A mild synthesis of substituted pyrazoles from one-pot three component reaction of simple starting materials

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Abstract
Pyrazole is an important nitrogen heterocycle which is found in a wide number of naturally occurring as well as synthetic molecules exhibiting diverse biological, medicinal and other properties. A mild synthesis of 3-phenyl-5(p-substitutedphenyl)-1H-pyrazoles from simple starting materials and reagents is presented here.

One-pot reaction of three reactants has been carried out under mild condition followed by treatment of the resultant mixture with bromate-bromide to accomplish the desired oxidation of initially formed pyrazolines. The reaction time was short and the yields were good.

Keywords: Araldehyde, Aryl methyl ketone, Hydrazine hydrochloride, Pyrazoles, Three component reaction.

Introduction

Heterocyclic compounds are widely distributed in nature and are important for life activities of plants and animals. Nitrogen heterocycles constitute by far the most useful class of such compounds as they play diverse therapeutic role[14]. Pyrazoles exhibit a broad spectrum of biological and medicinal activities. There are many pyrazoles containing compounds, natural and synthetic, that possess anti-inflammatory, analgesic, antipyretic, anti-rheumatic, antitumor, anticancer, antiviral, antimicrobial and cytotoxic activities (Figure 1)[3,9].

Pyrazolines, being able to absorb light of 300-400 nm and emit blue fluorescence, find important application as a fluorescent brightening agent[11]. In 1883, Ludwig Knorr accidentally synthesized 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one which has ananlgesic, antipyretic, anti-rheumatic activities[6]. The first natural pyrazole derivatives were 3-*n*-nonylpyrazole and *levo*-ß-(1-pyrazolyl) amino acid from the plant houttuyina and watermelon seeds respectively.

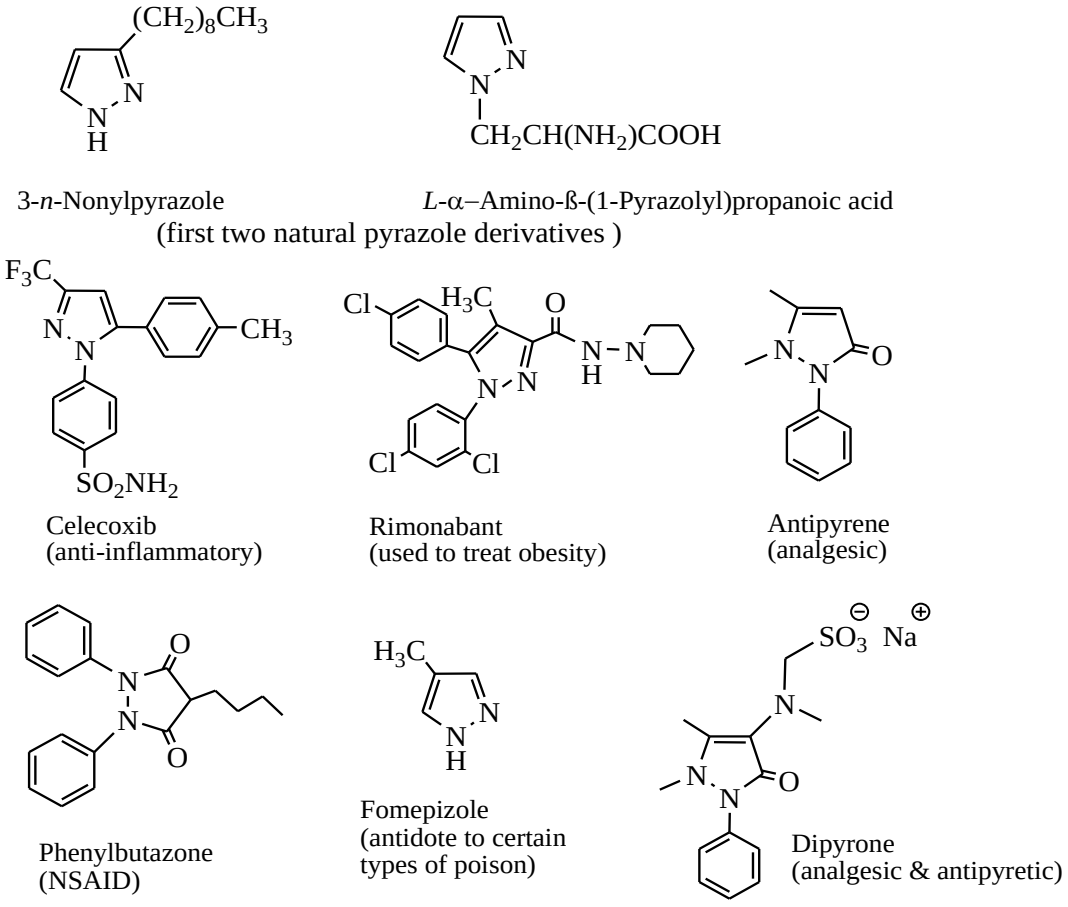


Figure 1: Some bioactive pyrazoles

The earliest synthetic route to pyrazole involves reaction between β-diketone and hydrazines in the presence of an acid[6]. Though most widely used, the main disadvantage of this method was the formation of a mixture of isomeric pyrazoles from an unsymmetrical β-diketone. A similar strategy was adopted in the synthesis of 1,3,5-trisubstituted pyrazoles using $Mg(ClO_4)_2$ as the catalyst[12].

It has also been prepared by reaction of α,β-unsaturated ketone and hydrazine[4,11] *via* 1,3-dipolar cycloaddition of diazo compounds[1] by four component coupling of terminal alkynes, hydrazines, CO and aryl iodides[2] etc. The last synthesis mentioned only gave moderate yield and also suffers from the problem of handling CO gas. Later another similar four component coupling reactions utilised $Cr(CO)_6$ which serves as a CO source and also $PdCl_2$ to synthesise pyrazoles[7].

Development of newer synthetic avenues for an existing class of molecules having biological potential is an everlasting challenge to synthetic chemists. The pursuit of such challenge becomes more exciting when the process involves low cost chemicals, non-hazardous reagents and mild conditions. Thus, our aim was to develop a simple method of synthesising pyrazole derivatives from one-pot reaction of methyl ketones, araldehyde and hydrazine hydrochloride. The resultant dihydropyrazoles were not isolated, rather were directly treated with aqueous $KBrO_3$-KBr mixture to afford pyrazoles as the product.

Material and Methods

All the chemicals were purchased from Merck India and are used without purification. Infrared spectra were recorded on a Perkin Elmer Spectrum Two spectrophotometer by analysing KBr pellets of the compounds. ^{1}H NMR spectra were recorded on Bruker DPX 300 MHz spectrometer in $CDCl_3$ and DMSO-d_6 as the solvent with TMS as the internal standard and the chemical shifts were recorded as delta in ppm units. The reaction products were purified by crystallisation and were identified from their physical constants, IR and ^{1}H NMR spectroscopic data.

General procedure for the synthesis of 3,5-disubstituted pyrazoles (3a-c): At first benzaldehyde (1a; 0.202 ml, 2 mM), acetophenone (2; 0.233ml, 2 mM), $NH_2NH_2.2HCl$ (0.21 g, 2 mM) and $NaOAc.3H_2O$ (0.272 g, 2 mM) were taken in 7 ml of rectified spirit in a 100 ml round bottomed flask and refluxed for 30 minutes.

During reflux, the colour of the reaction mixture changed from light yellow to yellowish orange, which indicated the completion of the reaction. Then the reaction mixture was first cooled to room temperature and further it was cooled with ice water. This solution was acidic in nature as was checked by pH paper. Then an aqueous solution of $KBrO_3$ (0.135 g, 1.2 equivalent) and KBr (0.47 g, 1.2 equivalent) was added to it with stirring by keeping the flask in cold water to maintain the temperature below 15°C.

The product formed was a sticky solid. Thus, it was extracted with ether (3×10 ml) in a separating funnel. The combined organic layer was then washed first with 5% aq. $NaHCO_3$ solution and finally with water. The pooled extract was then dried over anhydrous Na_2SO_4 and the solvent was evaporated off to get the crude product (3a; yield 80%). It was crystallised from ethyl acetate-hexane solution. All the substituted pyrazoles were synthesised by this method.

4,5-Dihydro-3,5-diphenyl-1*H*-pyrazole: Yellow crystals, m.p. 179-182°C[8]; IR (Potassium bromide pellets, cm^{-1}): 3055, 2533, 2399, 1611, 1577, 1455, 1413, 1368. ^{1}H NMR ($CDCl_3$, 300 MHz) chemical shift in ppm: 7.792 (2H, d, J=7.8 Hz), 7.506-7.291 (6H, m), 7.454 (2H, d, *J*=7.8 Hz) 5.242 (1H, t, *J*=8.4 Hz), 3.763 (1H, dd, J_1=17.1 Hz, J_2=10.2 Hz), 3.369 (1H, dd, J_1=17.1 Hz, J_2=7.2 Hz).

3,5-diphenyl-1*H*-pyrazole (3a): Yield: 80%; white crystals; melting point: 198-202°C[13]; IR (Potassium bromide pellets, cm^{-1}): 3098, 3065, 3002, 2859, 1462. ^{1}H NMR ($CDCl_3$, 300 MHz) chemical shift in ppm: 7.740 (4H, d, *J*=7.2 Hz), 7.43 (4H, t, *J*=7.2 Hz), 7.356 (2H, t, *J*=7.2 Hz), 6.862 (1H, s).

5-(4-Chlorophenyl)-3-phenyl-1*H*-pyrazole (3b): Yield: 78%; brown solid; melting point: 186-190°C[5]; ^{1}H NMR ($CDCl_3$, 300 MHz) chemical shift in ppm: 7.774-7.651 (4H, m), 7.474-7.232 (5H, m), 6.849 (1H, s).

5-(4-Nitrophenyl)-3-phenyl-1*H*-pyrazole (3c): Yield: 70%; yellow solid; melting point: above 250°C; ^{1}H NMR (DMSO-d_6, 300 MHz) chemical shift in ppm: 8.876 (1H, s), 8.380 (2H, d, *J*=8.4 Hz), 8.168 (2H, d, *J*=8.4 Hz), 7.947 (2H, d, *J*=7.2 Hz), 7.51 (2H, t, *J*=7.2 Hz), 7.637(1H, s).

5-(4-Chlorophenyl)-1-(2,4-dinitrophenyl)-3-phenylpyrazole (3d): Yield: 77%; orange solid; melting point: above 200°C; ^{1}H NMR (DMSO-d_6, 300MHz) chemical shift in ppm: 11.698 (1H, s), 8.885 (1H, dd, J_1=10.2 Hz, J_2=2.4 Hz), 8.699 (1H, s), 8.415-8.361 (2H, m), 8.108 (2H, dd, J_1=10.2 Hz, J_2=2.4 Hz), 7.966-7.942 (1H, m) 7.821 (2H, d, *J*=8.4 Hz), 7.560 (2H, d, *J*=8.4 Hz), 7.498-7.477 (1H, m).

Results and Discussion

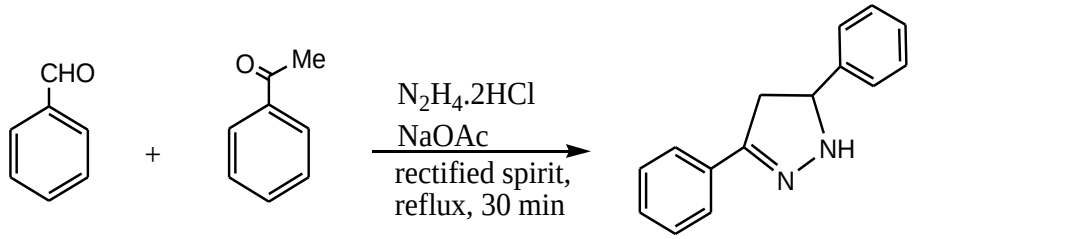
A mixture of benzaldehyde (1a), acetophenone (2) and hydrazine dihydrochloride (one equivalent of sodium acetate was taken in the reaction mixture to neutralise one equivalent of hydrochloride) in equimolar proportion was refluxed in ethanol for 30 minutes (Scheme 1). The isolated product was identified as the 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole from a comparison of its m.p. (179-182°C) and ^{1}H NMR data with the reported ones[8].

Thus, we concluded that it was pyrazoline, so oxidation must be needed for the formation of pyrazole from pyrazoline. We surveyed literature for the oxidation process, where we found many oxidising agents[11]. We undertook the oxidation reaction with bromine. But since liquid bromine is hazardous

and difficult to use, we decided to use bromine, formed *in situ* by using a mixture of $KBrO_3$ and KBr in acid medium[10].

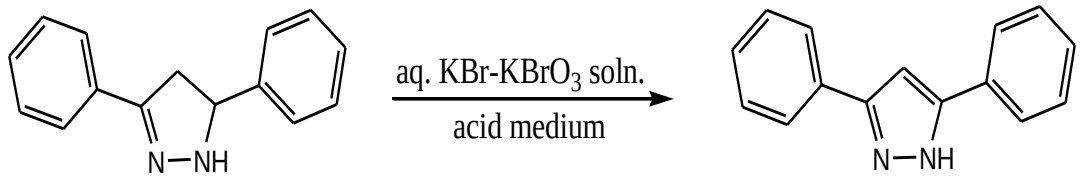
Accordingly, the pyrazoline we obtained was treated with $KBrO_3$-KBr under cold condition and the product was crystallised from ethyl acetate and hexane mixture (Scheme 2). Its melting point was found to be 198-202^{0}C which was same as reported[13]. The ^{1}H NMR data were also checked where we got ten aromatic protons and one deshielded singlet proton also in the aromatic region. The observed data were in accordance with the reported one. So we concluded that it was 3,5-diphenyl-1*H*-pyrazole (3a). Next, we repeated this one-pot reaction with different araldehydes without isolating the intermediate pyrazolines where we got 3,5-diaryl-1*H*-pyrazoles (3a-c) (Scheme 3).

In order to check the generality, we also carried out the reaction of equimolar amounts of each of *p*-chlorobenzaldehyde (1b) and acetophenone (2) with 2,4-dinitrophenylhydrazine in rectified spirit. Since 2,4-dinitrophenylhydrazine was not present in the form of hydrochloride, we added two drops of concentrated H_2SO_4 in the reaction mixture. The reaction mixture was refluxed for 40 minutes and then was treated with $KBrO_3$-KBr solution as before. The precipitated orange crude product (3d) was filtered under suction, washed with little cold ethanol and dried (Scheme 4).



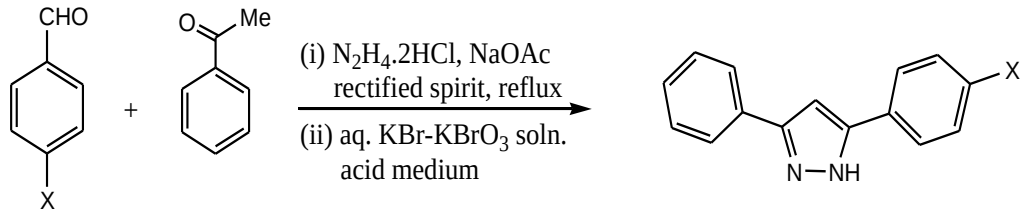
1a **2** 3,5-Diphenyl-4,5-dihydro-1*H*-pyrazole

Scheme 1: Reaction of benzaldehyde, acetophenone and hydrazine



3,5-Diphenyl-1*H*-pyrazole (**3a**)

Scheme 2: Oxidation of pyrazoline to pyrazole

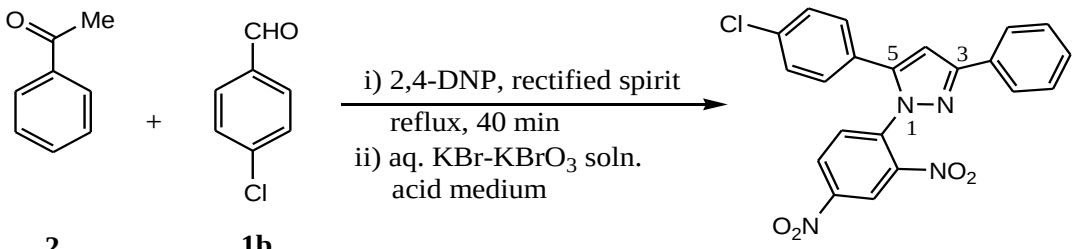


1a (X = H)
1b (X = Cl)
1c (X = NO_2)

2

3-Phenyl-5-(*p*-substitutedphenyl)-1*H*-pyrazole
3a (X = H), **3b** (X = Cl), **3c** (X = NO_2)

Scheme 3: One-pot reaction of araldehyde, acetophenone and hydrazine followed by oxidation



2 **1b**

5-(4-Chlorophenyl)-1-(2,4-Dinitrophenyl)-3-phenylpyrazole (**3d**)

Scheme 4: Reaction of *p*-chlorobenzaldehyde, acetophenone and 2,4-DNP

An analysis of the outcome indicates that the time of completion of reaction and the product yields have dependence on the electronic nature of the substituent present in the aromatic nucleus. With electron withdrawing group as the *p*-substituent, the reaction becomes sluggish and the yield decreases.

Conclusion

All the starting materials and reagents are very simple and are easily available in a laboratory. The main advantages of the method are mild reaction condition, short reaction time and simple work-up procedure. Use of hazardous chemical is avoided by *in situ* generation of bromine. Yield of the pyrazoles was moderate to good. A close insight into the probable mechanism indicates that the reaction can be extended to other keto methyl containing compounds and hydrazine derivatives to design a variety of similar heterocycles.

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