.5, 146.2, 146.7, 149.7, 152.7, 155.7 *δ*ppm; MS(m/z): 386, Elem. Anal. $C_{22}H_{18}N_4O_3$ Calcu: C, 68.38; H, 4.70; N, 14.50%. Found: C, 68.28; H, 4.58; N, 14.38%.

***N*-(2-methoxy-4-nitrophenyl)-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-3-amine (4b)**: Yellowish solid, Rf :0.37 (Hexane-EtOAc), IR(KBr): N-H (3440 cm^{-1}), C-H(3040 cm^{-1}), C=C(1553 cm^{-1}), C-C(1535 cm^{-1}), N-O(1415 cm^{-1}), C-N(1390 cm^{-1}). ^{1}H NMR: 2-OCH_3, 6H, at 3.81 *δ*ppm , -NH, 1H at 5.46 *δ*ppm, Ar-H, 13 H at 6.58 to 8.54 *δ*ppm., ^{13}C NMR: 53.4, 54.1,

92.5, 115.7, 119.1, 119.7, 127.9, 131.4, 132.4, 132.9, 134.8, 136.1, 137.4, 141.7, 142.8, 142.9, 145.5, 147.2, 147.5, 148.2, 151.7, 154.5, 159.8 *δ*ppm; MS(m/z): 416, Elem. Anal. $C_{23}H_{20}N_4O_4$: Calcu: C, 66.34; H, 4.84; N, 13.45%. Found: C, 66.24; H, 4.74; N, 13.38%.

5-(4-(fluorophenyl)-*N*-(2-methoxy-4-nitrophenyl)-1-phenyl-1*H*-pyrazole-3-amine(4c): Yellow solid, Rf : 0.29 (Hexane-EtOAc), IR(KBr): N-H(3623 cm^{-1}), C-H(3070 cm^{-1}), C=C(1564 cm^{-1}), C-C(1549 cm^{-1}), C-N(1450 cm^{-1}), N-O(1432cm^{-1}), C-F(1398 cm^{-1}). ^{1}H NMR: -OCH_3, 3H at 3.85 *δ*ppm, -NH, 1H at 5.31 *δ*ppm, Ar-H, 13 H at 6.55 to 8.50 δppm., ^{13}C NMR: 58.4, 90.3, 115.2, 118.09, 119.1, 120.7, 121.4, 125.7, 126.6, 132.8, 133.8, 133.9, 137.8, 141.6, 142.7, 142.8, 145.5, 146.2, 146.7, 149.7, 155.7, 165.7 δppm; MS(m/z): 404 (M+1), Elem. Anal. $C_{22}H_{17}FN_4O_3$: Calcu: C, 65.34; H, 4.24; N, 13.85%. Found: C, 65.37; H, 4.21; N, 13.55%.

5-(2-chlorophenyl)-*N*-(2-methoxy-4-nitrophenyl)-1-phenyl-1*H*-pyrazole-3-amine(4d): Yellow solid, Rf :0.34 (Hexane-EtOAc), IR(KBr): N-H (3440 cm^{-1}), C-H(3040 cm^{-1}), C=C(1553 cm^{-1}), C-C(1535 cm^{-1}), N-O(1415 cm^{-1}), C-N(1390 cm^{-1}). ^{1}H NMR: -OCH_3, 3H, at 3.81 *δ*ppm, -NH, 1H at 5.46 *δ*ppm, Ar-H, 13 H at 6.58 to 8.54 *δ*ppm, ^{13}C NMR: 57.4, 91.3, 112.2, 114.07, 115.1, 120.7, 121.4, 122.7, 124.6, 133.8, 134.8, 135.9, 136.8, 141.6, 142.7, 142.8, 145.5, 146.2, 146.7, 149.6, 152.2, 155.4 *δ*ppm; MS(m/z): 420, Elem. Anal. $C_{22}H_{17}ClN_4O_3$: Calcu: C, 62.79; H, 4.07; N, 13.31%. Found: C, 62.72; H, 4.17; N, 13.24%.

4-(3-((2-methoxy-4-nitrophenyl)amino)-1-phenyl-1*H*-pyrazole-5-yl) phenol (4e): Yellow solid, Rf :0.26 (Hexane-EtOAc), IR(KBr): N-H (3586 cm^{-1}), C-H(2900 cm^{-1}), C=C(1541cm^{-1}), C-C(1547 cm^{-1}), N-O(1412 cm^{-1}), C-N(1390 cm^{-1}). ^{1}H NMR: -OCH_3, 3H, at 3.81 *δ*ppm, -NH, 1H at 5.48 δppm, Ar-H, 13 H at 6.58 to 8.54δppm. –OH, 1H at 9.7 δppm, ^{13}C NMR: 55.7, 91.7, 115.8, 119.1, 119.7, 120.2, 124.7, 125.5, 128.1, 128.6, 130.9, 132.7, 140.6, 142.7, 143.8, 144.6, 147.2, 148.7, 149.1, 153.7, 159.7 *δ*ppm; MS(m/z): 402, Elem. Anal. $C_{22}H_{18}N_4O_4$: Calcu: C, 65.66; H, 4.51; N, 13.92%. Found: C, 65.56; H, 4.41; N, 13.78%.

2-(3-((2-methoxy-4-nitrophenyl)amino)-1-phenyl-1*H*-pyrazole-5-yl)phenol (4f): Cream solid, Rf : 0.32 (Hexane-EtOAc), IR(KBr): N-H (3680 cm^{-1}), C-H(3000 cm^{-1}), C=C(1553 cm^{-1}), C-C(1535 cm^{-1}), N-O(1415 cm^{-1}), C-N(1390 cm^{-1}). ^{1}H NMR: -OCH_3, 3H, at 3.82 *δ*ppm , -NH, 1H at 5.48 *δ*ppm, Ar-H, 13 H at 7.01 to 8.54 *δ*ppm., –OH, 1H at 9.5 δppm, ^{13}C NMR: 55.6, 91.2, 115.8, 118.1, 119.7, 120.2, 124.7, 126.5, 128.1, 128.6, 130.9, 133.7, 140.6, 142.7, 143.8, 144.6, 147.2, 148.7, 149.8, 153.2, 159.1 δppm; MS(m/z): 402, Elem. Anal. C22H18N4O4: Calcu: C, 65.66; H, 4.51; N, 13.92%. Found: C, 65.56; H, 4.41; N, 13.82%.

5-(4-(dimethylamino)phenyl)-N-(2-methoxy-4-nitrophenyl)-1-phenyl-1H-pyrazole-3-amine(4g): Orange solid, Rf : 0.28 (Hexane-EtOAc), IR(KBr): N-H (3580 cm^{-1}), C-H(3040 cm^{-1}), C=C(1553 cm^{-1}), C-C(1535 cm^{-1}), N-O(1415 cm^{-1}), C-N(1390 cm^{-1}). ^{1}H NMR: -$N(CH_3)_2$, 6H, at 2.98 δppm, -OCH_3, 3H, at 3.88 *δ* ppm, -NH, 1H at 5.46 *δ* ppm, Ar-H, 13 H at 6.58 to 8.54 *δ*ppm, ^{13}C NMR: 35.4, 35.6, 56.7, 93.2, 113.2, 118.04, 119.7, 121.7, 121.9, 125.7, 126.6, 132.8, 134.8, 135.9, 137.8, 141.6, 143.7, 143.8, 145.5, 146.2, 147.7, 150.1, 155.3,

159.2 δppm; MS(m/z): 429, Elem. Anal. $C_{24}H_{23}N_5O_3$: Calcu: C, 67.12; H, 5.40; N, 16.31%. Found: C, 67.02; H, 5.30; N, 16.21%.

***N*-(2-methoxy-4-nitrophenyl)-5-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-3-amine (4h):** Reddish solid, Rf: 0.25 (Hexane-EtOAc), IR(KBr): N-H (3440 cm^{-1}), C-H(3040 cm^{-1}), C=C(1553 cm^{-1}), C-C(1535 cm^{-1}), N-O(1415 cm^{-1}), C-N(1390 cm^{-1}). ^{1}H NMR: -OCH_3, 3H, at 3.85 *δ*ppm, -NH, 1H at 5.38 *δ* ppm, Ar-H, 13 H at 6.78 to 8.72 *δ* ppm, ^{13}C NMR: 55.4, 90.3, 117.2, 118.09, 118.1, 121.2, 121.4, 125.7, 126.6, 132.8, 133.8, 133.9, 137.8, 141.6, 142.7, 142.8, 145.5, 146.2, 146.7, 149.7, 151.7, 155.7 δppm; MS(m/z): 431, Elem. Anal. $C_{22}H_{17}N_5O_5$: Calcu: C, 61.25; H, 3.97; N, 16.23%. Found: C, 61.21; H, 3.88; N, 16.31%.

***N*-(2-methoxy-4-nitrophenyl)-1-phenyl-5-(p-tolyl)-1*H*-pyrazol-3-amine (4i)**: Cream solid, Rf : 0.38 (Hexane-EtOAc), IR(KBr): N-H (3452 cm^{-1}), C-H(3040 cm^{-1}), C=C(1543 cm^{-1}), C-C(1524 cm^{-1}), N-O(1447 cm^{-1}), C-N(1290 cm^{-1}). ^{1}H NMR: -CH_3, 3H at 2.34 *δ*ppm, OCH_3, 3H, at 3.81 *δ* ppm, -NH, 1H at 5.46 *δ* ppm, Ar-H, 13 H at 6.58 to 8.54 *δ* ppm., ^{13}C NMR: 18.9, 55.4, 94.3, 115.2, 118.09, 120.1, 120.7, 121.4, 125.7, 126.6, 132.8, 133.8, 134.9, 137.4, 141.0, 141.7, 142.7, 145.1, 145.2, 146.4, 148.7, 152.4, 158.5 *δ*ppm; MS(m/z): 400, Elem. Anal. $C_{23}H_{20}N_4O_3$: Calcu: C, 68.99; H, 5.03; N, 13.99%. Found: C, 68.91; H, 5.13; N, 13.99%.

***N*-(2-methoxy-4-nitrophenyl)-5-(2-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-amine (4j):** Yellow solid, Rf : 0.32 (Hexane-EtOAc), IR(KBr): N-H (3540 cm^{-1}), C-H(3140 cm^{-1}), C=C(1514 cm^{-1}), C-C(1537 cm^{-1}), N-O(1415 cm^{-1}), C-N(1380 cm^{-1}). 1H NMR: 2-OCH_3, 6H, at 3.81 δppm , -NH, 1H at 5.36 *δ*ppm, Ar-H, 13 H at 6.87 to 8.78 *δ*ppm., ^{13}C NMR: 53.5, 54.8, 92.5, 116.7, 119.5, 120.2, 126.9, 131.4, 132.4, 132.9, 134.8, 136.1, 137.4, 141.7, 142.1, 142.5, 145.8, 147.1, 147.2, 148.0, 151.4, 153.0, 158.5 *δ*ppm; MS(m/z): 416, Elem. Anal. $C_{23}H_{20}N_4O_4$: Calcu: C, 66.34; H, 4.84; N, 13.45%. Found: C, 66.21; H, 4.69; N, 13.41%.

***N*-(2-methoxy-4-nitrophenyl)-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-3-amine (4k):** Reddish solid, Rf : 0.37 (Hexane-EtOAc), IR(KBr): N-H (3570 cm^{-1}), C-H(2940 cm^{-1}), C=C(1541 cm^{-1}), C-C(1535 cm^{-1}), N-O(1345 cm^{-1}), C-N(1280 cm^{-1}). ^{1}H NMR: -OCH_3, 3H, at 3.87 *δ*ppm, -NH, 1H at 5.74 *δ*ppm, Ar-H, 13 H at 6.87 to 9.04*δ*ppm., ^{13}C NMR: 56.4, 92.3, 117.2, 118.09, 118.1, 122.2, 123.4, 125.7, 126.6, 132.8, 133.8, 133.9, 137.8, 141.6, 142.7, 142.6, 145.5, 146.2, 146.7, 150.0, 151.7, 156.4 δppm; MS(m/z): 431, Elem. Anal. $C_{22}H_{17}N_5O_5$: Calcu: C, 61.25; H, 3.97; N, 16.23%. Found: C, 61.21; H, 3.89; N, 16.13%.

5-(4-bromophenyl)-*N*-(2-methoxy-4-nitrophenyl)-1-phenyl-1*H*-pyrazol-3-amine (4l): Yellow solid, Rf : 0.35 (Hexane-EtOAc), IR(KBr): N-H (3447 cm^{-1}), C-H(3045 cm^{-1}), C=C(1553 cm^{-1}), C-C(1435 cm^{-1}), N-O(1421 cm^{-1}), C-N(1391 cm^{-1}). ^{1}H NMR: -OCH_3, 3H, at 3.81 *δ*ppm, -NH, 1H at 5.46 *δ*ppm, Ar-H, 13 H at 6.58 to 8.54 *δ*ppm., ^{13}C NMR: 56.4, 94.3, 113.2, 117.09, 112.1, 121.7, 121.8, 125.4, 126.0, 132.8, 133.0, 133.4, 137.7, 142.6, 142.9, 144.8, 145.5, 149.2, 149.0, 151.9, 155.3, 161.1 δppm; MS(m/z): 466, Elem. Anal. $C_{22}H_{17}BrN_4O_3$: Calcu: C, 56.79; H, 3.68; N, 12.04%. Found: C, 56.59; H, 3.62; N, 11.98%.

CONCLUSION

The study on synthesis and characterization of novel pyrazoles having nitro and methoxy functionality on aromatic ring has been demonstrated. Ethanol was emerged as good solvent for the reaction of various cinnamamides as well as pyrazole derivatives starting from 2-methoxy-4-nitro acetanilide. This process is quite simple and furnishing high yield of products. The purity of the final product can be determined by spectral analysis using IR, Mass and 1H NMR.

ACKNOWLEDGEMENTS

Authors are thankful for financial assistance given under to UGC-MRP, Sanction No.-47-605/13(WRO), Dated- 20/5/2014. We are also thankful to Shree M. & N. Virani Science College for providing Central Instrumentation Facility and Laboratory Facility.

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