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A Green Protocol for Catalyst-Free Syntheses of Pyrazole in Glycerol-Water Solution

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An efficient green protocol for preparing pyrazole derivatives using glycerol and water as a mixture solvent is described. The advantages of the present method lie in using economic and environmentally benign solvent, no use of catalyst, mild reaction conditions and good yields.

Keywords: Green chemistry, Glycerol, Reaction in water, Pyrazole.

INTRODUCTION

Pyrazole represents a significant class of biologically active five-membered heterocycle containing two adjacent nitrogen atoms and its derivatives exhibit various important medicinal properties such as anti-tumor, antimicrobial, anti-inflammatory, antiviral and anti-immune thrombocytopenias activities[1]. The heterocycle is the primary structural motif in several marked pharmaceuticals, such as celecoxib and lonazolac. In addition, pyrazole is also valuable intermediates in synthetic organic chemistry[2].

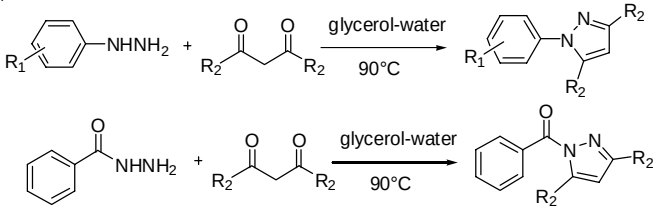
Several synthetic protocols have been reported for the synthesis of pyrazole[2b]. The widely accepted synthetic method for the heterocycle comprises of the condensation reaction of hydrazines with 1,3-dicarbonyl compounds. The reaction is generally carried out in absolute ethanol or other organic solvents in the presence of various acidic catalysts including hydrochloric acid and sulfuric acid[3]. Recently, some alternative methods have been reported, such as solvent-free syntheses catalyzed by $Sc(OTf)_3$ and layered zirconium sulfophenyl phosphonate [α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$], polystyrene-supported sulfonic acid (PSSA) and 12-tungstophosphoric acid catalyzed synthesis in aqueous medium[4]. Although being suitable for certain synthetic conditions sometimes, however, these methods have been associated with one or more drawbacks such as special care in handling, complex transition metal catalyst and strongly acidic conditions, thus leaving room for further improvements.

In the past few decades, the reactions using green solvents have continued to attract considerable interest in synthetic organic chemistry due to the pressure from environmentalists. Obviously, the most ideal green solvent is water, for which is a nonflammable, non-toxic, inexpensive, non-exhaustible solvent and has the additional advantage of strengthening the rate and selectivities of many organic reactions[5]. Nevertheless, its application is limited due to the poor solubility of non-polar starting materials in water, therefore, some organic cosolvents, surfactants and catalysts are used to overcome the shortcoming[6]. More recently, another green solvent, glycerol, has drawn great attentions as its being environmentally friendly, low cost, non-toxic, secure and biodegradable[7]. It has already been applied in Pd-catalyzed Heck and Suzuki cross-couplings, Cu-catalyzed cross-coupling of diaryl diselenides with aryl boronic acids, base- and acid-promoted condensations, catalytic hydrogenation and asymmetrical reduction[8]. Furthermore, it was demonstrated that the electrophilic activation of carbonyl compounds in glycerol-promoted reactions allowed eliminates the use of acidic catalysts[9].

In view of the explained above and as our continuous interest in the development of methods for the synthesis of bio-active heterocyclic compounds in aqueous mediums, we present here a green procedure for the synthesis of pyrazole derivatives using water-glycerol as solvent in the absence of a catalyst (**Scheme-I**).

EXPERIMENTAL

All reagents were commercially available and were used without further purification. Melting points were determined on a Mel-TEMP II melting point apparatus which was uncorrected. IR spectra were recorded on a Bruker VERTEX 70 instruments. Proton magnetic resonance spectra were recorded on a Bruker AV400 instrument. The spectra were recorded in $CDCl_3$ and chemical shifts are reported in parts per million



R_1=H, 4-Cl, 4-CH_3, 4-nitro, 2, 4-dinitro, furanone group, R_2= CH_3, $(CH_3)_2CH$

Scheme-I

(ppm) down field from tetramethyl silane (TMS) as the internal standard. Mass spectra were recorded on an Agilent 1100 LC/MSD Trap. The starting material, 3-*n*-butyl-6-hydrazinylisobenzofuran-1(3*H*)-one (Table-2, entry 8), was synthesized according to the literature method[10].

General procedure: Glycerol (2 mL) was dissolved in water (2 mL), then phenylhydrazine derivative (1 mmol) was added under stirring and the reaction mixture was heated to 90 °C followed by addition of 1,3-dicarbonyl compounds (1 mmol). The progress of reaction was monitored by TLC. When all the starting material had been consumed, the mixture was cooled to room temperature and extracted with ethyl acetate (2 × 5 mL). The organic phase was separated and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give crude product. The pure product was isolated by silica gel column chromatography to give the product as a yellow oil or powder. Data of some compounds are shown below:

3,5-Dimethyl-1-phenyl-1*H*-pyrazole (Table-2, entry 1)[4d]: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.28 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 6.01(s, 1 H, CH), 7.30-7.43 (m, 5H, ArH); IR (KBr, ν_{max}/cm^{-1}): 3057, 2978, 1342, 1045, 712; ESI-MS: 173 ([M + H]$^+$).

3,5-Diisopropyl-1-phenyl-1*H*-pyrazole (Table-2, entry 2): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, 6H, *J* = 4.6 Hz, $2CH_3$), 1.30 (d, 6H, *J* = 4.7 Hz, $2CH_3$), 2.99-3.04 (m, 2H, 2CH), 6.04 (s, 1 H, CH), 7.33-7.44 (m, 5H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.92, 25.48, 27.92, 99.51, 125.90, 127.65, 129.00, 140.23, 150.65, 159.19; IR (KBr, ν_{max}, cm^{-1}): 3057, 2986, 1340, 1041, 728; ESI-MS: 229 ([M+H]+).

1-(2,4-Dinitrophenyl)-3,5-dimethyl-1*H*-pyrazole (Table-2, entry 3)[4a]: Yellow solid, m.p. 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 6.11 (s, 1H, CH), 7.70 (d, 1H, *J* = 5.6 Hz, ArH), 8.54 (dd, 1H, J_1 = 5.8 Hz, J_2 = 1.6 Hz, ArH), 8.80 (s, 1H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3120, 3077, 2928, 1612, 1532, 1124, 671; ESI-MS: 263 ([M + H]$^+$).

3,5-Dimethyl-1-*p*-tolyl-1*H*-pyrazole (Table-2, entry 4)[4d]: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 5.98 (s, 1 H, CH), 7.24 (d, 2H, *J* = 5.4 Hz, 2ArH), 7.29 (d, 2H, *J* = 5.6 Hz, 2 ArH); (KBr, ν_{max}, cm^{-1}): 3054, 2975, 2928, 1342, 712; ESI-MS: 187 ([M + H]$^+$).

1-(4-Chlorophenyl)-3,5-dimethyl-1*H*-pyrazole (Table-2, entry 5)[4d]: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.01 (s, 1 H, CH), 7.37-7.42 (m, 4H, ArH); (KBr, ν_{max}, cm^{-1}): 3079, 2985, 1109, 709; ESI-MS: 207 ([M + H]$^+$).

3,5-Dimethyl-1-(4-nitrophenyl)-1*H*-pyrazole (Table-2, entry 6)[4a]: Yellow solid, m.p. 100-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.06 (s, 1H, CH), 7.66 (d, 2H, *J* = 5.6 Hz, ArH), 8.30 (d, 2H, *J* = 5.6 Hz, ArH); IR (KBr, ν_{max}, cm^{-1}): 3102, 2977, 1660, 1103, 852; ESI-MS: 218 ([M + H]$^+$).

(3,5-Dimethyl-1*H*-pyrazol-1-yl)(phenyl)methanone (Table-2, entry 7)[4a]: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 6.07 (s, 1H, CH), 7.45-7.56 (m, 3H, ArH), 7.98 (d, 2H, *J* = 7.2 Hz, ArH); IR (KBr, ν_{max}, cm^{-1}): 3058, 2977, 2926, 1698, 1342, 709; ESI-MS: 201 [M + H]$^+$.

3-Butyl-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)isobenzofuran-1(3*H*)-one(Table-2, entry 8): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, 3H, *J* = 14.2 Hz, CH_3), 1.34-1.53 (m, 4H, $2CH_2$), 1.76-1.85 (m, 1H, CHH), 2.04-2.14 (m, 1H, CHH), 2.30 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.52-5.55 (m, 1H, CH), 6.05 (s, 1H, CH), 7.53(d, 1H, *J* = 8.1 Hz, ArH), 7.85-7.88 (m, 2H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.55, 13.45, 13.83, 22.39, 26.75, 34.33, 81.36, 107.94, 120.40, 122.67, 127.09, 130.54, 139.62, 140.95, 148.28, 149.84, 169.72; IR (KBr, ν_{max}, cm^{-1}): 3076, 2982, 1749, 1613, 743; ESI-MS: 285 [M + H]$^+$.

RESULTS AND DISCUSSION

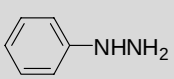
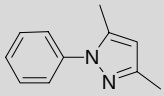
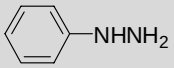
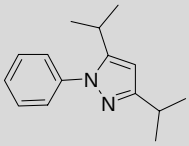
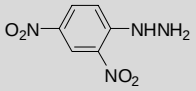
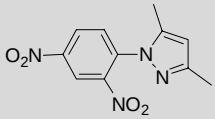
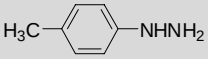
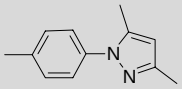
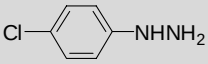
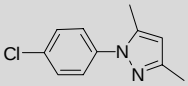
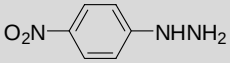
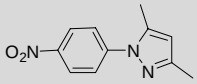
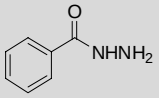
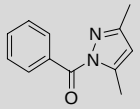
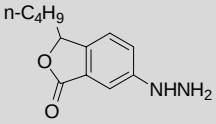
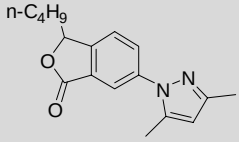
Initially, we carried out the reaction between phenyl hydrazine and acetylacetone using aqueous glycerol as a solvent to afford 1-phenyl-3,5-dimethypyrazole. A mixture of phenyl hydrazine (1 mmol) and acetylacetone (1 mmol) in aqueous glycerol was stirred at room temperature. It was observed that the starting materials were consumed after long reaction time as indicated by TLC analysis. To optimize the reaction conditions to afford the desired pyrazole in good yield, the same reaction was conducted at different temperature and it was observed that as temperature increases, rate of reaction increases and good amount of yield was obtained at 90 °C. At this temperature, different glycerol-water mixtures were used as solution, the best yield was obtained within 30 min as the solvent mixed in a 1:1 volume ratio (Table-1, entry 3). we also executed the same reaction in absence of water or glycerol, but the yield of the product decreased. For comparison, the reaction was performed in ethanol catalyzed. by hydrochloric acid (Table-1, entry 6), The results indicated that although the reaction in the glycerol-water (1:1) proceeded more slowly than that in ethanol, the yield was similar, importantly, the former didn't need acid as a catalyst. Thus the glycerol-water (1:1) was a suitable solvent for this transformation. Again the advantage of this protocol was, after the work-up procedure, glycerol-water system was successfully recovered and reused for another reaction without affecting the yields.

TABLE-1
SCREENING FOR OPTIMAL REACTION CONDITIONS

Entry	Solvent	Time (min)	Yield (%)
1	Glycerol	45	85
2	Glycerol:H_2O (2:1)	40	92
3	Glycerol:H_2O (1:1)	30	95
4	Glycerol:H_2O (1:2)	43	82
5	Glycerol:H_2O (1:4)	48	70
6[a]	C_2H_5OH	20	94

[a]Catalyzed by hydrochloric acid

TABLE-2
SYNTHESIS OF PYRAZOLE

Entry	Hydrazine/hydrazide	Dicarbonyl compound (R_2)	Product	Time (min)	Yield (%)
1		CH_3		30	95
2		$(CH_3)_2CH$		35	90
3		CH_3		28	98
4		CH_3		38	93
5		CH_3		32	96
6		CH_3		30	97
7		CH_3		35	95
8		CH_3		40	85

To expand the synthetic scope of this protocol, a variety of hydrazines and 1,3-dicarbonyl compounds were reacted under the optimized conditions to furnish the corresponding pyrazoles in good to excellent yields (Table-2, entries 1-8). The aromatic hydrazine containing both electron donating and electron withdrawing groups underwent the conversion smoothly. The benzylhydrazines with electron withdrawing substituents gave increased yields than the ones conjugated electron donating substituents (Table-2, entries 1, 3 and 6). The isopropyl substituted 1,3-dione rendered lower yields (Table-2, entry 1 and 2) due to the steric hindrance.

In conclusion, we have demonstrated an efficient protocol for preparing pyrazole derivatives using glycerol and water as a mixture solvent. The advantages of the present method lie in using economic and environmentally benign solvent, no use of catalyst, mild reaction conditions and good yields. This simple, convenient and practical approach may have wide applicability in both synthetic and medicinal chemistry.

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