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A mild and efficient method for halogenation of 3,5-dimethyl pyrazoles by ultrasound irradiation using *N*-halosuccinimides

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Abstract—The 4-halo-3,5-dimethyl pyrazoles have been synthetisized in good yields in short reaction times in the absence of a catalyst by reaction of 3,5-dimethyl pyrazoles with *N*-halosuccinimides (NBS, NCS and NIS) under ultrasound irradiation. Finally, the halogenation of pyrazoles with Br_2, ICl and I_2 was showed in similar conditions.

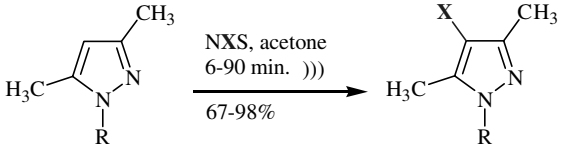
1. Introduction

Pyrazoles are an important class of compounds, which possess widespread pharmacological properties such as anti-hyperglycemic, analgesic, antiinflammatory, antipyretic, anti-bacterial, hypoglycemic and sedative-hypnotic activity.[1–5] Recently, some pyrazole derivatives were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[6] Extensive studies have been devoted to pyrazole derivatives such as celecoxib, the well-known cyclooxygenase-2 inhibitor.[7] In particular, 4-halopyrazoles are key substructures in a large variety of compounds of important biological activities.[8,9]

4-Halopyrazoles have been used as reagents in organic synthesis, especially in cross-coupling reactions with terminal acetylenes[9,10] organotin aryl derivatives,[11] or aryl boronic acids.[12] Ultrasound has increasingly been used in organic synthesis in the last three decades.[13] Compared with traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions can be carried out in high yields, shorter reaction time and milder conditions under ultrasound irradiation. We have recently reported a convenient and inexpensive ultrasound-assisted preparation of functionalized arylacetylenes using metallic lithium.[14] For the halogenation of pyrazoles nucleous, the examination of previously reported methods reveals serious synthetic drawbacks, such as mixture of products, long reaction time, high temperatures and use of catalyst.[15]

Stephens and co-workers described the methodology for the halogenation of 3,5-diarylisoxazoles using *N*-halosuccinimides.[16]

As a continuation of our program in sonochemistry, with the aim of improving the halogenation of 3,5-dimethyl pyrazoles we have explored the use of *N*-halosuccinimides, NXS (i.e., NCS, NBS and NIS) as more convenient and mild sources of electrophilic halogen. As a result of our work in this area, we wish to report



X = Cl, Br, I
R = H, Me, Ph, *p*-$NO_2C_6H_4$, C_6F_5

Scheme 1.

Keywords: Heterocycles; Pyrazoles; Halogenation; Ultrasound irradiation; *N*-Halosuccinimides.
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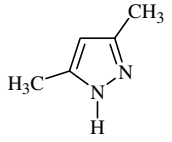
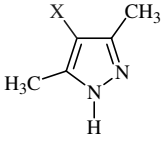
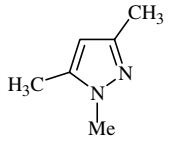
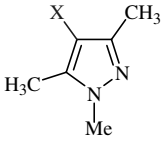
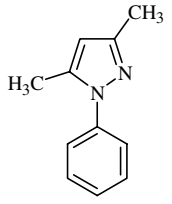
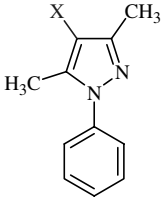
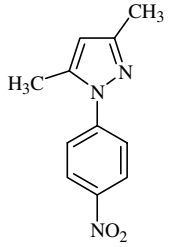
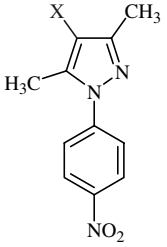
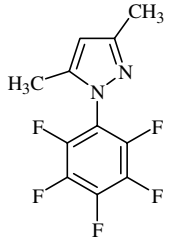
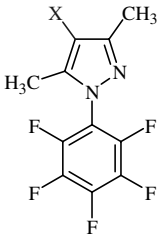
convenient C-4 halogenation of 3,5-dimethyl pyrazoles using *N*-halosuccinimides under ultrasound irradiation (Scheme 1).

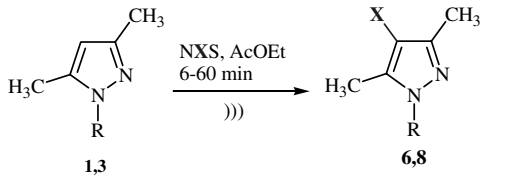
In preliminary experiments, we have observed a delicate compromise between the reaction and the catalyst, Amberlist 15, based on the work of Meshram et al.,[17] regarding the 2-halogenation of 1,3-keto-esters and cyclic ketones using *N*-halosuccinimides. First, the pyrazole **1** was chosen as a model substrate for bromination in order to find the optimal conditions. Compound **1** was treated with 1.5 equiv of NBS in the presence of Amberlist 15 in ethyl acetate, under ultrasound irradiation. The reaction was complete after 6 min to give the 4-halopyrazole derivative (**6a**), in 90% yield.

However, the same reaction in the absence of Amberlist 15 furnished the product with 98% yield. In our studies, we found that the acetone solvent reaction appropriated for these reactions gave the best results. The progress of the reactions was monitored by GLC. The important particularity of this reaction process is the work-up, in which we observed that the use of successive treatment of aqueous $Na_2S_2O_3$ gave the products without purifications. The 4-halo-3,5-dimethyl-pyrazoles (**6**–**10**) were synthesized treating 3,5-dimethyl pyrazoles with *N*-halosuccinimide (NXS, $X = Cl, Br, I$) in acetone and N_2 atmosphere using a ultrasound bath in short reaction times (6–90 min) and good yields (67–98%). The scope and generality of this process is illustrated by a series of five pyrazoles and the results are presented in Table 1.

Table 1. Halogenation of 3,5-dimethyl pyrazoles using NXS under ultrasound irradiation

Pyrazole **1**–**5**	4-Halopyrazole **6**–**10**	X	Equiv	Time (min)	Yield (%)[a]
 **1**	 **6**	(a) Cl	1.5	15	98
		(b) Br	1.5	6	98
		(c) I	1.5	20	85
 **2**	 **7**	(a) Cl	1.5	20	67
		(b) Br	1.5	6	86
		(c) I	1.5	15	75
 **3**	 **8**	(a) Cl	1.0	90	80
		(b) Br	2.0	15	96
		(c) I	3.0	60	92
 **4**	 **9**	(a) Cl	2.0	20	94
		(b) Br	2.0	15	91
		(c) I	2.0	20	76
 **5**	 **10**	(a) Cl	2.0	20	95
		(b) Br	2.0	10	90
		(c) I	2.0	90	97

[a] Yields of isolated products.

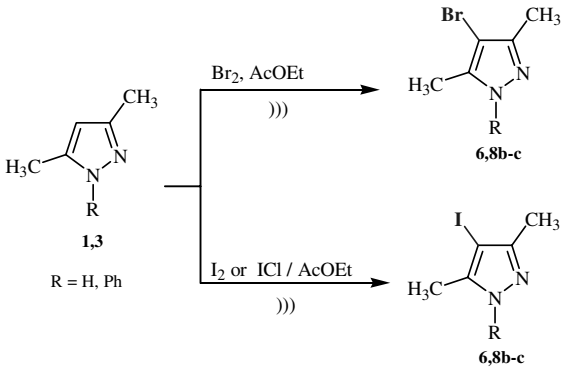


1,3 6,8

Product	R	X	Time (min)	Yield (%)[a]
6b	H	Br	15	80
6c	H	I	30	71
8b	Ph	Br	60	82
8c	Ph	I	60	70

[a] Yields of isolated products.

Scheme 2. Reaction in large scale (20 mmol).



Product	R	Reagent	Time (min)	X	Yield (%)[a]
6b	H	Br_2	15	Br	98
8b	Ph	Br_2	30	Br	96
6c	H	I_2	60	I	40
8c	Ph	I_2	60	I	17
6c	H	ICl	15	I	94
8c	Ph	ICl	15	I	90

[a] Yields of isolated products.

Scheme 3.

In addition, it was observed that the halogenation of 3,5-dimethyl pyrazole **1**,**3** on a large-scale (20 mmol) furnished the products **6b**, **6c**, **8b** and **8c** in good yields (70–82%) using the same reaction conditions (Scheme 2).

Scheme 3 shows that the reaction of Br_2, I_2 and ICl with 3,5-dimethyl pyrazoles (**1**,**3**) in acetone under ultrasound irradiation gave the desired products with 17–98% yields in 15–60 min, and the I_2 was the reagent less reactive for halogenation of these pyrazoles. In this context, we have found that the Br_2 and ICl are also versatile reagents for halogenation of pyrazoles by sonochemistry methodology. All halogenated pyrazoles (**6**–**10**) were characterized by NMR ^1H, ^{13}C and mass spectrometry.

In conclusion, we have developed a mild, convenient and improved protocol for 4-halogenation of 3,5-dimethyl pyrazoles with *N*-halosuccinimides (NBS, NCS and NIS). The present procedure is carried out in a shorter time, easier work-up and good yields. The method reported here is not only simple to operate but also efficient. Further development of the halogenation technology and extension of the approach to a wider range of valuable nitrogen heterocycles are underway.

2. Experimental

2.1. General methods

Starting pyrazoles (**1**–**5**) were prepared according to the literature and characterized by ^1H NMR and ^{13}C NMR.[18] All solvents and reagents were obtained from Merck or Aldrich and used without further purification, except acetone, which was distilled from CaH_2.

Sonication was performed in a Branson ultrasonic cleaner, Model-3510, frequency of 40 kHz and a nominal power of 130 W. Flash chromatography (FC) was performed using silica gel (Merck 60, 230–400 mesh) when necessary. Melting points are uncorrected. ^1H, ^{13}C and NMR spectra were acquired on a Bruker DPX 300 instrument (300.13 MHz for ^1H and 75.48 MHz for ^{13}C), at 300 K in $CDCl_3$ as solvent. Low resolution mass spectra were obtained on a Shimadzu QP5050*A* spectrometer operating at 70 eV.

2.2. General procedure

A mixture of 1,3-dimethyl pyrazole (2 mmol) and *N*-halosuccinimide (Table 1), in ethyl acetate (10 mL), was irradiated in a water bath of the ultrasonic cleaner at 25–30 °C for the appropriate time (see Table 1). After the indicated time, the organic phase was washed with a solution of $Na_2S_2O_3$ (3×20 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. Finally, the 4-halo-3,5-dimethyl pyrazoles were obtained in good purity.

Compound **6a**: $C_5H_{11}ClN_2$, MW 130.0, mp 103–106 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 6H, $2CH_3$), 10.2 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.3 ($2CH_3$), 107.7 (C-4), 140.9 (C-3, C-5); MS (*m*/*z*, %) 130 (M^+, 100), 95 (95), 42 (80).

Compound **6b**: $C_5H_7BrN_2$, MW 174.0, mp 124–125 °C, ^1H NMR ($CDCl_3$, 300 MHz) 2.26 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.6 ($2CH_3$), 96.5 (C-4), 143.4 (C-3, C-5); MS (*m*/*z*, %) 174 (M^+, 100), 95 (98), 65 (49), 42 (100).

Compound **6c**: $C_5H_7IN_2$, MW 222.0, 136–138 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.73 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1 ($2CH_3$), 62.6 (C-4), 146.4 (C-3, C-5). MS (*m*/*z*, %) 222 (M^+, 100), 65 (40), 42 (49).

Compound **7a**: $C_6H_9ClN_2$, MW 144.0, oil, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.21 (s, 6H, $2CH_3$) 3.85 (s, 3H, N-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2 ($2CH_3$), 32.7 (N-Me), 109.4 (C-4), 134.5, 144.7 (C-3, C-5); MS

(*m*/*z*, %) 144 (M^+, 100), 129 (35), 109 (51), 65 (34), 56 (60), 42 (49).

Compound **7b**: $C_6H_9BrN_2$, MW 188.0, 30–32 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.83 (s, 3H, N-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.3 (CH_3), 11.8 (CH_3), 36.7 (N-Me), 94.5 (C-4), 138.6, 145.3 (C-3, C-5); MS (*m*/*z*, %) 188 (M^+, 100), 109 (40), 56 (90), 39 (93), 28 (100).

Compound **7c**: $C_6H_9IN_2$, MW 236.0, 71–72 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ 1.99 (s, CH_3, 3H), 2.26 (s, CH_3, 3H), 3.79 (N-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2, 11.3 ($2CH_3$), 32.8 (N-Me), 109.4 (C-4), 135.3, 144.7 (C-3, C-5); MS (*m*/*z*, %) 236 (M^+, 100), 109 (95), 66 (65), 56 (100).

Compound **8a**: $C_{11}H_{11}ClN_2$, MW 206.1, oil, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 3H, CH_3) 2.29 (s, 3H, CH_3), 7.33–747 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.8, 11.4 ($2CH_3$), 124.5, 127.7, 129.2, 135.7 (6C, Ph), 106.9 (C-4), 139.7, 146.0 (C-3, C-5); MS (*m*/*z*, %) 206 (M^+, 100), 154 (50), 130 (35), 118 (53), 77 (100), 51 (75).

Compound **8b**: $C_{11}H_{11}BrN_2$, MW 250.0, oil, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 7.36–7.47 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.7, 12.3 ($2CH_3$), 96.4 (C-4), 125.8, 127.0, 129.1, 132.2 (6C, Ph), 137.5, 139.7 (C-3, C-5); MS (*m*/*z*, %) 250 (M^+, 75), 170 (55), 154 (48), 144 (46), 130 (60), 118 (74), 77 (100), 65 (65), 51 (85).

Compound **8c**: $C_{11}H_{11}IN_2$, MW 298.0, oil, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.32–7.47 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 14.2 ($2CH_3$), 65.6 (C-4), 124.4, 127.6, 129.0, 139.5 (6C, Ph), 140.5, 150.4 (C-3, C-5); MS (*m*/*z*, %) 298 (M^+, 88), 170 (35), 130 (50), 118 (60), 77 (100), 65 (50), 51 (70).

Compound **9a**: $C_{11}H_{10}ClN_3O_2$, MW 251.0, mp 145–147 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.32–7.47 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.4, 11.5 ($2CH_3$), 112.4 (C-4), 122.4, 124.6, 129.5, 144.5 (6C, Ph), 145.8, 147.9 (C-3, C-5); MS (*m*/*z*, %) 251 (100), 154 (45), 130 (50), 118 (65), 77 (100), 51 (85).

Compound **9b**: $C_{11}H_{10}BrN_3O_2$, MW 295.0, mp 139–141 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.66 (d, 2H, Ar, $J = 9$ Hz), 8.34 (d, 2H, Ar, $J = 9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.4 ($2CH_3$), 99.0 (C-4), 124.9, 125.8, 137.7, 144.6 (6C, Ar), 145.9, 149.5 (C-3, C-5); MS (*m*/*z*, %) 295 (M^+, 88), 207 (51), 169 (49), 129 (50), 117 (47), 76 (100), 63 (80), 50 (92), 44 (100).

Compound **9c**: $C_{11}H_{10}IN_3O_2$, MW 343.0, mp 119–120 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.64 (d, 2H, Ar, $J = 9$ Hz), 8.33 (d, 2H, Ar, $J = 9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.1 ($2CH_3$), 68.3 (C-4), 123.8, 124.7, 141.0, 144.5 (6C, Ar), 145.5, 152.4 (C-3, C-5); MS (*m*/*z*, %) 343 (M^+, 21), 39 (19), 28 (100).

Compound **10a**: $C_{11}H_6ClF_5N_2$, MW 296.0, oil, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H, CH_3), 2.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.29, 11.4 ($2CH_3$), 110.4 (C-4), 136.2, 139.5, 142.1, 145.6 (m, 6C, C_6F_5), 137.4, 148.9 (C-3, C-5); MS (*m*/*z*, %) 296 (M^+, 63), 261 (38), 208 (100), 194 (70), 117 (90), 93 (33).

Compound **10b**: $C_{11}H_6BrF_5N_2$, MW 340.0, mp 62–63 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.18 (s, 3H, CH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.3, 12.5 ($2CH_3$), 96.8 (C-4), 136.2, 139.5, 142.2, 145.6 (m, 6C, C_6F_5), 140.3, 150.5 (C-3, C-5); MS (*m*/*z*, %) 340 (M^+, 62), 208 (100), 117 (63), 65 (25).

Compound **10c**: $C_{11}H_6F_5IN_2$, MW 387.9, mp 76–79 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ 2.21 (s, 3H, CH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.4, 11.5 ($2CH_3$), 96.8 (C-4), 136.2, 139.5, 142.2, 145.6 (m, 6C, C_6F_5), 140.3, 150.5 (C-3, C-5); MS (*m*/*z*, %) 388 (M^+, 100), 208 (87), 167 (50), 117 (60), 65 (69).

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