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Syntheses and Reactions of Some Pyrazole-1-carboximide Derivatives under Dry Media Microwave

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Effects of microwaves in dry media organic reactions have shown synthetic utility for the preparation of chalcones (**2a-d**). (4E)-4-(4-arylidene)-5-imino-4,5-dihydro-3-hydroxy pyrazole-1-carboxamide (**5a-d**) were prepared. (4E)-4-arylidene-4,5-dihydro-3-hydroxy-5-iminopyrazole-1-carbonitrile (**6a-d**). Compounds **6a-d** underwent cyclization reaction when treated with hydrazine hydrate affording (**8a-d**) derivatives.

Key Words: Pyrazole-1-carboximide derivatives, Microwave syntheses.

INTRODUCTION

Microwave dielectric heating effect uses the ability of some liquids and solids to transform electromagnetic energy into heat and thereby drive chemical reactions. This *in situ* mode of energy conversion has many attractions to the chemists[1,2], because its magnitude depends on the properties of the molecules. This allows some control of the materials properties and may lead to reaction selectivity. There is a variety of methods for carrying out microwave assisted organic reactions using domestic or commercial ovens, this is basically known as MORE (Microwave Induced Organic Reaction Enhancement) chemistry[3]. The reactions were carried out in high boiling solvents (dimethylformamide). Heating is fast, but maximum temperatures were chosen below the boiling point of the solvent in order to avoid solvent evaporation. This one could work in open reaction vessels, could choose small amount of solvent when targeting for solubility at the reaction temperature. Bose[3] claims that the method is more cost effective (only simple glassware needed) and environment friendly (less solvent needed).

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To demonstrate the versatility of MORE chemistry, a variety of organic reactions have been done using domestic microwave ovens or commercial ovens.

Solid state reactions: Generally of three types[4].

(a) Reactions between neat reactants

(b) Reactions between supported reagents on solid mineral supports in dry media by impregnation of compounds on silica, alumina or clays.

(c) Phase transfer catalysis (PTC) conditions in the absence of organic solvent, *i.e.* when a liquid reagent acts both as a reacting and an organic phase. This method is specific for anionic reactions as it involves anionic activation.

The absence of solvents coupled with the high yields and short reaction times often associated with reactions of this type make these procedures very attractive for synthesis[5-8]. In present discussion, we describe the advantages of dry reaction techniques coupled with microwave activation and their applications to organic synthesis using solid supports.

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The purities of the compounds were checked on silica-gel-coated Al plates (Merck). Microanalyses were performed by micro analytical unit, NRC. All compounds gave satisfactory values for C, H, Cl, N and within range of ± 0.04. IR spectra (KBr, ν cm^{-1}) were recorded on Perkin Elmer 580 spectrophotometer. ^{1}H NMR and ^{13}C NMR were carried on JNM, FT-NMR-EX270, run ^{1}H NMR 270 MHz, in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. Mass spectra were recorded on Varian Mat 112 spectrometer.

Microwave/K_2CO_3 mediated synthesis of chalcones (2a-d)

General procedures: A mixture of equimolecular amounts of *p*-nitrobenzaldehyde and ketones (2-butanone, 2-chloro-cyclohexanone, acetophenone and 3-acetylindol, respectively) was dissolved in acetone (25 mL), then K_2CO_3 (3 g) was added and was stirred vigorously. After 15 min, the solvent was removed under vacuum and the dry powder was irradiated in microwave oven for the appropriate time at 800 W. After completion of reaction as followed by TLC examination, water was added to the reaction mixture. The obtained solid was filtered off, dried and crystallized from suitable solvent.

(z)-3-Methyl-4-(4-nitrophenyl)but-3-en-2-one (2a): Crystallization: ethanol; yield 87 %; m.f. $C_{11}H_{11}NO_3$; m.w. 205.22; m.p. 202-4 ºC; IR (cm^{-1}) 1655 ν(C=O); ^{1}H NMR: 1.84, 2.02 (s, 6H, $2CH_3$),7.58-7.94 (m, 4H, Ar-H), 7.90 (s,1H,CH). MS (EI): m/z (%): 205 (37%). Time of irradiation 3 min.

(E)-2-(4-nitrobenzylidine)-6-chlorocyclohexanone (2b): Crystallization: ethanol; yield 70 %; m.f. $C_{13}H_{12}NO_3Cl$; m.w. 265.69; m.p.162-4 ºC; IR (cm^{-1}): 1652 ν(C=O); ^{1}H NMR: 1.28, 1.35, 1.65 (m, 6H, CH_2), 3.95 (t, 1H, CH-Cl), 8.12 (s, 1H, CH=Ar), 7.65-7.96 (m, 4H, Ar-H); MS (EI): m/z (%): 264 (59 %), 265 (60 %) [M+1]. Time of irradiation 10 min.

(E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (2c): Crystallization: ethanol; yield 85 %; m.f. $C_{15}H_{11}NO_3$; m.w. 253.26; m.p.174-6 ºC; IR (KBr, cm^{-1}): 1560 ν(C=O); ^{1}H NMR: 7.41-7.86 (m, 9H, Ar-H), 7.89, 8.01 (s, 2H, CH=CH); MS (EI): m/z(%): Time of irradiation 5 min.

(E)-1-(1*H*-indol-3-yl)-3-(4-nitrophenyl)prop-2-en-1-one (2d): Crystallization: ethanol; yield 63 %; m.f. $C_{17}H_{12}N_2O_3$; m.w. 292.29; m.p. 254-256 ºC; IR (KBr, cm^{-1}): 1560 ν(C=O); ^{1}H NMR: 6.78,7.49 (s, 2H,CH=CH), 7.53-7.98 (m, 9H, Ar-H), 10.02 (b, 1H, NH indol); MS (EI): m/z (%): 292 (45 %). Time of irradiation 3 min.

Microwave/K_2CO_3 mediated synthesis of pyrazolines

Method A: A mixture of chalcones (**2a-d**) or ethylcyanoarylacrylate derivatives (**4a-d**) (2 mmol) and semicarbazide hydrochloride (2.2 mmol) was dissolved in acetone (20 mL), then K_2CO_3 (3 g) was added and was stirred vigorously. After 15 min, the solvent was removed under vacuum and the dry powder was irradiated in microwave oven for 10 min at 800 W. After completion of reaction as followed by TLC examination, water was added to the reaction mixture. The solid was obtained, which was filtered off, was dried and crystallized from suitable solvent.

Method B: A mixture of chalcones (**2a-d**) or ethylcyanoarylacrylate derivatives (**3a-d**) (2.2 mmol) and semicarbazide hydrochloride (2.2 mmol) was heated in presence of dry dioxane (50 mL), K_2CO_3 (3 g) and catalytic amounts of *t*-butylammonium bromide for 0.5 h. The reaction mixture was cooled and poured into ice water. It was collected by filtration and crystallized from suitable solvent.

3,4-Dimethyl-5-(4-nitrophenyl)-1*H*-pyrazole-1-carboximide (3a): Crystallization: ethanol; yield 43 %; m.f: $C_{12}H_{12}N_4O_3$; m.w. 260.25; m.p. 230-232 ºC; IR (cm^{-1}): 3430-3210 ν(NH_2, amide), 1560 ν(C=O amide); ^{1}H NMR: 1.98, 2.64 (2s, 6H, $2CH_3$), 6.21 (b, 2H, exchangeable with D_2O, NH_2 amide), 7.61-7.99 (m, 4H, Ar-H); MS (EI): m/z (%): 260 (72 %).

7-Chloro-4,5,6,7-hexahydro-3-(4-nitrophenyl)indazole-2-carboxamide (3b): Crystallizations: ethanol; yield 45 %; m.f. $C_{14}H_{13}ClN_4O_3$; m.w. 320.74; m.p. 205-7 ºC; IR (cm^{-1}): 3410-3210 ν(NH_2, amide), 1560 ν(C=O amide); ^{1}H NMR: 1.62, 1.71, 1.99 (m, 6H, CH_2, cyclohexane), 4.21 (t, 1H, CH-Cl), 6.04 (b, 2H, exchangeable with D_2O, NH_2 amide), 7.50-7.91 (m, 4H, Ar-H); MS (EI): m/z (%): 321 (34 %), 322 (24 %).

5-(4-Nitrophenyl)-3-phenyl-1*H*-pyrazole-1-carboximide (3c): Crystallization: ethanol; yield 68 %; m.f. $C_{16}H_{12}N_4O_3$; m.w. 308.30; m.p. 210-

212 ºC; IR (cm^{-1}): 3410-3210 ν(NH_2, amide), 1560 ν(C=O amide); ^{1}H NMR: 6.12 (b, s, 2H, exchangeable with D_2O, NH_3 amide), 6.32 (s, 1H, pyrazole), 7.765-7.99 (m, 9H, Ar-H); MS (EI): m/z(%): 308 (32 %).

3-(1*H*-indol-3-yl)- 5-(4-nitrophenyl)-1-H-pyrazole-1-carboximide (3d): Crystallization: ethanol; yield 54 %, m.f. $C_{18}H_{13}N_5O_3$; m.w. 347.34 m.p. 246-8 ºC; IR (cm^{-1}): 3382-3210 ν(NH_2, amide), 1560 ν(C=O amide); ^{1}H NMR: 6.12 (b, s, 2H, exchangeable with D_2O, NH_2 amide), 6.40 (s, 1H, pyrazole), 7.71-8.02 (m, 9H, Ar-H), 10.02 (b, 1H, NH indol); : MS (EI): m/z (%): 347 (67 %).

Preparation of (E)-ethyl-2-cyano-3-phenylacrylate (4a-d): Lit.[9]

(4E)-4-(4-methylbenzylidene)-5-imino-4,5-dihydro-3-hydroxy-pyrazole-1-carboxamide (5a): Crystallization: ethanol; yield 80 %; m.f. $C_{12}H_{12}N_4O_2$; m.w. 244.25 m.p. 224-6 ºC; IR (cm^{-1}): 3464-3420 ν(NH_2, amide), 3410 ν(OH), 1582 ν(C=O amide); ^{1}H NMR: 1.78 (s, 3H, CH_3), 3.2 (s, 1H exchangeable with D_2O, OH), 6.47 (b, s, 2H, exchangeable with D_2O, NH_2), 7.56-7.42 (m, 4H, Ar-H), 7.57 (s, 1H, CH=Ar), 10.43 (s, 1H, exchangeable with D_2O, NH); ^{13}C NMR: 26.5 (CH_3), 119.4 (=C-pyrazol), 124.5, 124.3, 129.2, 129.3, 137.6, 134.0 (C-Ar), 139 (C=Ar), 145.6 ($CONH_2$), 155.3 (C-OH), 167.8 (C=NH); MS (EI): m/z (%) : 244 (63).

(4E)-4-(4-methoxybenzylidene)-5-imino-4,5-dihydro-3-hydroxy-pyrazole-1-carboxamide (5b): Crystallization: ethanol; yield 73 %; m.f. $C_{12}H_{12}N_4O_3$; m.w. 260.25 m.p. 198-200 ºC; IR (cm^{-1}): 3460-3428 ν(NH_2 amide), 3410 ν(OH), 1582 ν(C=O amide); ^{1}H NMR: 3.14 (s,1H exchangeable with D_2O, OH), 4.25 (s, 3H, OCH_3), 6.21(b, s, 2H, exchangeable with D_2O, NH_2), 7.45-7.84 (m, 4H, Ar-H), 7.57 (s, 1H, CH=Ar), 10.13 (s,1H, exchangeable with D_2O, NH); ^{13}C NMR: 58.5 (OCH_3), 119.5 (=C-pyrazol), 126.7, 126.4, 129.2, 129.3, 137.6, 134.0 (C-Ar), 139 (C=Ar),145.6 ($CONH_2$), 156.6 (C-OH), 167.8 (C=NH); MS (EI): m/z (%): 260 (63%).

(4E)-4-(4-nitrobenzylidene)-5-imino-4,5-dihydro-3-hydroxy-pyrazole-1-carboxamide (5c): Crystallization: ethanol; yield 56 %; m.f. $C_{11}H_9N_5O_4$; m.w. 275.22; m.p. 264-6 ºC; IR (cm^{-1}): 3464-3420 ν(NH_2, amide), 3410 ν(OH), 1582 ν(C=O amide); ^{1}H NMR: 3.26 (s,1H, exchangeable with D_2O, OH), 6.47 (b, s, 2H, exchangeable with D_2O, NH_2), 7.53-7.84 (m, 4H, Ar-H), 8.02 (s, 1H, CH=Ar), 11.01 (s,1H, exchangeable with D_2O, NH), MS (EI): m/z (%): 275 (63%).

(4E)-4-(3-nitrobenzylidene)-5-imino-4,5-dihydro-3-hydroxy-pyrazole-1-carboxamide (5d): Crystallization: ethanol; yield 35 %; m.f. $C_{11}H_9N_5O_4$; m.w. 275.22; m.p. 270-2 ºC; IR (cm^{-1}): 3464-3420 ν(NH_2, amide), 3410 ν(OH), 1582 ν(C=O amide); ^{1}H NMR: 3.37 (s, 1H exchangeable with D_2O, OH), 6.52 (b, s, 2H, exchangeable with D_2O, NH_2), 7.56-7.42 (m, 4H, Ar-H), 7.95 (s, 1H, CH=Ar), 10.13 (s, 1H, exchangeable with D_2O, NH), MS (EI): m/z (%): 275 (54 %).

(4E)-4-arylidene-4,5-dihydro-3-hydroxy-5-iminopyrazole-1-carbonitrile (6a-d): To a solution of (**5a,b**) (1 g) in 25 mL of dry dioxane, 3 mL of phosphorous oxychloride was heated on water bath for 3 h. The reaction mixture was cooled, filtered off, dried and finally crystallized from suitable solvent.

6a: Crystallization: ethanol; yield 46 %; m.f. $C_{12}H_{10}N_4O$; m.w. 226.24; m.p. 120-2 ºC; IR (cm^{-1}): 3410 ν(OH), 2223 ν(CN); ^1H NMR: 1.42 (s, 3H, CH_3), 3.65 (s, 1H exchangeable with D_2O, OH), 7.53-7.42 (m, 4H, Ar-H), 8.01 (s, 1H, CH=Ar), 9.54 (s,1H, exchangeable with D_2O, NH), MS (EI): m/z (%): 226 (70 %).

6b: Crystallization: ethanol; yield 85 %; m.f. $C_{12}H_{10}N_4O_2$; m.w. 242.24 m.p. 146-8 ºC; IR (cm^{-1}): 3410 ν(OH), 2220 ν(CN); ^1H NMR: 4.02 (s, 3H, OCH_3), 4.37 (s, 1H exchangeable with D_2O, OH), 7.53-7.42 (m, 4H, Ar-H), 8.32 (s, 1H, CH=Ar), 9.14 (s, 1H, exchangeable with D_2O, NH), MS (EI): m/z (%): 242 (70 %).

6c: Crystallization: benzene; yield 64 %; m.f. $C_{11}H_7N_5O_3$; m.w. 257.21 m.p. 117-9 ºC; IR (cm^{-1}): 3410 ν(OH), 2220 ν(CN); ^1H NMR: 6.37 (s, 1H exchangeable with D_2O, OH), 7.53-7.42 (m, 4H, Ar-H), 7.98 (s,1H, CH=Ar), 9.14 (s, 1H, exchangeable with D_2O, NH), MS (EI): m/z (%): 257 (52 %).

6d: Crystallization: benzene; yield 35 %; m.f. $C_{11}H_7N_5O_3$; m.w. 257.21 m.p. 209-11 ºC; IR (cm^{-1}): 3410 ν(OH), 2220 ν(CN); ^1H NMR: 6.37 (s,1H exchangeable with D_2O, OH), 7.53-7.42 (m, 4H, Ar-H), 7.98 (s, 1H, CH=Ar), 9.14 (s,1H, exchangeable with D_2O, NH), MS (EI): m/z (%): 257 (32 %).

(4E)-4-benzylidene-1-(6-(9E)-4-benzylidene-4,5-dihydro-3-hydroxy-5-iminopyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazin-3yl)-4,5-dihydro-5-imino-1*H*-pyrazol-3-ol (8a,b): To a solution of (**6a,b**) and hydrazine hydrate in 2:1 equivalent ratio was irradiated in microwave oven for 10 min at 800 W. The reaction mixture was cooled and crystallized from suitable solvent.

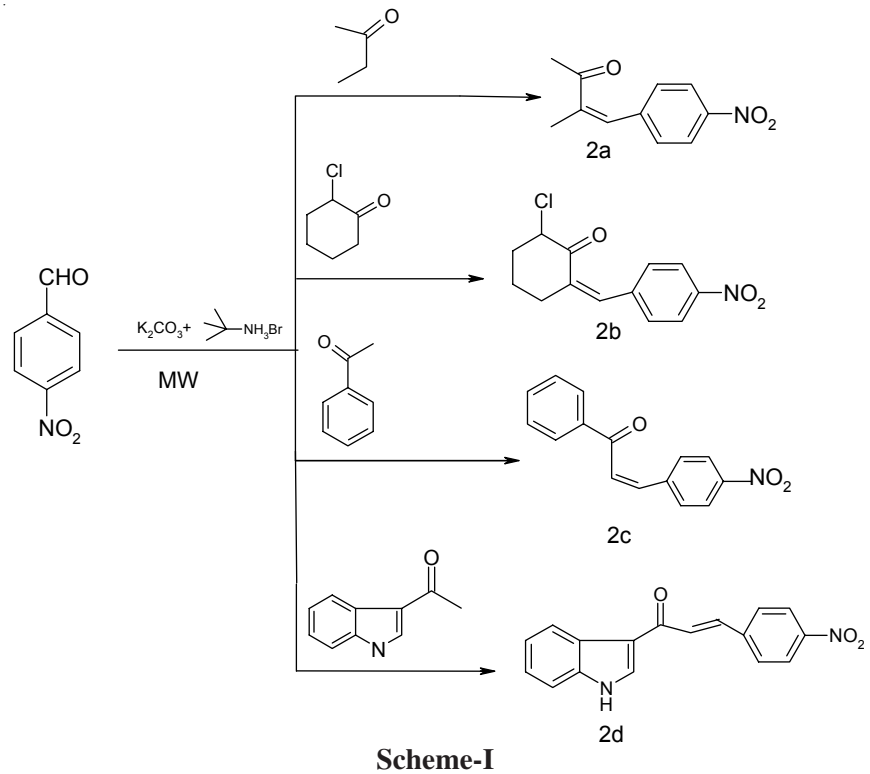
8a: Crystallization: ethanol; yield 46 %; m.f. $C_{24}H_{22}N_{10}O_2$; m.w. 482.51 m.p. 156-8 ºC; IR (cm^{-1}): 3410 ν(OH); ^1H NMR: 1.13,1.35 (s, 6H, $2CH_3$), 2.1,3.32 (b, 2s, 2H, exchangeable with D_2O, 2NH), 5.37, 5.62 (s, 2H exchangeable with D_2O, 2OH), 7.56-7.42 (m, 8H, Ar-H), 6.86,7.95 (2s, 2H, 2CH=Ar), 9.03, 9.23 (b, 2s, 2H, exchangeable with D_2O, 2NH); MS (EI): m/z (%): 485 (21 %).

8b: Crystallization: ethanol; yield 53 %; m.f. $C_{24}H_{22}N_{10}O_4$; m.w. 514.51 m.p.177-9 ºC; IR (cm^{-1}): 3410 ν(OH); ^1H NMR: 3.32, 2.65 (b, s, 2H, exchangeable with D_2O, 2NH), 5.374.02 (s, 2H exchangeable with D_2O, 2OH), 4.32, 4.51 (2s, 6H, $2OCH_3$), 7.56-7.42 (m, 8H, Ar-H), 7.95, 8.03 (s, 2H, 2 CH=Ar), 9.01, 9.20 (b, 2s, 2H, exchangeable with D_2O, 2NH); MS (EI): m/z (%): 516 (22 %).

RESULTS AND DISCUSSION

Under the frame work of Green Chemistry we have developed an environmentally benign solvent-free approach for the synthesis of pyrazolines. The desired pyrazolines were prepared by adsorbing equimolecular quantities of chalcones and semicarbazide over K_2CO_3 and subjected them to microwave irradiation. The elution of the products needs only water, so we eliminate the use of organic solvent from the work up stage (*cf.* exp.).

Therefore, the irradiation of a mixture of *p*-nitrobenzaldehyde and 2-butanone, 2-chlorocyclohexanone, 3-methylindolylketone and acetophenone, respectively, under phase transfer catalysis (PTC) conditions in the absence of organic solvent affording chalcone (**2a-d**) (**Scheme-I**).

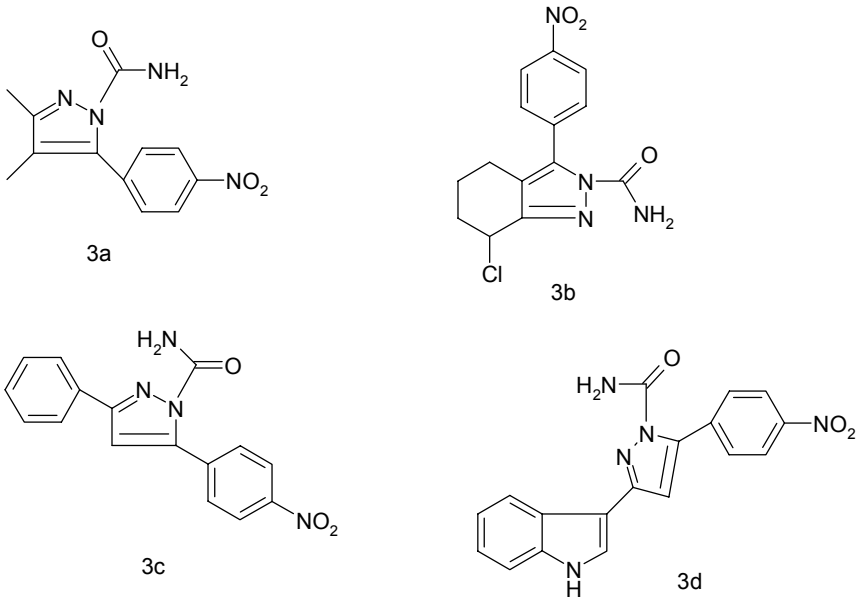


Scheme-I

The desired chalcones (**2a-d**) were synthesized thermally following Gupta *et al.*[10].

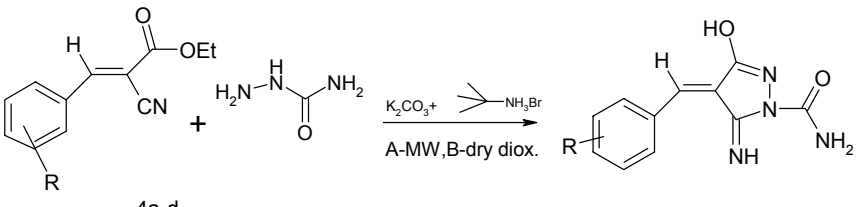
The pyrazolines reported to show a broad spectrum of biological activities including antibacterial[11], antifungal[12], antiinflammatory[13] and antidepressant activities[14]. This prompted us to synthesize various substituted pyrazoline derivatives using the microwave-assisted method.

Microwave irradiation of chalcones (**2a-d**) facilitates the polarization of the molecules causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state[15]. Neucleophlic attack of an amine on polarized carbonyl function (rate-determine step) is followed by an intramolecular cyclization affording the desired products (**3a-d**) (**Scheme-II**).



Scheme-II

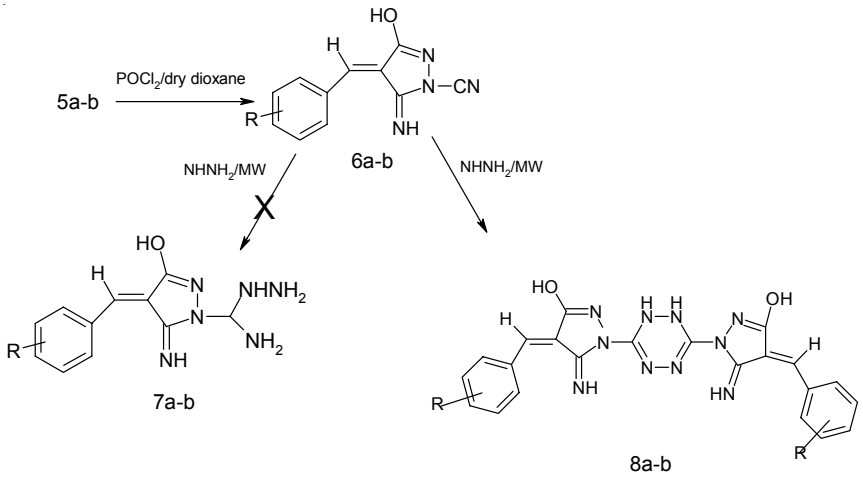
On the finding that, the ease of forming C-N and C=N bonds as opposed to N=N bond formation is reflected in their extensive use for the preparation of heterocyclic compounds. As the internal nitrogen atom of the hydrazine fragment is a softer neucleophlic centre than the terminal nitrogen which undergo cyclization. Therefore, the irradiation of ethylcyano-arylacrylate (**4a-d**) derivatives and semicarbazide afforded (4E)-4-(4-arylidine)-5-imino-4,5-dihydro-3-hydroxy- pyrazole-1-carboxamide (**5a-d**) (*cf.* exp., **Scheme-III**).



R, a= *p*-CH_3, b= *p*-OCH_3, c= *p*-NO_2, d= *m*-NO_2

Scheme-III

The structure of obtained products were confirmed *via* (i) their correct values in elemental analyses, (ii) their agreeable spectral data with the proposed structures. For example the ^{1}H NMR showed characteristics signals for CH=Ar at 7.57, 7.57, 8.02 and 7.95, ^{13}C NMR (**5a,b**) showed signal at 132, 132, respectively for CH=Ar, (iii) the obtained products were prepared thermally through the reaction of ethylcyanoarylacrylate derivatives (**4a-d**) with semicarbazide in presence of K_2CO_3/*t*-butylammonium bromide in dry dioxane (*cf.* exp.). The obtained products underwent farther chemical conformational reactions (*cf.* exp., **Scheme-IV**).



Scheme-IV

(4E)-4-arylidene-4,5-dihydro-3-hydroxy-5-iminopyrazole-1-carbonitrile (**6a-d**) were also obtained upon heating of **5a-d** with phosphorous oxychloride. IR (KBr) of **6a-d** showed significant peaks at 2220 cm^{-1} due to ν(CN).

It was reported that microwave technique could be applied in the cyclization of highly functionalized molecules. Therefore, compounds **6a,b** underwent cyclization reaction when treated with hydrazine hydrate under microwave irradiation affording tetrazine derivatives (**8a,b**) (*cf.* exp., **Scheme-IV**) inspite of carboxamidine derivatives.

The structure of **8a-d** were investigated according to their analytical and spectral data. ^{1}H NMR showed signals at 7.95, 7.92, 8.21 and 8.01 (Ar=CH) in addition to the characteristic signals for OH and NH.

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