*Int. J. Chem. Sci.: 12(1), 2014, 217-224*
*ISSN 0972-768X*
*www.sadgurupublications.com*

# SYNTHESIS OF NOVEL SUBSTITUTED-3, 5-DIMETHYL-1*H*-PYRAZOLYL PHTHALAZINE-1, 4-DIONES

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## ABSTRACT

A simple and convenient procedure has been developed for the synthesis of substituted 3, 5-dimethyl-*1H*-pyrazolyl phthalazine-1,4-diones **5(a-e)** by the condensation of 2-(3,5-di methyl-1H-pyrazol-1yl)acetohydrazide **3** with phthalic anhydride than followed by alkylation. The ambient conditions, excellent product yields, easy work up procedures and short reaction time make this synthetic strategy a better protocol for the synthesis of newer substituted, 3,5-dimethyl-*1H*-pyrazolyl phthalazine-1,4-diones **5(a-e)**. The structures of all these compounds were confirmed by their IR, $^{1}$H NMR, $^{13}$C NMR and mass spectral analysis.

**Key words**: Acetylacetone, Hydrazine hydrate, Bromoethyl ester, Phthalic anhydride.

## INTRODUCTION

The heterocyclic structure is common in numerous natural products and medicines that are associated with antitumor, antibacterial, antimalarial, and antifungal activities[1,2]. On the other hand, research on the synthesis and biological activity of heterocyclic compounds is an important developmental direction in medical and pesticidal chemistry. A variety of pyrazole and phthalazine heterocyclics could exhibit these activities. Pyrazoles are an important class of drug intermediates in the pharmaceutical industry, as the pyrazole core structure is found in numerous biologically active molecules[3]. Many pyrazole derivatives are known to exhibit a wide range of medicinal properties such as anti-inflammatory, hypoglycemic, analgesic, anti-pyretic, anti-bacterial, sedative-hypnotic and anticoagulant activity[4-7]. Recently, some arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitor activity[8] and carboxylate/carbohydrazide derivatives suppress A549 lung cancer cell growth[9-11].

A number of phthalazine derivatives show high potency as biologically active molecules since the discovery of hydralazine and are widely used in the pharmaceutical

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industry. Consequently, much attention and extensive research have been focused on the synthesis of phthalazine derivatives. Phthalazine have played a unique role in the design and synthesis of novel biologically active compounds serving as anticonvulsant[12], antimicrobial[13], antifungal[14], vasorelaxant[15], anti-HIV, anticancer activity[16], $PDE_3/PDE_4$ inhibitory agents[17], antiasthamatic[18], leishmanicidal[19], antidiabetic[20], etc.

Prompted by these observations, it was speculated that designing and synthesis of a new series of pyrazole embedded phthalazine derivatives would be worthwhile. Further, after extensive literature search, it was observed that, till date no effort has been made to combine these vital moieties as single molecular scaffold. So, keeping these observations in view and in continuation of our research on the synthesis of biologically significant heterocycles, we herein, report the synthesis of some new 3,5-dimethyl-*1H*-pyrazolyl phthalazine-1,4-diones, which entailed the union of two biologically active nuclei, *viz*, pyrazole and phthalazine.

## EXPERIMENTAL

Melting points were measured in open capillary on Buchi melting point B-540 apparatus and were uncorrected. IR spectra were recorded on Schimadzu FTIR-8400 spectrometer using KBr pellets. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in DMSO-$d_6$ on a Bruker WM-400 spectrometer with TMS as an internal standard. All the chemical shifts values were recorded as ppm. Mass spectra (EI-MS) were taken on Perkin-Elmer (SCIEX API-2000, ESI) at 12.5 eV. CHN analysis was carried out on Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents used were of commercial grade and were used without further purification unless otherwise stated. The progress of each reaction was monitored and purity of the compounds was checked by thin layer chromatography.

### General procedure for synthesis of 2,3-dihydro-2(2-(3,5-dimethyl-1*H*-pyrazol-1-yl) acetyl) phthalazine-1,4-dione (4)

To a solution of 2-(3,5-dimethyl-1H-pyrazol-1yl)acetohydrazide **3** (1 mmol) in methanol (20 mL) added phthalic anhydride (1.2 mmol) slowly than stirred and heated to reflux for 5 h (monitored by TLC). After completion of the reaction, the mixture was cooled to room temperature; precipitate is obtained, filtered, dried, and recrystallized with methanol. Yield: 82%; m.p: 225-227$^o$C, IR (K Br): 1678 and 1729, 3312 (-NH) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$ 400 MHz) (δ/ppm): 2.09 (s, 3H, -$CH_3$), 2.20 (s, 3H, -$CH_3$), 4.74 (s, 2H, -$CH_2$), 5.81 (s, 1H, -CH), 7.4-7.81 (m, 4H, Ar-H), 10.38 (br,1H,-NH). $^{13}$C NMR (DMSO-$d_6$ 100

MHz) (δ/ppm): 11.09, 13.68, 50.02, 105.26, 128.64, 129.84, 130.32, 131.76, 136.51, 140.46, 146.42, 166.52, 167.60, 168.02; MS (*m/z*): 299 (M+1); Anal. Calcd for $C_{15}$ $H_{14}$ $N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.34; H, 4.70; N, 18.69.

**Typical procedure for synthesis of substituted 3,5-dimethyl-1H-pyrazolylacetyl phthalazine-1, 4-diones 5(a-e)**

A mixture of compound **4** (1 mmol), alkyl/aryl/benzyl chlorides (1.2 mmol) and anhydrous $K_2CO_3$ (3 mmol) in acetone (25 mL) was stirred at reflux temperature for 5 to 6 h. After the completion of the reaction, as indicated by TLC conducted in 3 : 7 mixtures of ethyl acetate and n-hexane. The reaction mixture was poured into ice-cold water (30 mL) and extracted with dichloromethane (3 x 15 mL). The solvent was evaporated under reduced pressure to get the crude product. It was purified by column chromatography on silica gel (100-200 mesh, ethyl acetate: hexane, 2 : 8) to afford the pure compound.

**2,3-Dihydro-2-methyl-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)phthalazine-1,4-dione (5a)**

Yield: 78%; IR (KBr): 1490, 1642 and 1672 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$ 400 MHz) (δ/ppm): 2.42 (s, 3H, -$CH_3$), 2.46 (s, 3H, -$CH_3$), 2.70 (s, 3H, -$CH_3$), 4.68 (s, 2H, $CH_2$), 5.92 (s, 1H, -CH), 7.70-7.82 (m, 4H, Ar-H). $^{13}C$ NMR (DMSO-$d_6$ 100 MHz) (δ/ ppm): 10.68, 13.20, 35.62, 50.46, 105.24, 126.88, 127.20, 128.86, 131.66, 140.24, 146.64, 166.92, 164.40, 168.52; MS (*m/z*): 313 (M+1); Anal. Calcd for $C_{16}$ $H_{16}$ $N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.50; H, 5.12; N, 17.88.

**2-Ethyl-2,3-dihydro-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)phthalazine-1,4-dione (5b)**

Yield: 71%; IR (KBr): 1492, 1649 and 1682 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$ 400 MHz) (δ/ppm): 1.22 (t, 3H, -$CH_2$-$CH_3$), 2.44 (s, 3H, -$CH_3$), 2.49 (s, 3H, -$CH_3$), 3.28 (q, 2H, -$CH_2$-$CH_3$), 4.68 (s, 2H, -$CH_2$), 5.92 (s, 1H, -CH), 7.72-7.84 (m, 4H, Ar-H). $^{13}C$ NMR (DMSO-$d_6$ 100 MHz) (δ/ppm): 9.82, 10.72, 13.22, 36.20, 50.82, 105.42, 126.82, 127.18, 128.92, 131.82, 140.32, 147.12, 160.82, 162.22, 168.50; MS (*m/z*): 327 (M+1); Anal. Calcd for $C_{17}$ $H_{18}$ $N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.52; H, 5.48; N, 17.10.

**2,3-Dihydro-2-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)-3-propylphthalazine-1,4-dione (5c)**

Yield: 78%; IR (KBr): 1452, 1647 and 1686 $cm^{-1}$ ; $^1H$ NMR (DMSO-$d_6$ 400 MHz) (δ/ppm): 1.02 (t, 3H, -$CH_2$-$CH_2$-$CH_3$), 1.62 (m, 2H, -$CH_2$-$CH_2$-$CH_3$), 2.46 (s, 3H, -$CH_3$),

2.50 (s, 3H, -$CH_3$), 3.22 (t, 2H, -$CH_2$-$CH_2$-$CH_3$), 4.66 (s, 2H, -$CH_2$), 5.94 (s, 1H, -CH), 7.74-7.92 (m, 4H, Ar-H). $^{13}$C NMR (DMSO-$d_6$ 100 MHz) (δ/ppm): 11.38, 11.42, 13.26, 44.16, 51.88, 105.38, 127.28, 128.96, 132.32, 140.42, 146.94, 160.82, 162.48, 168.52; MS (*m/z*): 341 (M+1); Anal. Calcd for $C_{18}$ $H_{20}$ $N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.48; H, 5.88; N, 16.42.

**2,3-Dihydro-2-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)-3-phenylphthalazine-1,4-dione (5d)**

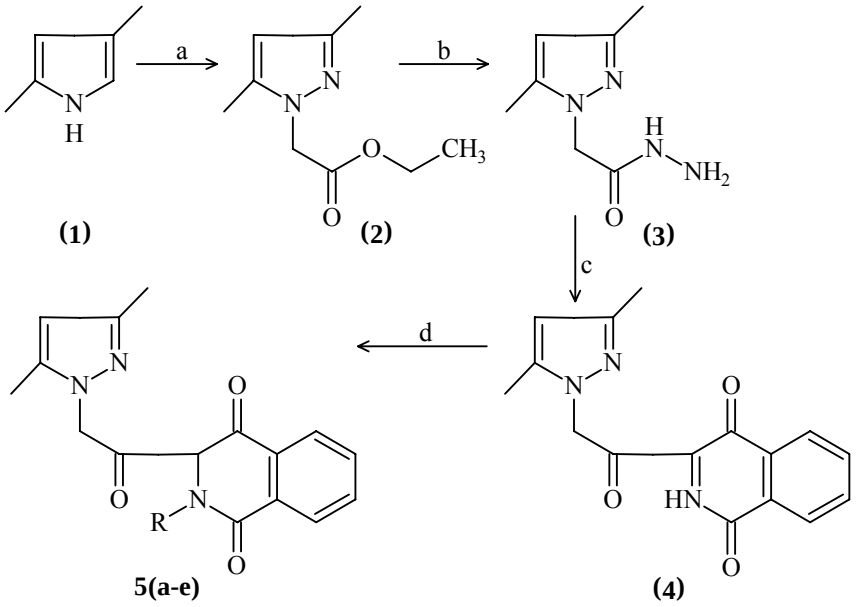
Yield: 82%; IR (K Br): 1472, 1648 and 1682 cm$^{-1}$ ; $^1$H NMR (DMSO-$d_6$ 400 MHz) (δ/ppm): 2.46 (s, 3H, -$CH_3$), 2.48 (s, 3H, -$CH_3$), 4.68 (s, 2H, -$CH_2$), 5.94 (s, 1H, -CH), 6.78-7.22 (m, 5H, Ar-H), 7.74-7.89 (m, 4H, Ar-H). $^{13}$C NMR (DMSO-$d_6$ 100 MHz) (δ/ppm): 10.70, 13.22, 50.42, 105.42, 122. 42, 126.50, 127.22, 128.92, 133.62, 140.22, 147.26, 162.83, 166.48, 168.48; MS (*m/z*): 375 (M+1); Anal. Calcd for $C_{21}$ $H_{18}$ $N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.32; H, 4.80; N, 14.92.

**2-Benzyl-2,3-dihydro-3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)phthalazine-1,4-dione (5e)**

Yield: 80%; IR (KBr): 1482, 1642 and 1689 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$ 400 MHz) (δ/ppm): 2.50 (s, 3H, -$CH_3$), 2.51 (s, 3H, -$CH_3$), 4.76 (s, 2H, -$CH_2$), 4.83 (s, 2H, -$CH_2$), 5.96 (s, 1H, -CH), 7.23-7.56 (m, 5H, Ar-H), 7.91-7.93 (m, 4H, Ar-H). $^{13}$C NMR (DMSO-$d_6$ 100 MHz) (δ/ppm): 10.72, 13.29, 50.78, 105.46, 124.16, 128.13, 128.45, 128.98, 129.47, 135.42, 140.25, 142.42, 146.80, 164.95, 168.58, 206.55; MS (*m/z*): 389 (M+1); Anal. Calcd for $C_{22}$ $H_{20}$ $N_4O_3$: C, 68.03; H, 5.19; N, 14.42. Found: C, 68.92; H, 5.14; N, 14.28.

## RESULTS AND DISCUSSION

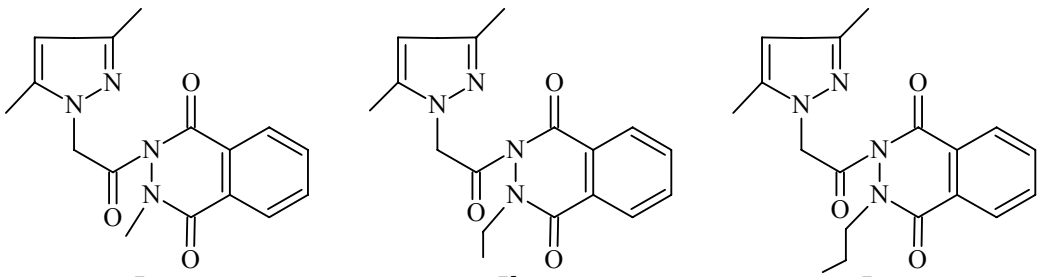
The reaction sequences employed for the synthesis of intermediates and target compounds are shown in the **Scheme 1**. A mixture of acetylacetone and hydrazine hydrate was refluxed for 3 h in ethanol and evaporated to remove solvent to get compound 3,5-dimethyl pyrazole (**1)** in very good yields[21]. Thus obtained compound (**1)** was treated with acetone, ethyl bromoacetate and solid $K_2CO_3$ were added, and the resulting mixture was refluxed for 14 h to get compound **(2)**. Then hydrazine hydrate and alcohol were added and stirred for 4 h at the room temperature to form compound **(3)**,[22] which was mixed with phthalic anhydride compound **(4)** was obtained after 4 h by refluxing in alcohol. Alkylation of 2-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl) acetyl phthalazine-14-dione **(4)** with alkyl/aryl/aralkyl chlorides in refluxing acetone containing anhydrous $K_2CO_3$ afforded the substituted 3,5-dimethyl-*1H*-pyrazolyl acetyl phthalazine-1,4-diones **(5a-e)**.




**Scheme 1**

**Reagents and conditions**: (a) Ethyl bromo ester, $K_2CO_3$, acetone, reflux; (b) Hydrazine hydrate, MeOH; (c) Phthalic anhydride, MeOH, reflux; (d) Alkyl/aralkyl chlorides, $K_2CO_3$, acetone reflux.

The IR spectrum of compound **5e** exhibited characteristic absorption band around 1498, 1642 and 1678 $cm^{-1}$ accounting for carbonyl groups. The $^1H$ NMR spectrum of the compound **5e** showed two singlets at δ 2.50 and 2.51 ppm corresponding to characteristic two $–CH_3$ protons, two singlets appeared at δ 4.76 and 4.83 ppm corresponding to the protons of $–CH_2$, another singlet at δ 5.96 ppm assignable for –CH proton and the aromatic protons appeared as multiplet at δ 7.23-7.50 and δ 7.91-7.93 ppm. The $^{13}C$ spectrum of **5e** exhibited signals at δ 164.58 and 168.95 ppm and δ 206.55 ppm for carbonyl carbons.

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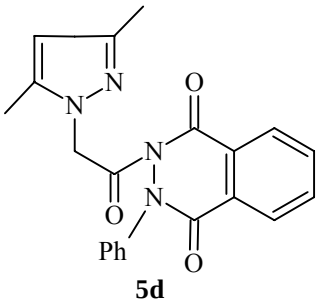
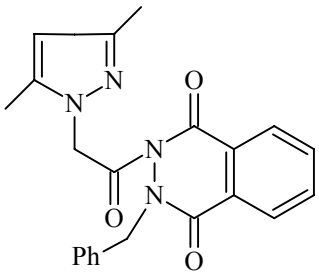



**5d**




**5e**

The compound **5e** was well confirmed by its mass spectrum, which showed molecular ion peak at m/z 389 (M+1), which is in agreement with the molecular formula $C_{22}H_{20}N_4O_3$. The elemental analysis values are in good agreement with theoretical data. Similarly, all the compounds were characterized on the basis of spectral data and elemental analysis. A full characterization details were provided in experimental section.

## CONCLUSION

We have reported an efficient, convenient, and rapid synthesis of novel substituted 3,5-di methyl-1*H*-pyrazolyl-acetylphthalazine-1,4-diones **5(a-e)** by condensation of phthalic anhydride and 2-(3,5-dimethyl-1*H*-pyrazol-1yl)acetohydrazide **(3)** than followed by alkylation of 2,3-dihydro-2(2-(3,5-dimethyl-1*H*-pyrazol-1-yl) acetyl) phthalazine-1,4-dione (**4)** in good yields.

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*Revised : 25.09.2013* *Accepted : 28.09.2013*