Reactions of 3-Hydrazino-5-Hydroxy-4-Phenyl-Azopyrazole with Different Reagents

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Abstract: The resection of 3-hydrazinopyrazole derivative **1** with acetylacetone, malononitrile, diethylmalonate and ethyl acetoacetate gave N-pyrazolyl pyrazole derivatives **3a-e**. Heating **1** with benzil gave pyrazolotriazine **6**. Reaction of **1** with diethyloxolate gave pyrazolotriazine-3,4-dione **7**. Condensation of **1** with p-nitrobenzaldehyde gave pyrazolo[5,1-c]triazole **8**. The reaction of **1** with phenyl isothiocyanate afforded the corresponding thiocarbamoyl hydrazine **9**. Subsequent ring closure in basic medium yielded pyrazolo[5,1-c]triazole derivative **10**. [Journal of American Science 2010; 6(9):889-892]. (ISSN: 1545-1003).

Keywords: Cycloadditions, Hydrazones, Pyrazoles, Triazines, Triazoles.

1. Introduction:

Pyrazoles and their substituted derivatives are interesting as potential pharmaceuticals, and intermediates in dye industry. Despite the enormous number of substituted pyrazoles reported in the literature only a limited number of bispyrazole derivatives have so for been reported. Our interest in synthesis and reactivity of the parent compound and its substitution products arises from promise medicinal chemistry[1-3] and organometallic complex reactivity. The present investigation is in continuation of our pervious work on aminopyrazoles and deals with the synthesis of different fused heterocycles pyrazoles[3-8].

In the present work we report the reactivity of 3-hydrazino-5-hydroxy-4-phenylazopyrazole with different reagent to make new compounds for biological testing.

2. Experimental

Melting points were determined with a Büchi 510 apparatus and are reported uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 283 spectrophometer. ^{1}H-NMR spectra were obtained on a Brucker Ac 200 F instrument. Mass spectra were obtained at 70 eV by using a VG2AB-3F spectrometer. Satisfactory microanalysis (C, H, N) could be obtained for all the products. All reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merck).

1-(5-Hydroxy-4-phenylazo-1H-pyrazol-3-yl)-3,5-dimethyl pyrazole 3a

To a solution of compound **1** (0.22 g, 1 mmol) in ethanol (20 mL), acetylacetone (0.10 g, 1 mmol) was added. The reaction mixture was heated under reflux for 5h. The solvent was evaporated under reduced pressure, the residue was recrystallized from ethanol gave a pure product in a yield (0.13 g, 46%), m.p. 180°C.

IR: 3500 (OH), 3250 (NH), 3052 (CH, aliphatic), 1635 (C=N), and 1553, 1541, 1350, 1106 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ1.4 (d, 6H,. 2CH_3), 6.2 (br, 1H, OH), 7.2-7.7 (m, 6H, aromatic protons) and 12.8 (br, 1H, NH) ppm;

1-(5-Hydroxy-4-phenylazo-1H-pyrazol-3-yl)-3,5-diaminopyrazole 3b

To a solution of compound **1** (0.22g 1 mmol) in ethanol (20 ml), malononitrile (0.07 g, 1 mmol) was added. The reaction mixture was heated under reflux for 20 h. The solvent was evaporated under reduced pressure, the residue was recrystallized from ethyl acetate and gave a yellow product in a yield (0.10 g, 35%), m.p. 240°C.

IR: 3600 (OH), 3383, 3280 (NH_2), 3280 (NH), (634 (C=N) and 1562, 1591, 1489, 1394, 1230, 1107 cm^{-1}. The ^{1}H-NMR (DMSO-d_6): δ 4.6 (br, 1H, OH), 7.0-80 (m, 10H; Ph, 2NH_2, CH-pyrazole proton) and 11.3 (br, 1H, NH). MS: m/z: 284 (M^+, 22%), 264 (10%), 203 (10%), 167 (32%), 149 (63%) and 55 (100%).

1-(5-Hydroxy-4-phenylazo-1H-Pyrazol-3-yl)-3.5-dihydroxypyrazole 3c

A mixture of compound **1** (0.22, 1 mmol) and diethylmalonate (3 ml) was heated under reflux for 4 h. upon cooling, the precipitated product was

filtered off, dried and recrystallized from methanol and gave (0.16 g, 56%), m.p. 120°C. IR: 3501 (OH), 3139 (NH), 3059 (CH-aromatic), 1630 (C=N) and 1488, 1372, 1225, 1026 cm^{-1}. MS: m/z: 286 (M^+, 45%), 258 (5%), 203 (5%), 167 (40%) and 149 (100%).

1-(5-Hydroxy-4-phenylazo-1H-Pyrazol-3-yl)-5-amino-3-hydroxypyrazole 3d

To a solution of compound **1** (0.22, 1 mmol) in glacial acetic acid (20 ml), ethyl cyanoacetate (0.11 g, 1 mmol) was added. The reaction mixture was heated under reflux for 10 h. the reaction mixture was diluted with water and the precipitate was filtered off, dried and recrystallized from ethanol and gave (0.15g, 52%) m.p.: 190°C.

IR: 3541, 3405 (NH_2), 3321 (NH), 3047 (CH-aromatic), 1673 (C=O) and 1596, 1402 cm^{-1}. MS: m/z: 285 (M^+, 40%), 203 (23%), 149 (100%) and 55 (65%).

1-(5-Hydroxy-4-phenylazo-1H-pyrazol-3-yl)-5-hydroxy-3-methylpyrazole 3e

A mixture of compound **1** (0.22 g, 1 mmol) and ethyl acetoacetate (0.13 g; 1 mmol) was refluxed in absolute ethanol (20 ml) containing few drops of acetic acid for 14 h. the solvent was evaporated in vacuo and the residue was recrystallized with diethylether to give (0.11 g, 39%), m.p.: 170°C. IR: 3500-3450 (OH and/or NH), 3070 (CH-aromatic), 1655 (C=N) and 1559, 1446, 1340, 1225, 1109 cm^{-1}. the ^{1}H-NMR (DMSO-d_6): δ2.4 (s, 3H, CH_3) 5.0 (dd, 2H, protons of pyrazolone), 5.9 (br, 1H, OH), 7.2 – 7.8 (m, 5H, Ph), 11.8 (br, 1H, NH) ppm. MS: m/z: 283 (M^+, 58%), 258 (7%), 203 (35%), 167 (55%), 149 (100%) and 55 (67%).

3,4-Diphenyl-6-hydroxy-7-phenylazopyrazolo[5,1-c]-1, 2, 4-triazine 6

A mixture of compound **1** (0.22, 1 mmol) and benzil (0.21 g, 1 mmol) in absolute ethanol (20 ml) was refluxed for 5h. upon cooling, the precipitated product was filtered and recrystallized from ethyl acetate to give (0.14 g, 36%), m.p.: 180°C. IR: 3650 (OH), 3070 (CH-aromatic), 1662 (C=N) and 1590, 1440 cm^{-1}.

6-Hydroxy-7-phenylazopyrazolo[5,1-c]triazin-3,4-dione 7

To a solution of the compound **1** (0.22 g, 1 mmol) in ethanol (25 ml), diethyl oxalate (0.15 g, 1 mmol) was added. The reaction mixture was heated under reflux for 1h. upon cooling, the precipitated product was filtered and recrystallized from ethanol to give (0.13 g, 48%), m.p.: 150°C.

3-(p-Nitrophenyl)-6-hydroxy-7-phenylazopyrazolo-[5,1-c]-1H-1,2,4-triazole 8

To a solution of compound **1** (0.22 g, 1 mmol) in ethanol (15 ml), P-nitrobenzaldehyde (0.15 g, 1 mmol) was added. The reaction mixture was concentrated to half its volume and cooled in an ice-bath. The yellow product was filtered and recrystallized from ethanol to give (0.13 g, 37%), m.p. 142°C. IR: 3500 (OH), 3200 (NH), 3050 (CH-aromatic), 1630 (C=N), 1550 (C=C) and 1445 cm^{-1}. the ^{1}H-NMR (DMSO-d_6): δ7.0-8.3 (m, 9H, aromatic protons), 10.1 (S, 1H, NH) and 11.6 (S, 1H, OH) ppm.

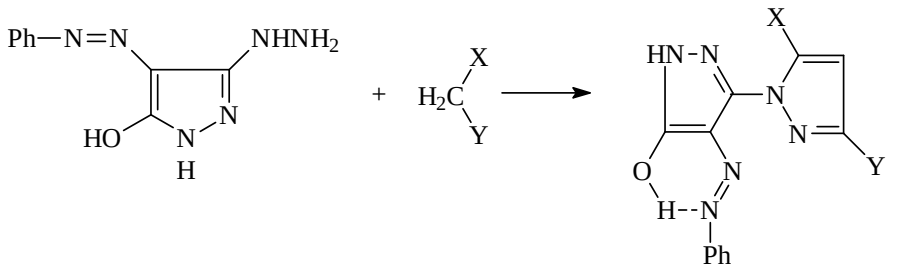
Reaction of 3-hydrazino-5-hydroxy-4-phenylazo-pyrazole 1 with phenyl isothiocyanate:

i) To solution of compound **1** (0.22 g, 1 mmol) in ethanol, phenyl isothiocyanate (0.14 g, 1 mmol) was added. The reaction mixture was refluxed for 20 h. the solution was concentrated to a small volume and poured into ice-cold water. A light yellow product was filtered and recrystallized from methanol to give 2-(5-hydroxy-4-phenylazo-1H-pyrazol-3-yl)-N-hydrazinophenylthiocarbamoyl) (0.11 g, 31%), m.p.: 120ºC. IR: 3450-3100 (4NH), 3046 (CH-aromatic), 1672 (C=O), 1617 (C=N), 1510 (C=C) and 1200 (C=S) cm^{-1}. MS: m/z: 353 (M+, 45%), 203 (100%), 126 (66%), 93 (87%) and 77 (85%).

ii) To a solution of compound **9** (0.35 g, mmol) in methanolic sodium hydroxide (30 ml, 20%) was refluxed for 6h. the cooled reaction mixture was filtered and the filtrate was evaporated, the residue was washed several times with water and recrystallized from ethanol to give 10 (0.15, 54%), m.p.: 200ºC. IR: 3530, 3350, 3225 (OH, 2NH), 3060 (CH-aromatic), 1640 (C=N), 1490 and 1440 cm^{-1}.

3. Results and Discussion

The synthesis of 3-hydrazino-5-hydroxy-4-phenylazopyrazole from 3-diazo-5-hydroxy-4-phenylazopyrazole and stannous chloride in the presence of conc. HCl has been described previously[9]. Condensation of hydrazinopyrazole **1** with acetylacetone, malonomitrile, diethylmalonate, and ethyl acetoacetate in presence of ethanol and/or acetic acid gave 1-(5-hydroxy-4-phenylazo-1H-pyrazole-3 yl) pyrazole derivatives **3a-e** as shown in scheme 1. The structures of compounds **3a-e** were confirmed by their analytical and spectral data.

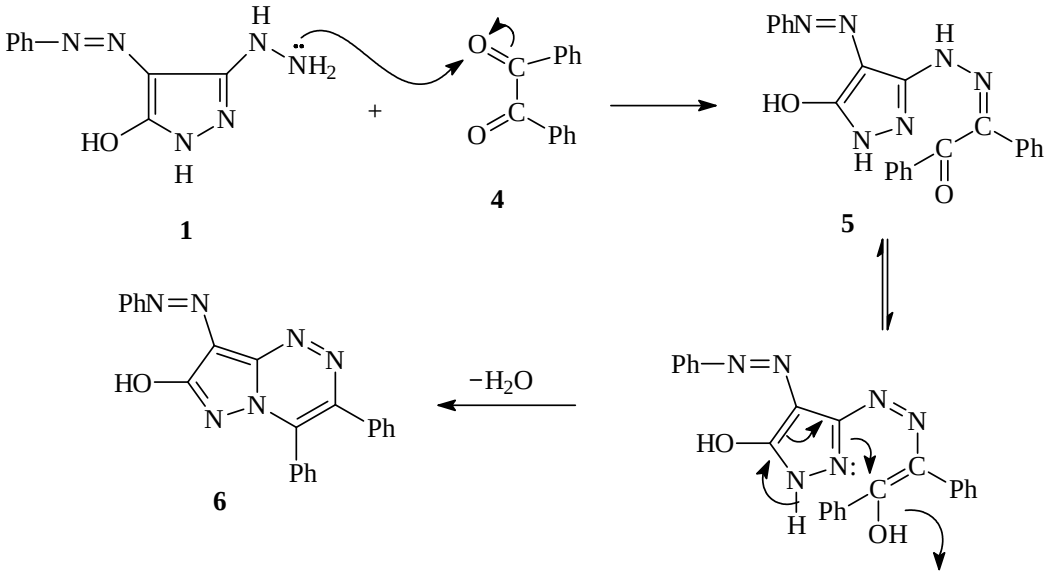


1 **2**a, X=Y= $COCH_3$ **3**a, X=Y=CH_3
b, X=Y=CN b, X=Y=NH_2
c, X=Y=COOEt c, X=Y=OH
d, X=CN, Y=COOEt d, X=NH_2, Y=OH
e, X=$COCH_3$, Y=COOEt e, X=CH_3, Y=OH

Scheme 1

The reaction of **1** with α-dicarbonyl compound was assumed to involve one or both the carbonyl groups in the condensation. Thus, heating equimolar amounts of **1** and benzil in ethanol undergo cyclodehydration to give pyrazolotriazines **6**.

Mechanistically the formation of the pyrazolotriazines **6** involves, the initial formation of the corresponding monohydrazone **5** which undergoes immediate intramolecular nucleophilic attack of pyrazole-nitrogen on the other carbonyl group with elimination of water molecule as shown in scheme 2.



Scheme 2

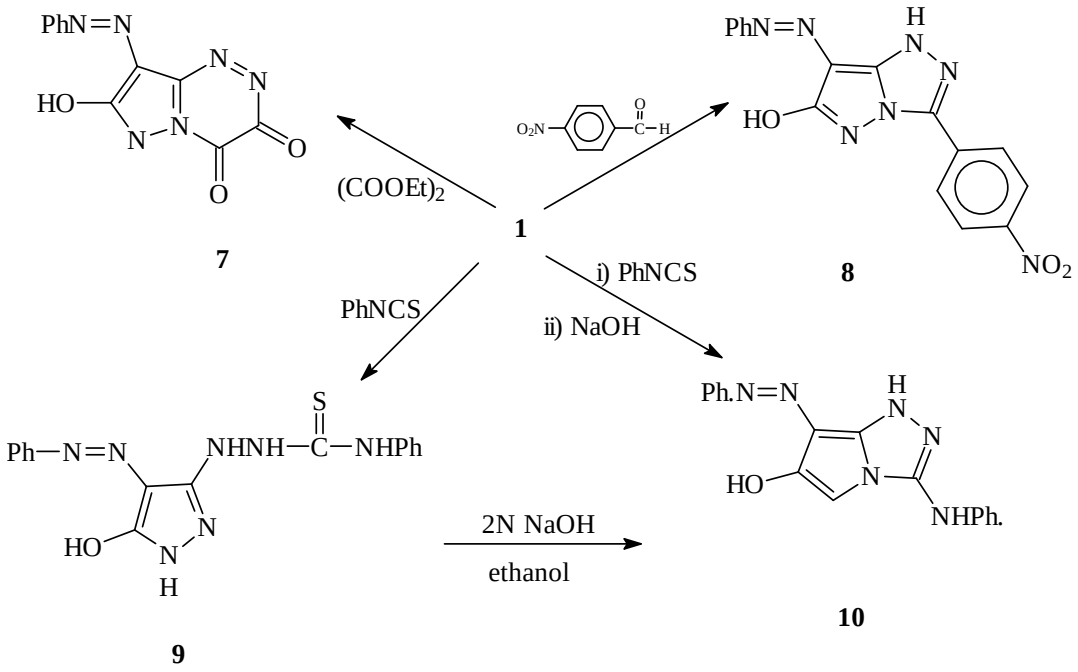
Treatment of hydrazinopyrazole **1** with diethyloxalate gave pyrazolo [5,1-c]-1,2,4-triazine-3,4-dione *via* 1,2-dihydropyrazolo[5,1-c]-1,2,4-triazine-3,4-dione **7**. The infrared spectrum of compound **7** showed the presence of two carbonyl groups at 1668 and 1675 cm^{-1}. The mass spectrum of **7** showed ion peaks at m/z: 272, for M^+.

The condensation of **1** with p-nitrobenzaldehyde gave corresponding hydrazones which undergo oxidative cyclization to give the corresponding pyrazolo [5,1-c]-1H-1,2,4-triazole **8**.

The reaction of **1** with phenyl isothiocyanate afforded the corresponding thiocarbamoylhydrazine, **9**; subsequent ring closure in basic medium yielded pyrazolo- [5,1-c]triazole derivative **10**.

Mechanistically, the formation of the compound **10** from **1** and phenyl isothiocyanate in refluxing ethanolic sodium hydroxide involves the

initial formation of **9** which undergoes intramolecular nucleophilic attack of ring-nitrogen on the thione group with elimination of hydrogen sulfide molecule as shown in scheme 3.



Scheme 3

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