A Simple and Environmentally Benign Nitration of Pyrazoles by Impregnated Bismuth Nitrate

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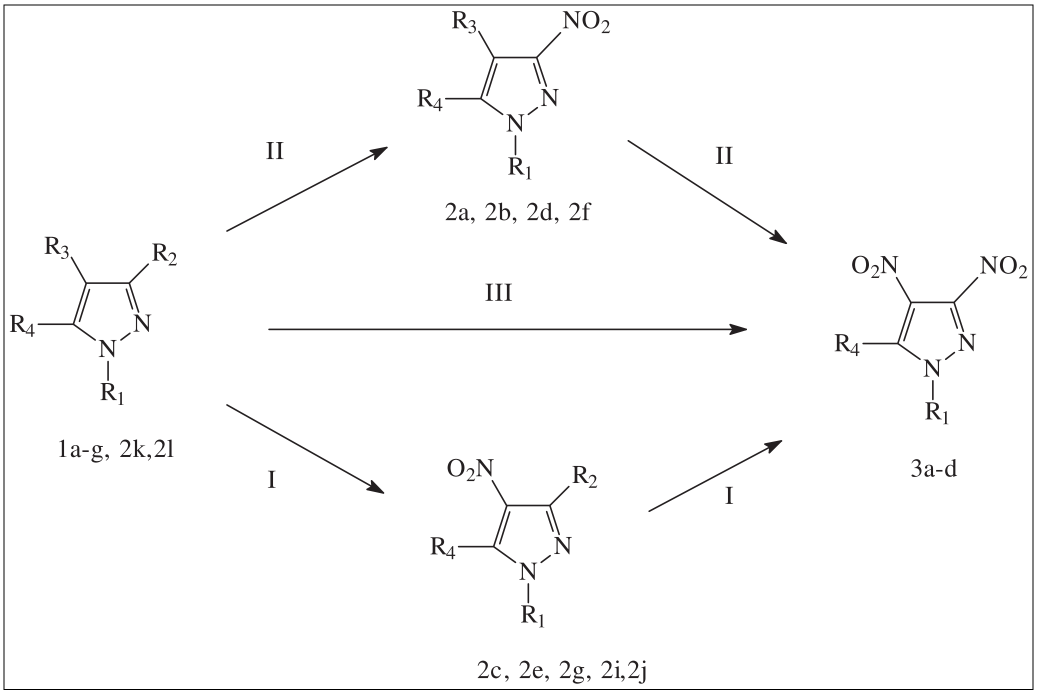

We report herein a facile, rapid, and environmentally friendly synthesis of nitropyrazoles in good yields using silica-bismuth nitrate and silica-sulfuric acid-bismuth nitrate at room temperature for the first time. The relatively non-toxic nature, ease of handling, easy availability, and low cost make the present procedure attractive for the nitration of a wide variety of diazoles in the drug and pharmaceutical industries.

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INTRODUCTION

Nitropyrazoles are structural units found in biologically active compounds (cholesterol lowering, anti-inflammatory, anti-cancer, anti-depressant, and anti-psychotic agents), dyestuffs, and explosives [1–8]. The presence of nitro group in the pyrazole ring considerably enlarges the possibility of functionalization of various types of biologically active compounds. The nitration of pyrazoles has been performed using nitric acid–sulfuric acid [5–11], nitric acid–acetic anhydride [5–11], or nitric acid–trifluoroacetic anhydride [12]. The C-nitropyrazoles have been synthesized by thermal rearrangement of *N*-nitropyrazoles in chlorobenzene, nitrobenzene, anisole, aniline, *N*-methylformamide, propylene glycol, xylene, benzonitrile, *n*-decane, or mesitylene at 120–200°C for 3–7 h. Normally, C-nitropyrazoles are formed quantitatively and in some instances side reactions particularly denitrations of *N*-nitropyrazoles are observed [9,11]. The problems associated with the conventional nitration mixtures have prompted the researchers to search for the alternative methodologies. The limitations and drawbacks of the traditional nitration methodologies such as tedious work-up, strongly acidic media, oxidation ability of the reagents, thermal rearrangements, and safety problems can be avoided using the impregnated metal nitrates.

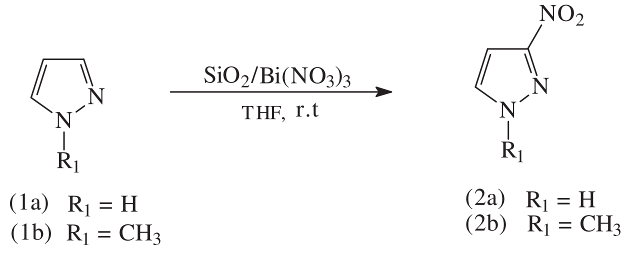
The supported metal nitrates such as $Bi(NO_3)_3/SiO_2$ or clay [13,14], $AgNO_3/BF_3$ [15] $Cu(NO_3)_2$/clay [16], Ce $(NH_4)_2(NO_3)_6/H_2SO_4/SiO_2$ [17], $Fe(NO_3)_3$/clay [18], and other metal nitrates/clay activated by acetic anhydride [19] have been used for the nitration of a variety of aromatic compounds. Bismuth nitrate is an inexpensive, easy-to-handle, and commercially available solid being used for the nitration [13,14]. The supported bismuth nitrate is the most active and long-lived catalyst for the nitration of arenes [20–24]. Also, it is easier to handle, readily separable from the products by simple filtration, recyclable, and require the milder reaction conditions. Though the synthesis of nitropyrazoles using different nitration mixtures are known however, to our knowledge synthesis of these compounds with silica-bismuth nitrate and silica-sulfuric acid-bismuth nitrate has not yet been reported. We report herein the nitration of different pyrazoles using silica-bismuth nitrate (method A) and silica-sulfuric acid-bismuth nitrate (method B) at room temperature.

RESULTS AND DISCUSSION

Pyrazoles are usually nitrated at position 4, facilitated by electron-donating and retarded by electron-withdrawing groups [21–27]. Mixing the starting materials with silica-bismuth nitrate or silica-sulfuric acid-bismuth nitrate in tetrahydrofuran (THF) and evaporation of the solvent under vacuum comprise the reaction conditions for successful, regiospecific nitration with a series of pyrazoles. To ascertain the optimum conditions, several reactions were carried out on pyrazole (**1a**) and 1-methylpyrazole (**1b**) as the model substrates by varying the amounts of impregnated bismuth nitrate in THF at room temperature (Scheme 1).

Pyrazoles with electron-donating groups readily underwent nitration in excellent yields (> 92%). The deactivated substrates underwent nitration in good yields (> 80%). The substrates with electron-donating and electron-withdrawing groups and their corresponding nitro compounds using silica impregnated with bismuth nitrate (method A) and silica-sulfuric acid impregnated with bismuth nitrate (method B) are summarized in Table 1. Pyrazole (**1a**) and methylpyrazoles (**1b–g**) have been nitrated in excellent yields with silica-bismuth nitrate and silica-sulfuric acid-bismuth nitrate. The general scheme for the nitration of pyrazoles is shown (Scheme 2). 1,3-Dimethylpyrazole (**1e**) and 1,4-dimethylpyrazole (**1f**) were also nitrated to nitropyrazoles (**2e** and **2f**) in higher yields via the nitration routes I and II. The reaction was very selective and no side-chain substitution products were observed. The reaction rates of methylpyrazoles were increased with increasing number of methyl groups. An exceptionally higher yield of 3,5-dimethyl-4-nitropyrazole (**2g**) was obtained from 3,5-dimethylpyrazole (**1g**) in 3 h. The crude obtained after the nitration of **1a** and **1b** irrespective of nitration mixture and reaction conditions contains 4-nitropyrazoles (<10%). Thus, 1-methyl-4-nitropyrazole has been observed to be a major side product in the synthesis of 1-methyl-3-nitropyrazole (**2b**) and 1-methyl-3,4-dinitropyrazole (**3b**). The prolonged nitration of **1a**, **1b** or mononitro compounds (**2a**, **2b**) gave higher yields of polynitropyrazoles (**3a–3c**) using acid-bismuth nitrate in two or three folds via direct nitration (III).

Scheme 1. Nitration of pyrazoles.

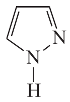
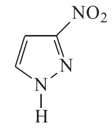
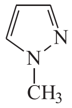
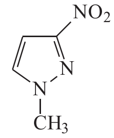
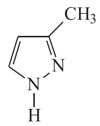
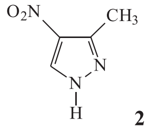
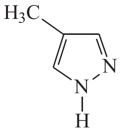
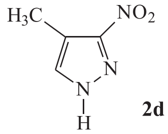
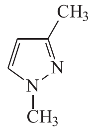
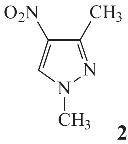
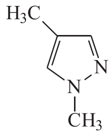
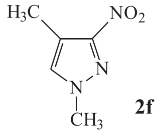
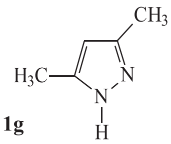
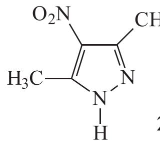
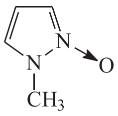
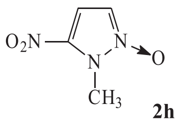


Herve *et al.* [6] obtained 1-methyl-3,4,5-trinitropyrazole (**3c**) by the stepwise nitration followed by the methylation of alkali salts of 3,4,5-trinitropyrazole (**3d**). 1-Methylpyrazole (**1b**) on nitration gave 76% (method A) and 88% (method B) yields of trinitro compound (**3c**). However, we have detected no nitration of **3b** even after 48 h rather recovered the quantitative amount of dinitro compound (**3a**). The deactivated substrates (**2b**, **2l**) underwent nitration in good yields. 3,5-Dinitropyrazole (**2k**) and 1-methyl-3,5-dinitropyrazole (**2l**) have not been formed as the by-products in the synthesis of **3a** and **3b**. Our attempts to obtain 1-methyl-3,4-dinitropyrazole (**3b**) from 1-methyl-4-nitropyrazole were unsuccessful, even the nitration was carried out at 120°C for 6 h. The mono-, (**2a**, **2b**) and dinitro compounds (**3b**) are formed presumably by the nitration of pyrazole (**1a**, **1b**). 3-Nitropyrazole (**2a**) and 1-methyl-3-nitropyrazole (**2b**) have been obtained by the [1,5]-sigmatropic rearrangement of 3*H*-pyrazole and l-methyl-2-nitropyrazolium species, respectively [9–11]. The synthesis of 1-methyl-3,4-dinitropyrazole (**3b**) from 1-methyl-3-nitropyrazole (**2b**) shows that it cannot be from 1-methyl-4-nitropyrazole. The nitration of 1-methylpyrazole-2-oxide (**1h**) gave 52% (method A) and 67% (method B) of 1-methyl-5-nitropyrazole-2-oxide (**2h**) (Scheme 3).

4-Nitro-1-phenylyrazole (**1i**) and 1-benzyl-4-nitropyrazole (**1j**) have also been nitrated to examine the position of substitution in the substrate. It has been known that the use of mixed acid leads to nitration of the conjugate acid of the base, whilst nitric acid–acetic anhydride nitrates the free base, the change in the reacting form of the substrate leading to the change of orientation. The orientation of mononitration of **1i** depends on the reagent being used: mixed acid gives 1-(*p*-nitrophenyl)pyrazole, whilst nitric acid–acetic anhydride gives 4-nitro-1-phenylpyrazole [23–27]. The *para* substituted products (**2i** and **2j**) have been obtained from 1-(*p*-nitrophenyl)-4-nitropyrazole (**2i**) and 1-(*p*-nitrobenzyl)-4-nitropyrazole (**2j**), respectively.

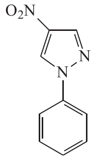
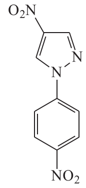
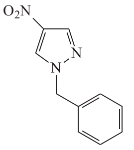
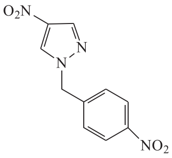
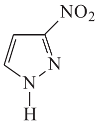
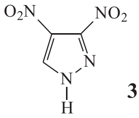
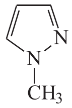
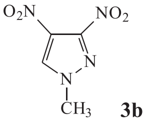
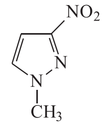
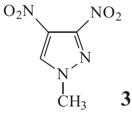
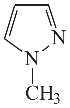
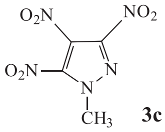
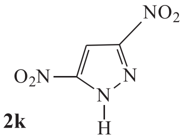
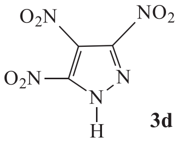
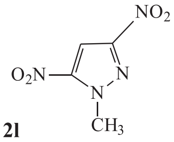
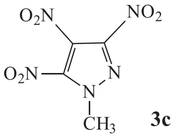
Table 1

Nitration of pyrazoles using impregnated bismuth nitrate.

			Method A		Method B		m.p. (°C)	
Entry	Substrate	Product	Time (h)	Yield (%)	Time (h)	Yield (%)	Found	Literature
1	 **1a**	 **2a**	6	78	6	83	162–163	160–162 [9]
2	 **1b**	 **2b**	6	95	6	98	80–82	80–83 [9]
3	 **1c**	 **2c**	6	91	6	96	155–157	156–157 [9]
4	 **1d**	 **2d**	6	94	6	96	186–187	186–187 [9]
5	 **1e**	 **2e**	3	86	3	95	160–162	162–163 [5]
6	 **1f**	 **2f**	3	92	3	97	96–97	96–97 [23]
7	 **1g**	 **2g**	3	95	3	98	126–127	126–128 [5]
8	 **1h**	 **2h**	6	52	6	67	108–109	109–111 [22]

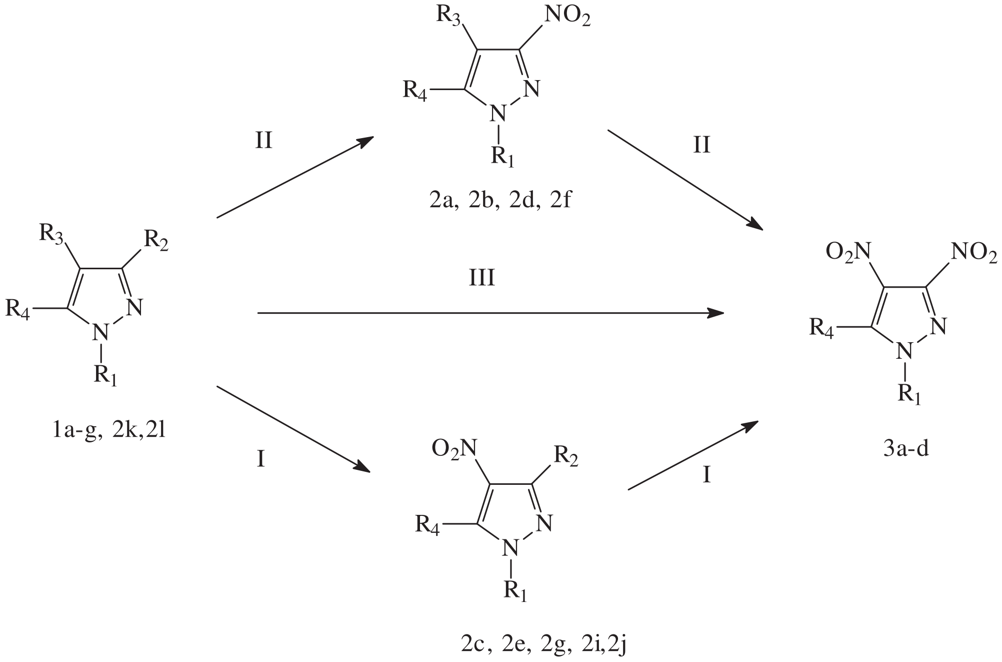
(*Continued*)

Table 1
(Continued)

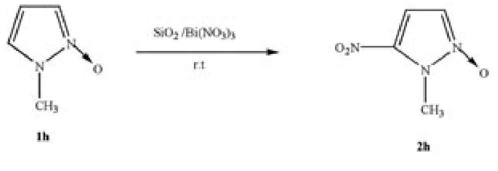
			Method A		Method B		m.p. (°C)	
Entry	Substrate	Product	Time (h)	Yield (%)	Time (h)	Yield (%)	Found	Literature
9	 **1i**	 **2i**	3	88	3	93	162–163	162–163 [24]
10	 **1j**	 **2j**	3	94	3	97	91–92	90–91 [25]
11	 **2a**	 **3a**	4	92	4	95	86–88	87–89 [9]
12	 **1b**	 **3b**	6	88	6	92	21–22	20–22 [9,21]
13	 **2b**	 **3b**	4	91	4	94	21–22	20–22 [9,21]
14	 **1b**	 **3c**	10	76	10	88	91–92	91–93 [6]
15	 **2k**	 **3d**	3	93	3	98	189–190	188–189 [6]
16	 **2l**	 **3c**	4	91	4	96	90–92	91–92 [6]

Finally, the recycling of impregnated bismuth nitrate was done by evaporating the solvent after completion of the reaction and the recovered solid was dried. It has been found that the impregnated bismuth nitrate works efficiently up to third cycle thereafter it loses its activity.

Scheme 2. Nitration of pyrazoles using silica impregnated with bismuth nitrate (method A) and silica-sulfuric acid impregnated with bismuth nitrate (method B). The scheme showing the nitration of pyrazoles via 4-nitropyrazoles (route I), 3-nitropyrazoles (route II), and the polynitration of pyrazoles (route III).



Scheme 3. Nitration of 1-methylpyrazole-2-oxide.



CONCLUSION

In summary, we have shown a simple, rapid, and environmentally benign nitration of different pyrazoles with silica-bismuth nitrate and silica-sulfuric acid-bismuth nitrate avoiding thermal rearrangements of *N*-nitropyrazoles. Exceptionally higher yields of 1-methyl-3-nitro pyrazole (**2b**), 3-methyl-4-nitropyrazole (**2c**), 4-methyl-3-nitropyrazole (**2d**), 1,4-dimethyl-3-nitropyrazole (**2f**), and 3,5-dimethyl-4-nitropyrazole (**2g**) have been obtained. Moreover, the silica-sulfuric acid-bismuth nitrate catalyzed reactions have been found to be superior in terms of yields of the products and time of the reaction over silica-bismuth nitrate. The relatively non-toxic nature, ease of handling, easy availability, and low cost make the present procedure attractive for the nitration of a wide variety of diazoles in the drug and pharmaceuticals industries.

EXPERIMENTAL

All the reagents and solvents have been obtained from Merck, Alfa-Aesar or Aldrich and used without further purification. Melting points were recorded by a capillary melting point apparatus and were uncorrected. Analytical thin layer chromatography silica gel GF-254 type was routinely used to monitor the progress of reactions. IR spectra were recorded on Perkin–Elmer FT-IR-1600 spectrophotometer in KBr matrix. The peak signals are reported in wave numbers (cm^{-1}). ^1H-NMR and ^{13}C-NMR spectra were recorded on 300 MHz Varian instrument with $CDCl_3$ or DMSO-d_6 solvent. The chemical shift values are reported in δ units (ppm) relative to TMS as the internal standard. GC-MS was carried out with glass columns packed with 3% OV-17 on Chromosorb W, 100-120 mesh, treated with DMCS in a Varian 1400 instrument fitted with flame ionization detector, nitrogen being used as carrier gas.

Caution: All polynitropyrazoles are considered as dangerous and proper precaution should be taken in handling and storage.

Silica-sulfuric acid. Silica-gel of 100–200 mesh (60.0 g) was soaked with 98% sulfuric acid (75 mL), repeatedly washed with water and filtered to get a white solid. Then it was dried at 120–130°C for 24 h to give silica-sulfuric acid (76.0 g). The catalyst was re-activated prior to use by heating in the oven at 120°C for 6 h.

Silica-bismuth nitrate. Bismuth nitrate (10 mmol) was added to acetone (188 mL) in 500 mL evaporating flask. The mixture was stirred vigorously for 15 min. Silica-gel (15 g) was added in small amounts and stirring was continued for another 15 min. The solvent was removed using rotary evaporator on a water bath keeping the temperature 30–35°C and the obtained solid was crushed to get floury powder.

Silica-sulfuric acid-bismuth nitrate. Silica-sulfuric acid (0.8 g, 0.24 mol) and bismuth nitrate (0.16 g, 0.036 mol) taken in a mortar was grinded to get homogeneous floury powder.

General procedure for the synthesis of nitropyrazoles.

Method A. The mixture of silica-bismuth nitrate (1.5 g) and pyrazole (17 mmol) in THF (20 mL) was stirred for required time. The reaction was monitored by TLC with ethyl acetate and hexane (3:2) as solvent. Silica-sulfuric acid was filtered off and the solvent was removed to get nitro compounds. The pure compounds were obtained from column chromatography.

Method B.. The mixture of silica-sulfuric acid-bismuth nitrate (0.96 mg) and pyrazole (17 mmol) in THF (20 mL) was stirred for required time. The reaction was monitored by TLC with ethyl acetate and *n*-hexane (3:2) as solvent. Silica-sulfuric acid-bismuth nitrate was filtered off and the solvent was removed to get nitro compounds. The pure compounds were obtained from column chromatography.

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