INTRODUCTION

Knorr pyrazole synthesis is an organic reaction used to synthesize pyrazole through condensation of hydrazine or its derivatives and 1,3-dicarbonyl by using an acid catalyst [1]. Pyrazole, a five-membered nitrogen-containing aromatic heterocycle, possesses a wide range of activities in pharmaceutical [2] and agrochemical industries. [3] Numerous pyrazole derivatives exhibit potential medicinal properties, such as anticancer, anti-inflammatory, antibacterial, analgesic, and antifungal activities [4–7]. These derivatives constitute the core structure of known drugs, such as Viagra, Celebrex, and Acomplia. Pyrazole derivatives are also applied as novel ligands in cross-coupling reactions catalyzed by transition metals [8]. In addition, some 1,5-diarylpyrazole derivatives exhibit non-nucleoside HIV-1 reverse transcriptase inhibitory activities [9].

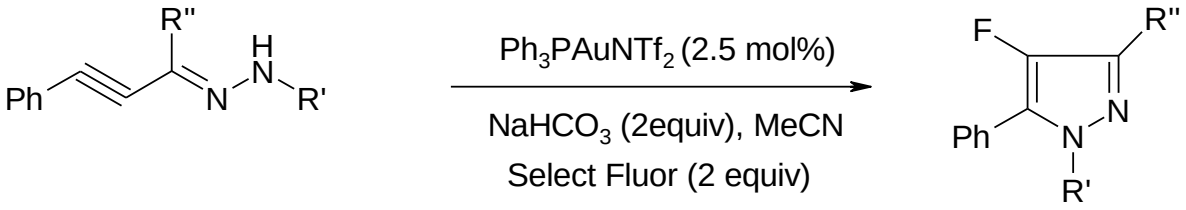
Substituted pyrazoles are efficient estrogen receptor ligands because of their high binding activities and selective transcriptional efficiency for ER-α subtype. [10] Synthesis of these compounds has considerably improved [11–18]. However, organic synthesis presents several limitations, such as use of organic solvents and non-sustainable catalysts, long reaction times, high cost, low yields, and purification issues.

Solvent- and catalyst-free reactions are highly significant both economically and synthetically. These reactions ensure an essential facet of green chemistry to reduce adverse risks to humans and the environment.

In this research project, we propose a new and highly efficient approach for Knorr pyrazole synthesis under solvent- and catalyst-free planetary ball milling conditions.

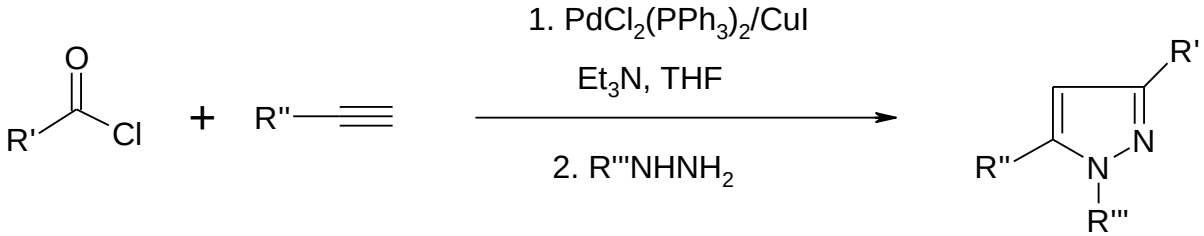
REVIEW OF LITERATURE

Qian et al [11], showed that the synthesis of fluoropyrazole derivatives are accessible, when they used alkyne moieties as backbones involving a gold-catalyzed tandem aminofluorination of alkynes in the presence of selectfluor (Scheme. 1).



Scheme. **1** Synthesis of fluoropyrazole derivatives using gold-catalyzed.

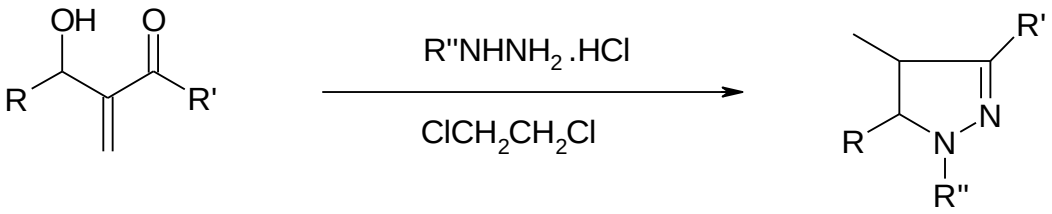
Jiang et al.[12] developed the synthesis of pyrazoles derivatives *via* a one-pot reaction of acid chlorides, terminal alkynes and hydrazines using $Pd(PPh_3)_2Cl_2$/CuI as a catalyst (Scheme. 2). The reaction started by coupling reaction of acid chlorides and terminal alkynes to form enones which undergo a cycloadditon with hydrazines and were converted in situ into pyrazoles.



Scheme. **2** One-pot synthesis of pyrazoles using $Pd(PPh_3)_2Cl_2$/CuI as a catalyst.

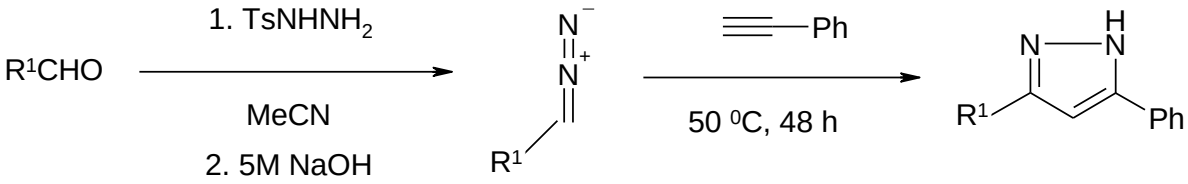
A series of tetrasubstituted pyrazole derivatives were synthesized by Baylis–Hillman adduct and phenyl hydrazine for about 6 hrs in dichloroethane at 50-70°C. The synthesized

pyrazole derivatives were obtained in very high regioselectivity in 89% yield (Scheme. 3)[13].



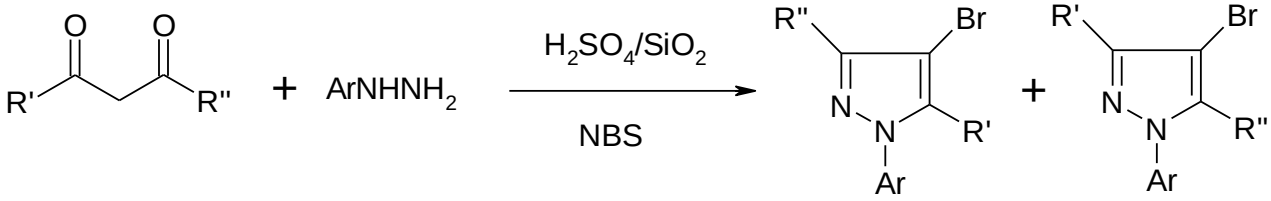
Scheme. **3** Synthesis of pyrazole derivatives using Baylis–Hillman adduct.

Aggarwal et al [14] reported another important method for the synthesis of pyrazole derivatives by 1,3-dipolar cycloaddition of diazo compounds, which derived from aldehydes and terminal alkynes (Scheme. 4).



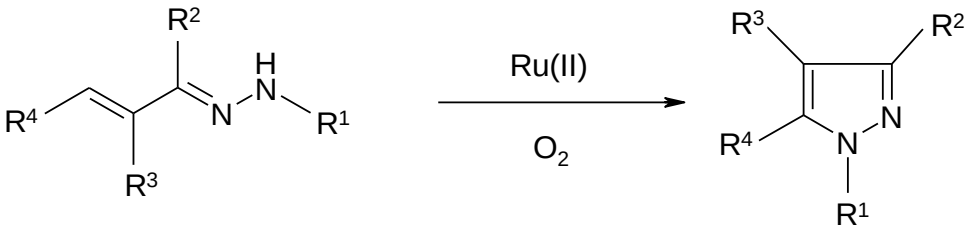
Scheme. **4** Synthesis of pyrazole derivatives *via* 1,3-dipolar cycloaddition.

Alinezhad and co-workers [15] developed a regioselective solvent-free synthesis of 4-bromopyrazoles by one-pot reaction of 1,3-diketones, arylhdrazines and N-bromosaccharin (NBS) in the presence of silica gel supported sulfuric acid (H_2SO_4/SiO_2) (Scheme. 5).



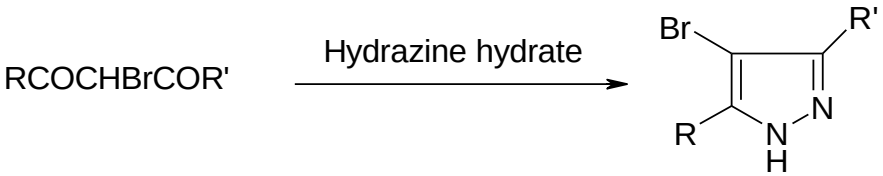
Scheme. **5** Regioselective synthesis of bromopyrazoles.

Hu et al [16] reported the tri and tetrasubstituted pyrazoles synthesis with high yields by the Ru(II)-catalyzed oxidative C-N coupling for starting materials (Scheme. 6). Dioxygen gas is used as oxidizing agent which plays a critical role in the catalytic cycle C-H activation.



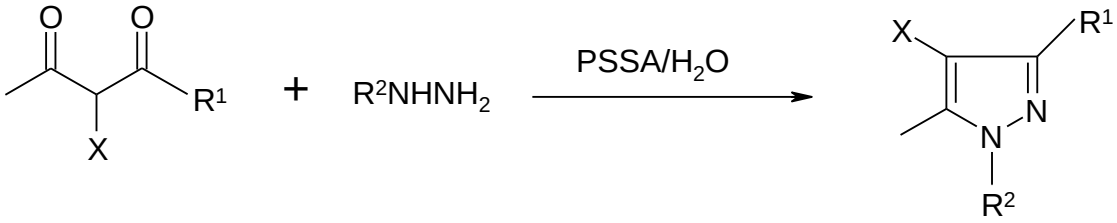
Scheme. **6** Synthesis of pyrazole derivatives by the Ru(II)-catalyzed.

Grag et al [17] showed that the reaction of 2-bromo dialkylpropane-1,3-dione derivatives with hydrazine hydrate provided the corresponding bromopyrazoles (Scheme. 7).



Scheme. **7** Bromopyrazoles synthesis by condensation reaction 1,3-diketones with hydrazine hydrate.

Polshettiwar et al [18] has extended the synthesis of pyrazole derivatives at room temperature by condensation reaction of 1,3-diketones and hydrazines using water as the solvent (Scheme. 8). The protocol involves polystyrene supported sulfonic acid (PSSA) as catalyst.

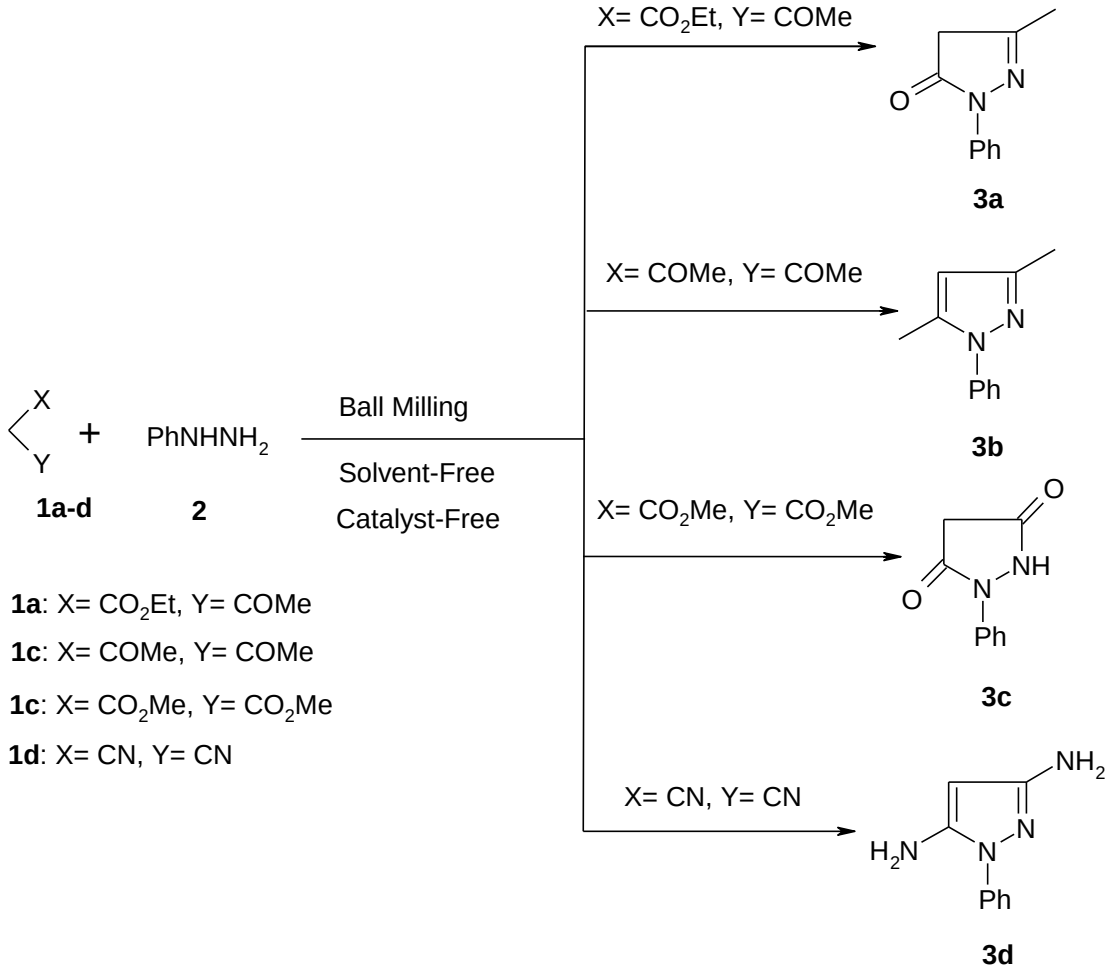


Scheme. **8** Synthesis of pyrazoles using PSSA as catalyst.

RESULTS AND DISCUSSION

As a continuation of our research on the applications of ball milling in organic synthesis [19-21], we report an eco-friendly, effective, and high-yield Knorr pyrazole synthesis. In this technique, ethyl acetoacetate and phenyl hydrazine are directly placed in a simple planetary ball mill under solvent- and catalyst-free conditions (Scheme 9).

To optimize the conditions for Knorr pyrazole synthesis, we placed ethyl acetoacetate (0.01 mol), and phenyl hydrazine (0.01 mol) (with a total mass of 3.04 g) in a tempered vial. We subsequently added 18.24 g of balls (ratio of the ball weight to the reagent weight is equal to 6) [21]. The progress of the reaction was monitored every 10 min of the milling cycle via thin-layer chromatography (TLC). The reaction was completed after 20 min. Similar conditions were applied to different reactions, and all the synthesized products were obtained in the same time.



Scheme . 9 Knorr pyrazole synthesis under ball milling Solvent-free catalyst-free

The spectral data correspond to different synthesized products. Product **3b** (Table 1) shows a characteristic single peak in the ^{1}H-NMR spectra at approximately 5.96 ppm (s, 1H). This peak corresponds to the proton of the sp^2 carbon (CH=) in the pyrazole ring. The signal in the ^{13}C-NMR spectra at approximately 148.9 ppm belong to the carbone sp^2 (N=C) in the pyrazole ring.

Table. 1 Knorr pyrazole synthesis under ball milling Solvent-free catalyst-free.

Entry	X	Y	Product	Yield(%)
1	CO_2Et	COMe	**3a**	99
2	COMe	COMe	**3b**	98
3	CO_2Me	CO_2Me	**3c**	98
4	CN	CN	**3d**	98

SPECTRAL DATA

The spectroscopic data for synthesized products in this chapter are recorded in the experimental part.

We provide for example the NMR spectrum of the product **3b**

The 1 H NMR spectrum of the product **3b**

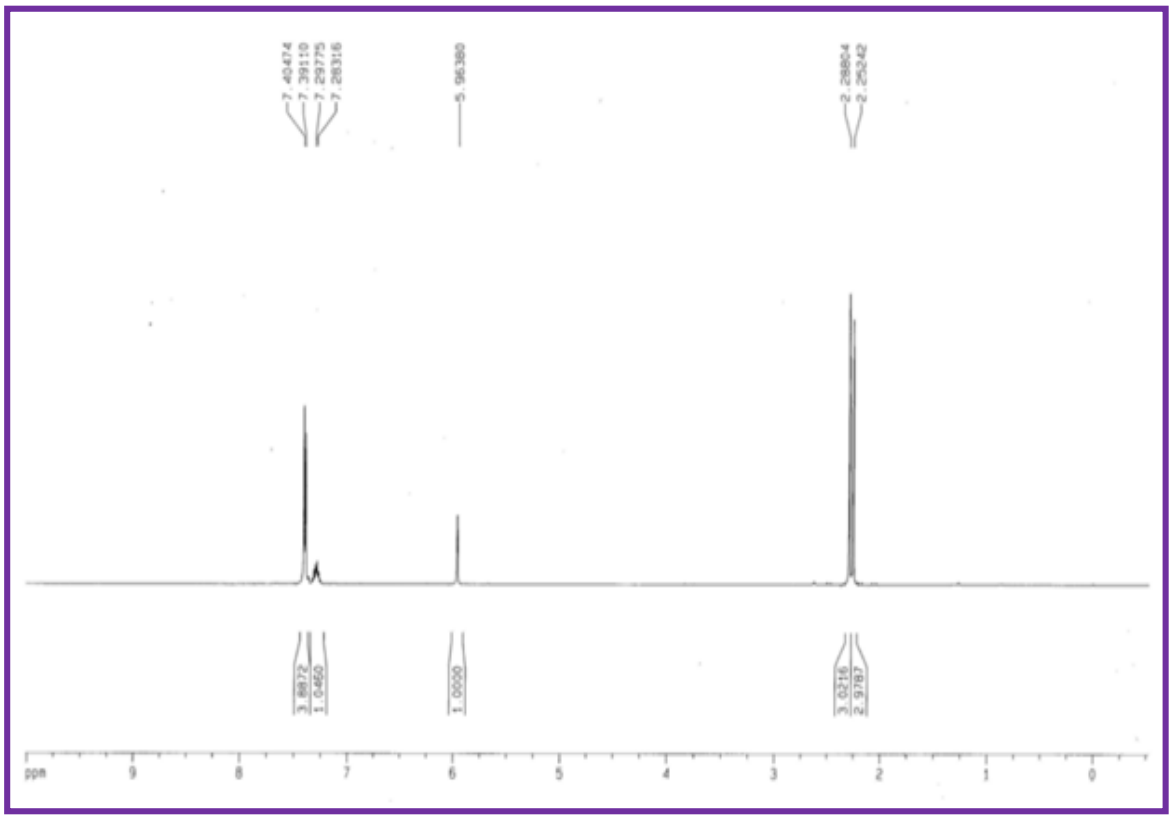


Figure I: ^{1}H NMR spectrum of compound **3b** in $CDCl_3$

The ^{13}C NMR spectrum as an example for the product **3b**

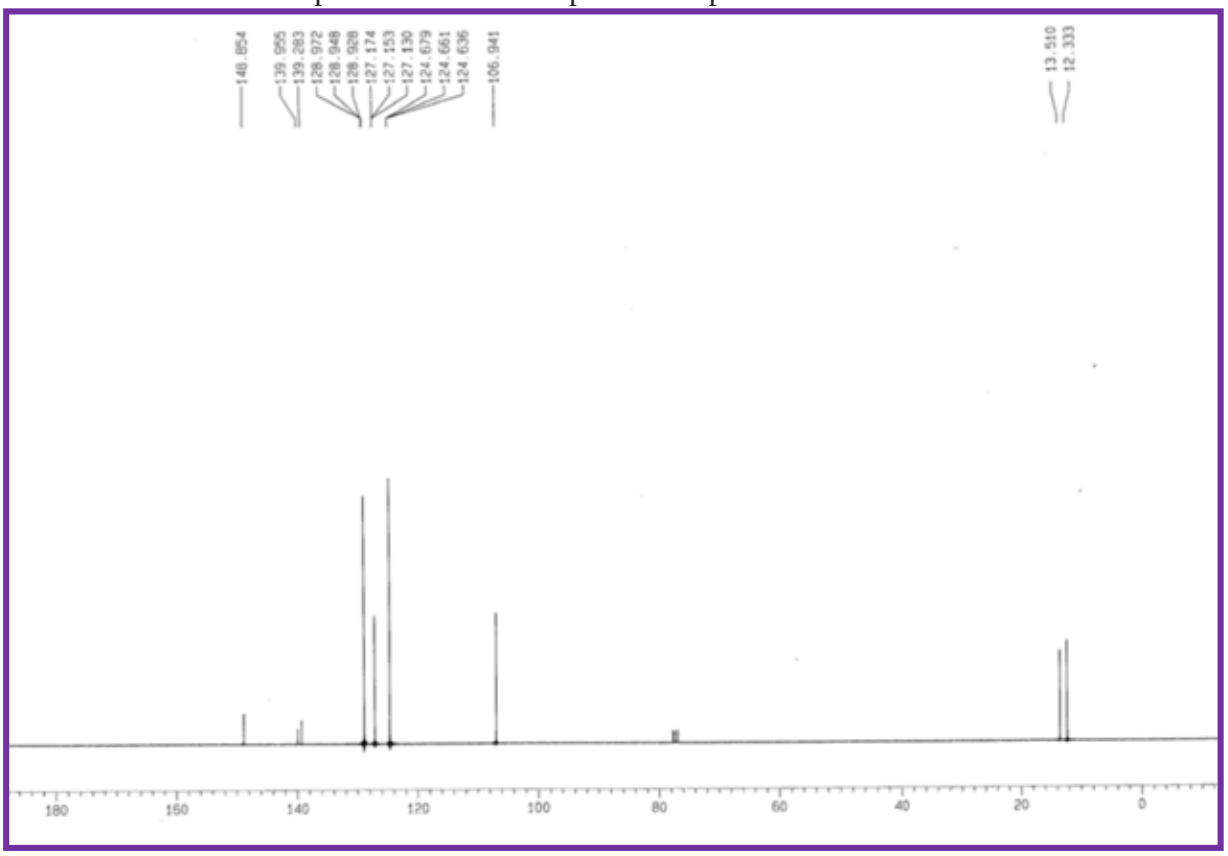


Figure II: ^{13}C NMR spectrum of compound **3b** in $CDCl_3$

CONCLUSION

We described a simple, operational, and green one-pot of Knorr pyrazole synthesis (Table 1) by applying the ball milling technique. This economical and eco-friendly method can be used to synthesize all products in a short period of time and with high yields**.**

EXPERIMENTAL PART

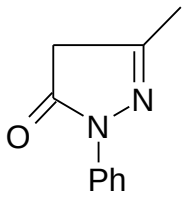
1. Materials and Techniques

The ball mill used in this study was a Planetary Micro Mill PULVERISETTE 7 classic line with 10 cm^3 stainless steel vials. Melting points were determined using the Stuart Melting point apparatus SMP10. The IR spectra were obtained using an FT-IR-Tensor 27 spectrometer in KBr pellets. The ^1H and ^{13}C NMR spectra were determined using a BRUKER 300 NMR spectrometer in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed as δ ppm units. The progress of all reactions was monitored via TLC on silica gel 60 (Merck) by using a chloroform–ethanol system.

2. General Procedure for the Synthesis of Pyrazole Compound 3a

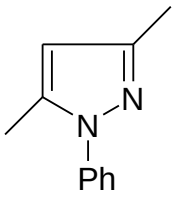
A mixture of ethyl acetoacetate **1a** (0.01 mol) and phenyl hydrazine **2** (0.01 mol) with a total mass equal to 2.38 g was placed in stainless steel vials with 14.28 g of stainless steel balls (12 mm in diameter). The vials were closed and then placed in a Planetary Micro Mill PULVERISETTE 7 classic line. Crude compound **3a** was obtained after 60 min of milling time and purified via recrystallization in ethanol.

5-Methyl-2-phenyl-2,4-dihydro-pyrazol-3-one (3a). M.P.:128-127 ^0C; IR (KBr) ν_{max}/cm^{-1}: 3039, 2920, 1610, 1500. ^1H NMR (300MHz, $CDCl_3$): δ (ppm) 2.15 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 7.26-7.78 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.80, 42.25, 113.20, 125.61, 128.23, 138.29, 154.30, 170.19.



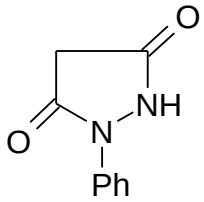
3a

3,5-Dimethyl-1-phenyl-1H-pyrazole (3b). M.P.:158-160 ^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3059, 2923, 1598, 1555. ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 2.25 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 5.96 (s, 1H, CH), 7.28-7.40 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 12.3, 13.5, 107.0, 124.6, 127.2, 128.9, 139.3, 139.9, 148.9.



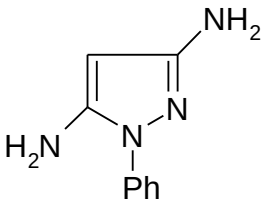
3b

1-Phenyl-pyrazolidine-3,5-dione (3c). M.P.:192-191 ^{0}C; ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 2.86 (s, 2H, CH_2), 7.27-7.48 (m, 5H, ArH), 7.67 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 43.23, 121.96, 126.06, 128.39, 136.53, 166.91, 176.25.



3c

1-Phenyl-1H-pyrazole-3,5-diamine (3d). M.P.:159-161 ^{0}C; ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 3.95 (s, 4H, $2NH_2$), 4.62 (s, 1H, CH), 7.13-7.31 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 91.43, 120,17, 128.18, 129.29, 136.31, 143.97, 156.28.



3d

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