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# Enaminones as building blocks: Synthesis of novel substituted pyrazoles as possible antioxidants

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An efficient synthesis of some new novel series of 1,5-disubstituted pyrazole derivatives have been achieved by reacting different enaminones with various hydrazines. The structures of the newly synthesized compounds have been elucidated from elemental analysis and spectral data. The newly synthesized compounds have been screened for their antioxidant activity.

**Keywords:** Pyrazole, enaminone, hydrazide, DMF-DME, DPPH scavenging assay

Enaminones are versatile building blocks in organic synthesis and their chemistry has received considerable interest[1]. Enaminone derivatives, which are usually prepared from formamide acetals and active methylene compounds are highly reactive intermediates useful in the synthesis of heterocyclic compounds. They have multiple electrophilic and nucleophilic centers and undergo a variety of cycloaddition and self condensation reactions. For these reasons they are considered as versatile synthetic intermediates[2-5]. The prominent and straightforward method for the synthesis of enaminones is by the condensation of carbonyl compounds with amines. Another widely employed approach is by the reaction of active methylene substrates with N-dialkoxyl-N,N-dialkylamines such as N,N-dimethyl formamide dimethylacetal (DMF-DMA) to provide N,N-dialkyl masked enaminones.

Formamideacetals are useful reagents in organic synthesis. N,N-dimethylformamide dimethylacetal (DMF-DMA) is potentially valuable as a building block for heterocyclic synthesis. It has been utilized in the synthesis of arylpyrazoles, benzofurans, pyridones and quinolinecarbonitiles[6,7]. All the aforementioned structural moieties utilize DMF-DMA's ability to form enamines *via* enolate-type chemistry.

Among the different methodologies for the synthesis of the pyrazoles, several examples of the reaction between arylhydrazine derivatives and enaminones have been reported[8]. N-Substituted pyrazole derivatives are a very interesting class of heterocyclic compounds that have remarkable pharmacological activities such as antibacterial-antifungal, hypoglycemic, tumor necrosis inhibitor, anti-thromboembolic disorders, anti-angiogenic agent, hyperlipidemia, anti-obesity, insecticidal, anti-inflammatory and antioxidant property[9-14].

Prompted by these observations, we utilized N,N-dimethylformamide dimethylacetal (DMF-DMA) in the construction of hitherto unreported novel series of pyrazoles *via* different enaminone precursors. Thus this work describes the synthesis of pyrazoles by the reaction of different enaminones with suitable hydrazine derivatives and the antioxidant property of these novel pyrazoles.

## Result and Discussion

### Chemistry

The pyrazoles **5** were prepared by the reaction of equimolar amounts of enaminones with different hydrazine in xylene medium. Initially, this reaction was carried out using the solvents such as methanol, acetone and also with dimethyl formaldehyde and dimethyl sulfoxide. However, the reaction did not proceed and the reaction remained incomplete. Finally, xylene was used as the effective solvent for this reaction. Also, in the case of enaminones derived from sydnones and triazole, the required pyrazoles were obtained by the use of catalytic amount of *p*-toluene sulfonic acid (PTSA). But in case of enaminone derived from of *p*-nitrophenyl group, reaction proceeded without the use of any catalyst.

Four different hydrazine derivatives namely, hydrazine hydrate, phenyl hydrazine, 2,4,6-trichlorophenyl hydrazine and 2-bromo-pyrimidinyl-5-hydrazines were employed in the present work. Structures of the newly synthesized enaminones and the final pyrazole derivatives were confirmed on the basis of spectral and analytical data. Characterization data of these compounds are given in Table I. In the IR spectrum of 4-acetyl-[5-methyl-1-(*p*-nitrophenyl)-1*H*-1,2,3-triazole] **3** the absorption band corresponding to C-H stretching was seen at 2954 $cm^{-1}$. Characteristic C=O stretching frequency was observed at 1672 $cm^{-1}$. Asymmetric and symmetric stretching for the nitro group is observed at 1518 and 1338 $cm^{-1}$ respectively. Also, the structures of the synthesized enaminone intermediates were confirmed by recording their $^1$H NMR spectra.

In the $^1$H NMR spectrum of 3-(dimethylamino)-1-(*p*-nitrophenyl)prop-2-en-1-one **3c**, the signal due to two methyl groups appeared as two singlets each integrating for three protons at δ 2.96 and 3.18, thereby indicating the magnetic non equivalency of these two methyl protons. The olefinic protons came into resonance as two doublets with coupling constant $J$ = 12.4 Hz each at δ 5.89 and 7.82 respectively. *Meta* and *ortho* protons of *p*-nitrophenyl group appeared as two doublets with $J$ = 8.8 Hz each integrating for two protons at δ 8.12 and 8.27.

## Antioxidant studies

The newly synthesized pyrazoles **5** were evaluated for antioxidant property. The free radical scavenging activity of test sample was measured by DPPH scavenging assay according to the method of Brand-Williams *et al*.[15] Free radical scavenging activity of the test compounds were carried out based on the scavenging activity of stable DPPH. 100 µg/mL of each test sample and standard BHT were taken in different test tubes and the volume was adjusted to 1 mL using MeOH. Freshly prepared 3 mL of 0.1 mM DPPH solution was mixed and vortexed thoroughly and left in dark for 30 min. The absorbance of stable DPPH radical was measured at 517 nm. The DPPH control (containing no sample) was prepared using the same procedure. Radical scavenging activity was expressed as the inhibition percentage and was calculated using the equation of DPPH radical scavenging activity.

$$\text{DPPH radical scavenging activiy (\%)} = \frac{\text{(Abs Control - Abs Sample)}}{\text{(Abs Control)}} * 100$$

where Abs Control is the absorbance of DPPH radical + methanol; Abs Sample is the absorbance of DPPH radical + test sample/standard BHT. The antioxidant study results are tabulated in Table II. The DPPH scavenging activity for tested compounds showed activity ranging from 72.6% to 42.1%, whereas standard drug BHT showed 90.42% inhibition. Compounds **5a**, **5c** and **5j** displayed significant radical scavenging activity *i.e.* 72.6%, 70.2% and 70.0% respectively among the set of compounds tested in the present study. Whereas compounds **5d**, **5g** and **5i** showed moderate antioxidant activity *i.e.* 68 to 69.8% respectively.

## Experimental Section

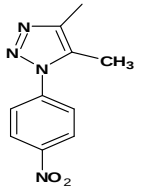
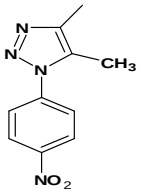
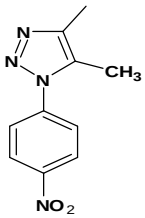
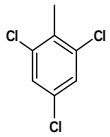
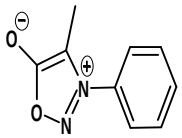
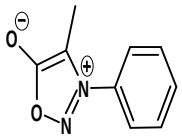
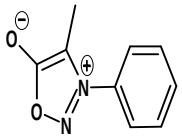
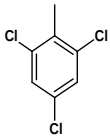
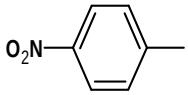
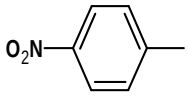
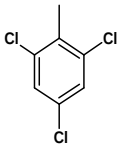
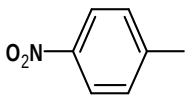
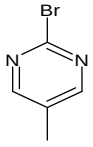
Melting points were determined in open capillary tubes in Innovative DTC-967A digital melting point apparatus and are uncorrected. IR spectra were recorded by dispersing the compounds in KBr pellets on a Shimadzu FT-IR 157 spectrophotometer. $^1$H NMR spectra were recorded on a 400MHz or 500 MHz Bruker Avance II NMR spectrometer and all the chemical shift values were reported as δ (ppm), downfield from TMS and proton signals are indicated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded either on a Waters UPLC-MS spectrometer or LCMS (API 3000, Applied Bio Systems) operating at 70 eV. Elemental analysis was carried out on a Shimadzu Elementar Vario EL III model elemental analyser. The X-ray diffraction measurements were carried out in Bruker SMART APEXII CCD area-detector diffractometer. The homogeneity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates.

The starting materials namely 4-acetyl-[5-methyl-1-(*p*-nitrophenyl)-1*H*-1,2,3-triazole **1a** and 2-acetyl-3-phenylsydnone **1b** were prepared as per the procedures reported in the literature[16,17]. *p*-Nitroacetophenone of AR grade was obtained commercially and used as such without further purification.

### General procedure for the synthesis of dimethylaminopropenone[18], 3

A mixture of required acetyl compound **(1a/1b/1c)** (0.01 mol) and dimethylformamide dimethylacetal **2** (0.02 mol) was refluxed in oil bath for 6-8 h. The resulting solid obtained was filtered, and washed successively with ethanol and water. Thereafter, it was purified by recrystallization from ethanol-DMF mixture (Scheme I). The compounds prepared according to this procedure are:

Table I — Characterization data of pyrazole derivative **5a-i**

| Compd | R | $R^1$ | m.p.°C (Yield %) | Mol. Formula (Mol. Wt) | Found % (Calcd) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **5a*** |  | H | 120-124 (76) | $C_{12}H_{10}N_6O_2$ (270.24) | 53.31 (53.33 | 3.75 3.73 | 31.12 31.10) |
| **5b*** |  | Ph | 150-154 (78) | $C_{18}H_{14}N_6O_2$ (346.34) | 62.44 (62.42 | 4.08 4.07 | 24.29 24.27) |
| **5c*** |  |  | 215-217 (70) | $C_{18}H_{11}Cl_3N_6O_2$ (449.67) | 48.10 (48.08 | 2.49 2.47 | 18.71 18.69) |
| **5d** |  | H | 256-258 (75) | $C_{11}H_8N_4O_2$ 228.20 | 57.91 (57.89 | 3.55 3.53 | 24.85 24.55) |
| **5e*** |  | Ph | 238-240 (76) | $C_{17}H_{12}N_4O_2$ 304.30 | 67.12 (67.10 | 3.99 3.97 | 18.43 18.41) |
| **5f*** |  |  | 230-232 (75) | $C_{17}H_9Cl_3N_4O_2$ 407.63 | 50.11 (50.09 | 2.25 2.23 | 13.76 13.74) |
| **5g** |  | Ph | 210-212 (75) | $C_{15}H_{11}N_3O_2$ 265.26 | 67.94 (67.92 | 4.20 4.18 | 15.86 15.84) |
| **5h** |  |  | 235-238 (70) | $C_{15}H_8Cl_3N_3O_2$ 368.60 | 48.91 (48.88 | 2.21 2.19 | 11.42 11.40) |
| **5i** |  |  | 228-230 (68) | $C_{13}H_8BrN_5O_2$ 346.13 | 45.13 (45.11 | 2.35 2.33 | 20.25 20.23) |

Solvent for recrystallization: Ethanol + DMF mixture.

* Reaction was carried out in the presence of PTSA.

**3-(Dimethylamino)-1-[5-methyl-1-(*p*-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]prop-2-en-1-one, 3a**: Yield 71%. m.p.148-49°C. Anal. Calcd for $C_{14}H_{15}N_5O_3$: C, 55.81; H, 5.02; N, 23.24. Found: C, 55.83; H, 5.00; N, 23.22%.

**3-(Dimethylamino)-1-(3-phenyl-sydnon-4-yl)prop-2-en-1-one, 3b**: Yield 65%. m.p.106-108°C. Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.24; H, 5.07; N, 16.23%.

**3-(Dimethylamino)-1-(*p*-nitrophenyl)prop-2-en-1-one, 3c**: Yield 78%. m.p.112-14°C. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.97; H, 5.50; N, 12.74%.

**General procedure for the synthesis of pyrazoles, 5**

To a solution of dimethylaminopropenone **3** (0.01 mol) taken in xylene (25 mL), was added appropriate hydrazines **4** (0.01 mol). The contents were refluxed for about 8-12 h. Completion of the reaction was monitored by thin layer chromatography. The solid product separated was collected by filteration, washed thoroughly with water and ethanol. It was dried and purified by recrystallization from DMF-ethanol mixture (Scheme I). The characterization data of these pyrazoles are given in Table I.

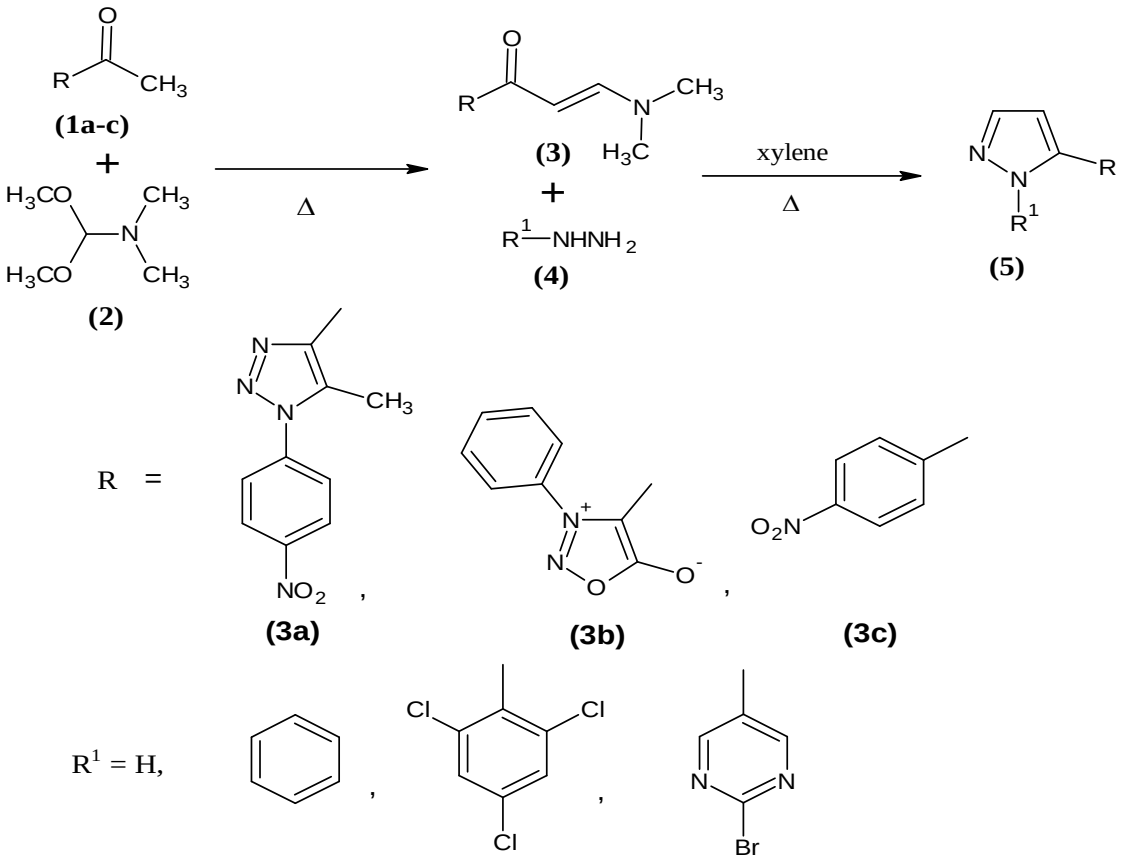
However, in case of enaminone **3b** and **3c** catalytic amount of PTSA (*p*-toluene sulfonic acid) was used. After completion of the reaction, excess solvent was decanted and the gummy residue was triturated with ethanol to get the solid product.

The spectral data for these compounds are given below.

**5-[5-Methyl-1-(*p*-nitrophenyl)-1,2,3-triazole-4-yl]-1*H*-pyrazole, 5a**: IR (KBr): 3187.7 (N-H), 3035.1 (C-H), 1560.1(C=N), 1535.8 (asym. $NO_2$), 1347.5 $cm^{-1}$ (sym. $NO_2$); $^1H$ NMR (500MHz, $CDCl_3$): δ 2.71 (s, 3H, $CH_3$), 7.83-7.79 (m, 4H, 3-H and 4-H of pyrazole and *meta* protons of *p*-nitrophenyl), 8.49 (d, 2H, *J* = 8.5 Hz, *ortho* protons of *p*-nitrophenyl), 11.49 (s, 1H, NH); LC-MS: *m/z* 271.2 ($M^+$+1), (Mol.Formula $C_{12}H_{10}N_6O_2$).

Table II — DPPH radical assay of pyrazoles **5a-i**

| Compd | **5a** | **5b** | **5c** | **5d** | **5e** |
|---|---|---|---|---|---|
| DPPH Assay in % | 72.6 | 47.6 | 70.2 | 69.8 | 57.1 |
| Compd | 5f | 5g | 5h | 5i | 5j BHT |
| DPPH Assay in % | 60.1 | 68.1 | 62.6 | 69.3 | 70 90.42 |




Scheme I — Synthetic scheme for the synthesis of pyrazoles

**5-[5-Methyl-1-(*p*-nitrophenyl)-1,2,3-triazole-4-yl]-1-phenyl-pyrazole, 5b**: IR (KBr): 3120.4 (N-H), 1545.3 (C=N), 1498.1 (asym. $NO_2$), 1365.2 $cm^{-1}$ (sym. $NO_2$); $^1H$ NMR (500MHz, $CDCl_3$): δ 2.53 (s, 3H, $CH_3$), 6.44 (d, 1H, *J* = 11Hz, pyrazole 4-H), 7.70 (d, 2H, *J* = 8.8Hz, *meta* protons of *p*-nitrophenyl), 7.79 (d, 1H, *J* = 11 Hz, pyrazole 3-H), 8.01-7.81 (m, 5H, Ar-H of phenyl group), 8.38 (d, 2H, *J* = 8.6 Hz, *ortho* protons of *p*-nitrophenyl); LC-MS: *m/z* 347 ($M^+$+1), (Mol.Formula $C_{18}H_{14}N_6O_2$).

**5-[5-Methyl-1-(*p*-nitrophenyl)-1*H*-1,2,3-triazole-4-yl]-1-(2,4,6-trichloro phenyl)pyrazole, 5c**: IR (KBr): 3078.4 (N-H), 1575.8 (C=N), 1514.1 (asym. $NO_2$), 1340.5 $cm^{-1}$ (sym. $NO_2$); $^1H$ NMR (500MHz, $CDCl_3$): δ 2.72 (s, 3H, $CH_3$), 6.28 (d, 1H, *J* = 11Hz, pyrazole 4-H), 7.74 (d, 2H, *J* = 9Hz, *meta* protons of *p*-nitrophenyl), 7.88 (d, 1H, *J* = 12 Hz, pyrazole 3-H), 8.01 (s, 2H, 3-H and 5-H of trichloro phenyl group), 8.45 (d, 2H, *J* = 8.5 Hz, *ortho* protons of *p*-nitrophenyl); LC-MS: *m/z* 449, 451, 453,455 ($M^+$+1), ($M^+$+3), ($M^+$+5 and $M^+$+7), (Mol.Formula $C_{18}H_{11}N_6O_2Cl_3$).

**5-(3-Phenyl sydnone-4-yl)-1*H*-pyrazole, 5d**: IR (KBr): 3180.1 (N-H), 3005.1 (C-H), 1755.2 (C=O), 1560.1 $cm^{-1}$ (C=N); $^1H$ NMR (400MHz, $CDCl_3$): δ 6.37 (d, 1H, pyrazole 4-H), 7.54-7.22 (m, 5H, Ar-H of sydnone phenyl), 7.65 (d, 1H, pyrazole 3-H), 9.12 (s, 1H, -NH); LC-MS: *m/z* 228 ($M^+$), (Mol.Formula $C_{11}H_8N_4O_2$).

**5-(3-Phenyl sydnone-4-yl)-1-phenyl-pyrazole, 5e**: IR (KBr): 3201.1 (N-H), 2986.3 (C-H), 1742.2 (C=O), 1548.1 $cm^{-1}$ (C=N); $^1H$ NMR (400MHz, $CDCl_3$): δ 6.12 (d, 1H, pyrazole 4-H), 7.48-7.31 (m, 8H, Ar-H of sydnone phenyl and phenyl group), 7.54 (d, 1H, pyrazole 3-H), 7.76-7.59 (m, 2H, Ar-H phenyl); LC-MS: *m/z* 305.3 ($M^+$+1), (Mol.Formula $C_{17}H_{12}N_4O_2$).

**5-(3-Phenyl sydnone-4-yl)-1-(2,4,6-trichloro phenyl)-pyrazole, 5f**: IR (KBr): 3059 (C-H), 1738 (C=O), 1582 (C=N), 1528 (asym. $NO_2$), 1343 $cm^{-1}$ (sym. $NO_2$); $^1H$ NMR (300MHz, $CDCl_3$): δ 6.23 (d, 1H, pyrazole 4-H), 7.31-7.86 (m, 7H, Ar-H of sydnone and 2,4,6-trichloro phenyl), 7.61(d, 1H, pyrazole 3-H); LC-MS: *m/z* 407 ($M^+$+1) and cluster of isotope peaks were observed at 409 ($M^+$+3), 411($M^+$+5), 413($M^+$+7).

**5-(*p*-Nitrophenyl)-1-phenyl-1*H*-pyrazole, 5g**: IR (KBr): 3159.1 (C-H), 1562.2 (C=N), 1509.3 (asym. $NO_2$), 1341.2 $cm^{-1}$ (sym. $NO_2$); $^1H$ NMR (300MHz, $CDCl_3$): δ 6.23 (d, 1H, pyrazole 4-H), 7.34-7.20 (m, 7H, Ar-H of phenyl and *meta* protons of *p*-nitro phenyl), 7.59(d, 1H, pyrazole 3-H), 8.12 (d, 2H, *J* = 8.8 Hz, *ortho* protons of *p*-nitrophenyl); LC-MS: *m/z* 266.6 ($M^+$+1), (Mol.Formula $C_{15}H_{11}N_3O_2$).

**5-(*p*-Nitrophenyl)-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole, 5h**: IR (KBr): 3084.1 (C-H), 1593.2 (C=N), 1521.8 (asym. $NO_2$), 1344.3 $cm^{-1}$ (sym. $NO_2$); $^1H$ NMR (300MHz, $CDCl_3$): δ 6.17 (d, 1H, pyrazole 4-H), 7.45-7.27 (m, 4H, Ar-H of 2,4,6-trichlorophenyl and *meta* protons of *p*-nitro phenyl), 7.89 (d, 1H, pyrazole 3-H), 8.20 (d, 2H, *J* = 8.7 Hz, *ortho* protons of *p*-nitrophenyl); LC-MS: *m/z* 370.1 ($M^+$+1), (Mol.Formula $C_{15}H_8Cl_3N_3O_2$). The cluster of isotope peaks were observed at *m/z* 368, 370, 372, 374, corresponding to ($M^+$+1), ($M^+$+3), ($M^+$+5) and ($M^+$+7) peaks.

**5-(*p*-Nitrophenyl)-1-(2-bromopyridine-5-yl)-1*H*-pyrazole, 5i**: IR (KBr): 2996 (C-H), 1601 (C=N), 1538 (assym. $NO_2$), 1341 $cm^{-1}$ (sym. $NO_2$); $^1H$ NMR (300MHz, DMSO-$d_6$): δ 6.2 (d, 1H, pyrazole 4-H), 7.41 (d, 2H, *J*=8.8 Hz, *meta* protons of *p*-nitro phenyl), 7.91 (d, 1H, pyrazole 3-H), 8.16 (d, 2H, *J* = 8.8 Hz, *ortho* protons of *p*-nitrophenyl), 8.1 (s, 2H, pyrimidy-4-H and 6-H); LC-MS: *m/z* 346 ($M^+$+1) and 348 ($M^+$+3) with relative intensity of 1:1 (Mol.Formula $C_{13}H_8BrN_5O_2$).

## Conclusion

In this study, a series of 5-substituted-N-arylpyrazoles have been prepared using novel enaminones as building blocks. The newly synthesized pyrazoles have been tested as antioxidant agents and the results obtained are promising.

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