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N-Bromosuccinimide assisted oxidation of 5-aminopyrazoles: formation of bis diazenylderivatives

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Abstract—Treatment of 5-amino-4-cyanopyrazoles with *N*-bromosuccinimide, in DMF at rt gave azo dyes resulting from dimerization through the amino groups and further oxidation.With bromine water the dimer was also formed but, bromination occurred on the aryl ring, either at reflux or rt. Reduction of the azo group with zinc in acetic acid originated the corresponding pyrazoles.

Pyrazoles are an important class of compounds, which display widespread pharmaceutical and agrochemical properties.[1–5]

Recently, NBS has received considerable attention as a catalyst in various organic transformations,[6] and it is applied as a brominating reagent. Furthermore, it is also used in oxidation and free radical reactions under mild conditions to afford the desired products in excellent yields and with high selectivity. However, to our knowledge, there are no examples of the use of NBS as a catalyst for the oxidation of 5-aminopyrazoles.

As a part of our ongoing research program on heterocyclic compounds, which may serve as leads for designing novel biologically active agents, we were particularly interested in pyrazoles[7] namely of type **1**.[8] We wish to report here in the simple and efficient use of NBS as a catalyst for the synthesis of bis diazenylpyrazole derivatives, under mild conditions.

Bromination of aromatics and heteroaromatics is an electrophilic substitution reaction of immense synthetic and industrial value. Brominated pyrazoles are useful either as synthetic intermediates or targets in the search for pharmacologically active compounds, such as antidiabetic[5b] and bradykinin B1 receptor antagonists.[5c] A number of methods have been described previously for the halogenation of pyrazoles.[9–12] Our search of the literature showed no precedent for direct bromination of 5-amino-4-cyanopyrazoles **1a–d**. Use of NBS for nuclear bromination in polar media such as DMF,[13a] MeCN,[13b,c] aqueous NaOH,[13d] in the presence of acids,[13e–g] and isopropylamine[13h] is well documented.

Initially, the reaction was performed by mixing 5-aminopyrazole **1a** with *N*-bromosuccinimide (1 equiv) in DMF solution, at rt. However, to our surprise, no brominated pyrazole was observed, the only product which was obtained, in high yields, under these conditions was dimer **3a**, possibly formed by oxidative dimerization. Recently, the formation of an azo bond from the corresponding aromatic amine with quinolinium tribromide was reported.[14b]

The amino group protons were no longer observed in the ^{1}H NMR, only the phenyl protons and the pyrazole ring proton H-3 at δ 8.11 ppm. The presence of the cyano group was confirmed by the observation of an absorption band at 2233 cm^{-1} in its IR spectrum. The elemental analysis result was as expected for the proposed structure and the mass spectrum gave the correct molecular ion. To the best of our knowledge, this type of dimerization was not described with heterocyclic amines before this work. This rather unexpected turnout of the reaction led us to investigate further substrates to confirm these findings.

We first concentrated on the behavior of precursor **1b** that gave the same result and it was decided to vary

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Table 1. Reaction conditions and the yield of diazenyl products **2** and **3a–d**

Entry	Pyrazole	Conditions[a]	Time (h)	Product	Yield (%)	Mp (°C, DMF)
1	**1b**	NBS/DMF	0.5	**3b**	84	260–262
2	**1b**	NBS/DMF (heat)	2	**3b**	80	261–263
3	**1b**	NBS/AcOH	3	**3b**	27	259–260
4	**1b**	NBS/AcOH(heat)	2	**3b**	54	260–261
5	**1c**	NBS/DMF	0.5	**3c**	70	308–309
6	**1c**	NBS/CH_2Cl_2 (rt, ultrasound)	0.5	**3c**	80	308–310
7	**1c**	NBS/CH_2Cl_2	2	**3c**	35	306–308
8	**1b**	Br_2/H_2O	7	**2**	88	268–270 ($CHCl_3$)
9	**1b**	Br_2/H_2O (heat)	7	**2**	95	270–271 ($CHCl_3$)
10	**1a**	NBS/DMF	0.5	**3a**	75	236–237
11	**1b**	Br_2/H_2O (heat)	7	**3b**	42	260–261
12	**1c**	NBS/DMF	0.5	**3c**	68	309–310
13	**1d**	NBS/DMF	0.5	**3d**	70	286–287 ($CHCl_3$)

[a] Reactions were performed at room temperature, unless otherwise indicated, and using (1 equiv) of NBS except for entry 5 (2 equiv). For entry 11 (0.5 g) of Br_2 were used.

the reaction conditions to observe their effect on the formation of diazenyl derivative **3b** (Table 1). We, therefore, submitted precursors of type **1b** to the following reagents and conditions: NBS/DMF (1 equiv) at room temperature and in refluxing DMF for 2 h; acid medium NBS/AcOH (1 equiv) at room temperature and in refluxing AcOH for 2 h (entries 3 and 4). The same product **3b** was obtained in each case.

The ^{1}H NMR of compound **3b** showed the singlet at δ 2.49 for the two CH_3 groups, two doublets for the *p*-tolyl moiety at δ 7.35 (d, 4H, $J = 9$ Hz, Ar-H), 7.69 (d, 4H, $J = 9$ Hz, Ar-H), and one singlet for the pyrazole ring protons H-3 at δ 8.08 ppm.

Some conclusions can be drawn from these experiments. The reaction is very efficient with 1 equiv of NBS (Table 1, entry 1).[14a,15a] No bromination was observed when we used 2 equiv of NBS, and only the oxidation product was obtained (Table 1, entry 5). An increase in the reaction temperature had some influence on the yield only when AcOH was used as the solvent (Table 1, entries 3 and 4). Ultrasound irradiation in CH_2Cl_2 as the solvent gives the same product in a shorter reaction time and higher yields (Table 1, entries 6 and 7).[15b]

To collect more evidence on this reaction, we examined the behavior of other precursors **1a–d**, under different conditions and the diazenyl pyrazole derivatives instead of the brominated pyrazoles were obtained. Based on these observations and previous reports,[14a,15a] the mechanism in Figure 1 is proposed. The amino group of the pyrazole is first activated by NBS then either dimerization with loss of two HBr or attack by another amino group to eliminate HBr, followed by oxidation, produces the final diazenyl product **3**.

Attempted bromination of pyrazole **1** in bromine water at room temperature gave an orange solid, which proved to be a dimer of the pyrazole brominated on the aryl ring **2** (Table 1, entry 8) based on the NMR data. ^{1}H NMR, elemental analysis and mass spectrometry confirmed the molecular composition. The position of the bromine atom in each phenyl ring was not disclosed at once, only after obtaining the ^{13}C NMR spectrum.

The one dimensional, ^{1}H NMR of compound **2** showed the signal at δ 2.49 singlet (6H, CH_3), two doublets and one double doublet for *p*-tolyl moiety at δ 7.44 (d, 2H, $J = 8$ Hz, Ar-H), 7.70–7.74 (dd, 2H, $J = 8$, 2.4 Hz, Ar-H), 7.93 (d, 2H, $J = 2.4$ Hz, Ar-H), and one singlet

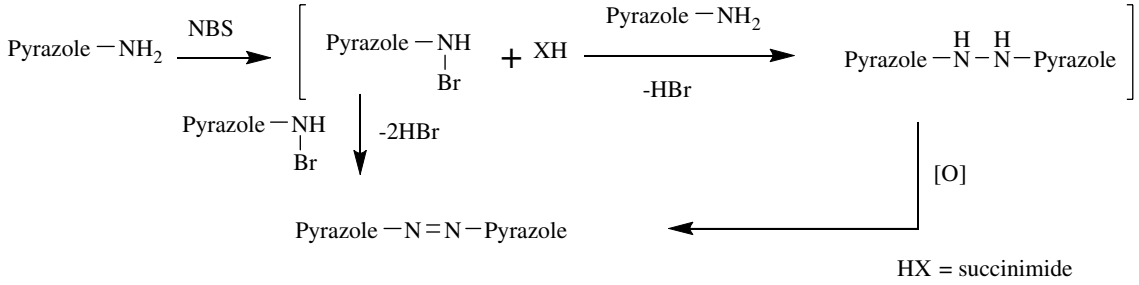
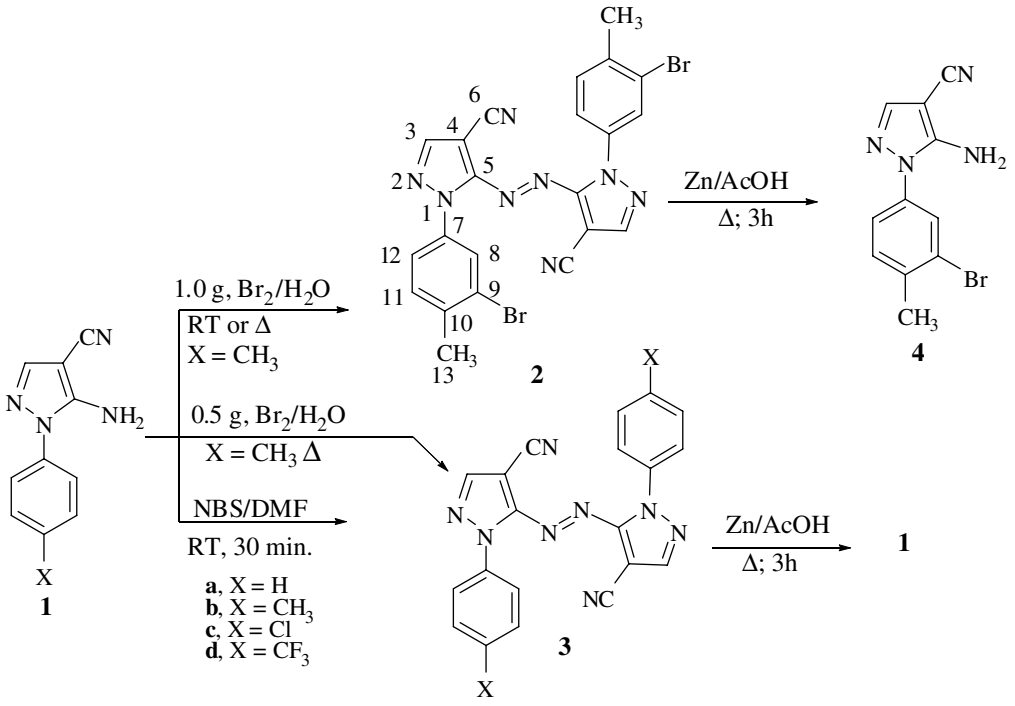


Figure 1. Proposed mechanism for the dimerization of 5-aminopyrazole catalyzed by NBS.



Scheme 1. Oxidation of 5-amino-4-cyanopyrazole by Br_2/H_2O or NBS.

for the pyrazole ring H-3 at δ 8.10 ppm. In the ^{13}C NMR spectrum, 11 signals were found (half of the structure). The HMQC and HMBC NMR spectra allowed us to make an unambiguous assignment in the ^{1}H and ^{13}C NMR spectra.[16] In the HMBC spectrum, intense correlation peaks at 2.49/125.2, 131.4 and 139.9 ppm (CH_3/C-9, C-10, and C-11), which are characteristic for structure **2** (monobrominated compound) were observed. Intense correlation peaks at 7.44/125.2 and 135.7 ppm (H-11/C-9 and C-7), and also at 7.93/124.2 and 139.9 ppm (H-8/C-12 and C-10) were found (Scheme 1).

The bromination was then repeated at reflux temperature and the same product was originated (Table 1, entry 9).

The reaction with bromine water was repeated using 0.5 g of Br_2, (Table 1, entry 11) no bromination was observed, only the oxidation product was obtained in yield lower than in the experiment with NBS (Scheme 1, Table 1, entry 1).

To confirm the structure it was decided to reduce the azo bond of dye **2** with Zn in acetic acid and the brominated pyrazole **4** was obtained.[16] Similarly, from the reduction of dye **3a–d** the starting pyrazole **1** was obtained.

In conclusion, the bromination of 1-arylsubstituted 5-amino-4-cyanopyrazole in (a) NBS/DMF, (b) DMF/AcOH or (c) bromine/water afforded an azo dimer as the major product. In the case of the reaction with bromine (1.0 g, 2 equiv) in water, bromination occurred on the aryl ring and no substitution was observed in the heterocycle. When half of the amount of bromine (0.5 g, 1 equiv) in water was used only the oxidation reaction took place in moderate yield.

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16. *Reaction with bromine water, (Method A)*: A solution of 5-amino-1-(4-methylphenyl)pyrazole-4-carbonitrile (1.98 g, 0.01 mol), Br_2 (1.00 g), and H_2O (50 ml) was heated under reflux for 7 h. The product separated from the solution after standing at room temperature overnight was washed with ethanol, filtered off and then crystallized from $CHCl_3$ to afford the bis brominated dye. *Method B*: The same reaction was repeated with stirring at rt for 7 h to afford the same product as shown by TLC and spectroscopic analysis.
5,5′-(Diazene-1,2-diyl)bis(1-(3-bromo-4-methylphenyl)-1H-pyrazole-4-carbonitrile) **2**: Red needles; mp 270–271 °C, IR (cm^{-1}): 2233 (CN); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.49 (s, 6H, $2CH_3$), 7.44 (d, 2H, $J = 8$ Hz, Ar-H), 7.70–74 (dd, 2H, $J = 8$, 2.4 Hz, Ar-H), 7.93 (d, 2H, $J = 2.4$ Hz, Ar-H), 8.10 (s, 2H, H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) = 22.7 (CH_3), 83.4 (C-4), 112.2 (CN), 124.2 (C-12), 125.1 (C-Br), 128.4 (C-8), 131.4 (C-11), 135.7 (C-7), 139.9 (C-10), 144.36 (C-3), 153.2 (C-5); FBMS = 449 (M), 551 (M^+), 553 (M+2), 554 (M+4). Anal. Calcd for $C_{22}H_{14}Br_2N_8$: C, 48.02; H, 2.56; N, 20.37. Found: C, 47.77; H, 2.56; N, 20.23.
General procedure for the synthesis of the bis diazenyl derivatives **3a–d**: (*Method A*): To a stirred solution of 5-amino-4-cyanopyrazole (0.01 mol) in dry DMF (10 ml) NBS (0.01 mol) was added, and the reaction mixture was stirred at rt for 0.5 h. The solid product formed was filtered off and washed with ethanol, dried and crystallized from $CHCl_3$ to produce the bisdiazenyl derivatives.
Method B from Br_2/H_2O: The same reaction was repeated as shown in the previous experiment using **1b** (0.01 mol) with (0.5 g) of Br_2 and H_2O (50 ml) heated under reflux for 7 h to afford the same product as shown by TLC, mp, mixed mp and spectroscopic analysis.
5,5′-(Diazene-1,2-diyl)bis(1-phenyl-1H-pyrazole-4-carbonitrile) **3a**: Orange-red crystals; mp 236–237 °C; IR (cm^{-1}): 2234 (CN); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.54–7.58 (m, 6H, Ar-H), 7.78–7.80 (m, 4H, Ar-H), 8.11 (s, 2H, H-3). FBMS = 365 (M+1, 23%). Anal. Calcd for $C_{20}H_{12}N_8$ (364.36): C, 65.93; H, 3.32; N, 30.75; Found: C, 65.90; H, 3.66; N, 30.53.
5,5′-(Diazene-1,2-diyl)bis(4-methylphenyl-1H-pyrazole-4-carbonitrile) **3b**: Orange-red needles; mp 260–262 °C; IR (cm^{-1}): 2233 (CN); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.44 (s, 6H, $2CH_3$), 7.35 (d, 4H, $J = 9$ Hz, Ar-H), 7.69 (d, 4H, $J = 9$ Hz, Ar-H), 8.08 (s, 2H, H-3). Anal. Calcd for $C_{22}H_{16}N_8$ (392.42): C, 67.34; H, 4.11; N, 28.55; Found: C, 66.90; H; 4.29; N, 28.39.
5,5′-(Diazene-1,2-diyl)bis[1-(4-chlorophenyl)-1H-pyrazole-4-carbonitrile] **3c**: Orange-red needles; mp 308–309 °C; IR (cm^{-1}): 2236 (CN); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.54 (d, 4H, $J = 9$ Hz, Ar-H), 7.79 (d, 4H, $J = 9$ Hz, Ar-H), 8.13 (s, 2H, H-3). FBMS = 433 (M+1, 49%), 435 (M+3, 29%). Anal. Calcd for $C_{20}H_{10}Cl_2N_8$ (433.25): C, 55.44; H, 2.33; Cl, 16.37; N, 25.86; Found: C, 55.28; H, 2.44; N, 25.76.
5,5′-(Diazene-1,2-diyl)bis{1-[4-(trifluoromethyl)phenyl-1H-pyrazole-4-carbonitrile} **3d**: Shinny dark orange needles; mp 286–287 °C; IR (cm^{-1}): 2235 (CN); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.85 (d, 4H, $J = 9$ Hz, Ar-H), 8.02 (d, 4H, $J = 9$ Hz, Ar-H), 8.18 (s, 2H, H-3). Anal. Calcd for $C_{22}H_{10}F_6N_8$ (500.36) C, 52.81; H, 2.01; N, 22.39. Found: C, 52.84, H, 2.15; N, 22.16.
Reduction by Zn/AcOH: To a solution of 5,5′-(diazene-1,2-diyl)bis[1-(3-bromo-4-methylphenyl)-1*H*-pyrazole-4-carbonitrile] (0.01 mol) in glacial acetic acid (25 ml) Zn dust (2 g) was added. The reaction mixture was refluxed for 2 h during which the color turned pale yellowish green. The reaction mixture was filtered while hot, allowed to cool to rt and then poured on to crushed ice (25 g). The precipitated solid was collected by filtration and recrystallized from $CHCl_3$ to afford:
5-Amino-1-(3-bromo-4-methylphenyl)-1H-pyrazole-4-carbonitrile **4**: Pale yellow powder; yield 65%; mp 175–177 °C (EtOH); IR (cm^{-1}): 3339 (NH_2), 2218 (CN); ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) = 2.38 (s, 3H, CH_3), 6.76 (s, 2H, NH_2), 7.40–7.47 (dd, 1H, $J = 8.4$, 2.1 Hz, Ar-H), 7.50 (d, 1H, $J = 8$ Hz, Ar-H), 7.68 (d, 1H, $J = 1.1$ Hz, Ar-H), 7.78 (s, 1H, H-3). Anal. Calcd for $C_{11}H_9BrN_4$: C, 47.68; H, 3.27; N, 20.22. Found: C, 47.68; H, 3.37; N, 19.96.