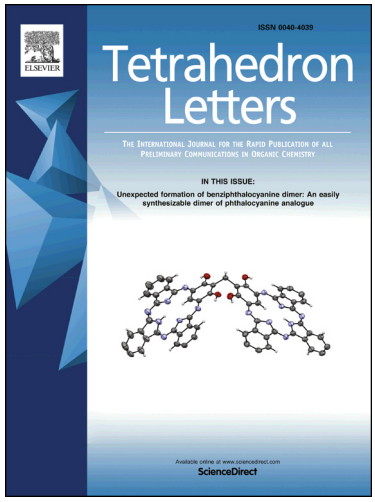

A mild halogenation of pyrazoles using sodium halide salts and Oxone

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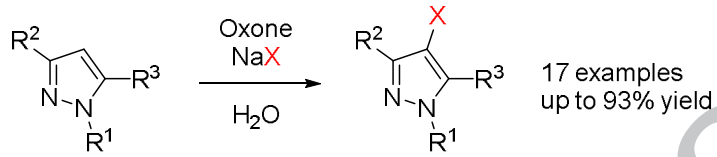
Kathryn L. Olsen, Matthew R. Jensen, James A. MacKay*



R^1 = H, alkyl, allyl, aryl, benzyl
R^2, R^3 = H, alkyl, aryl

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A mild halogenation of pyrazoles using sodium halide salts and Oxone

Kathryn L. Olsen, Matthew R. Jensen, James A. MacKay*

Department of Chemistry and Biochemistry, Elizabethtown College, 1 Alpha Drive, Elizabethtown PA

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ABSTRACT

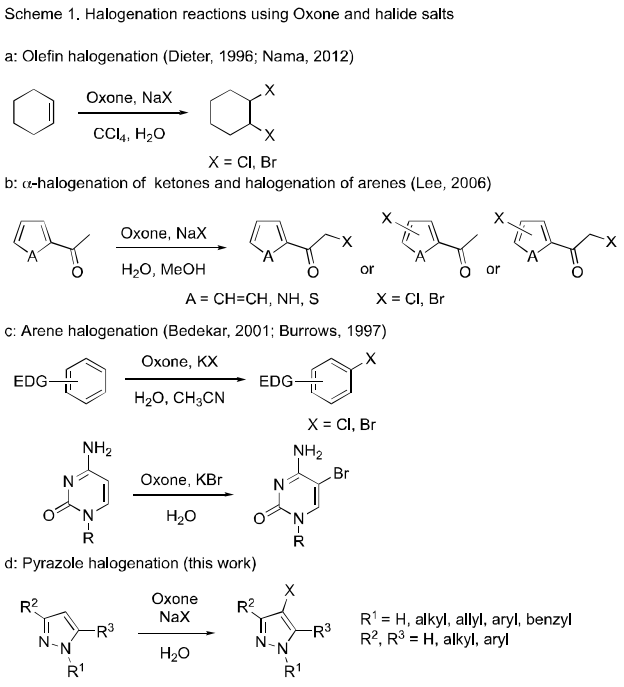
A mild, inexpensive, and operationally simple pyrazole halogenation method utilizing Oxone and sodium halide salts is reported. This work documents 17 examples of alkyl, aryl, allyl, and benzyl substituted 4-chloro and 4-bromopyrazoles, obtained in up to 93% yield. Reactions are performed in water under ambient conditions and generation of organic byproducts is avoided.

Pyrazoles are an intriguing class of molecules that are uncommon in nature yet have become a ubiquitous heterocyclic substructure among bioactive molecules.[1] In particular, 4-halopyrazoles are common in both pharmaceuticals and agrochemicals where the halogen atom may be employed to enhance biological properties.[2] Additionally, the halogen atom can be utilized as a synthetic handle to install further functionalization, allowing for elaboration of the ring system and providing access to more complex systems. Most notably, halogenated pyrazoles can be used in cross-coupling reactions to afford various 4-substituted products.[3]

Pyrazoles are highly electron rich heterocycles and therefore readily undergo electrophilic aromatic substitution at the 4-position with a host of different halogenating agents.[4] However, many of the known halogenation methods require harsh conditions and/or generate unwanted organic byproducts. For example, several reports utilize *N*-halosuccinimides in organic solvents,[4c-e] including reactions assisted by microwaves[4c] or sonication.[4d] These methods are robust and provide products in high yields, yet the use of *N*-halosuccinimides produces stoichiometric succinimide as an unwanted organic byproduct. One report utilizes I_2/H_2O_2 to accomplish the desired transformation with the generation of minimal waste, however the methodology is limited to iodination.[4b] We were interested in an inexpensive, operationally simple, and green method that would be more general for incorporating chlorine and bromine onto the pyrazole ring.

Oxone is a triple salt with the composition $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. The active oxidant, potassium peroxymonosulfate, has various commercial and practical applications, including use as a swimming pool shock oxidizer, wool shrinkproofing, odor control in wastewater treatment, and use as a component of denture bleaches. Owing to its low cost, ease of handling, relative stability, water solubility, and generally 'green' chemical profile, Oxone has become a common oxidant in organic synthesis. Synthetic applications of Oxone include olefin epoxidation[5], oxidation of alcohols[6] and aldehydes,[7] oxidative cleavage of alkenes,[8] and the Hoffman rearrangement of carboxamides.[9] Halogenation reactions employing Oxone in the presence of halide salts have also been explored (Scheme 1).

Scheme 1. Halogenation reactions using Oxone and halide salts

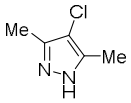
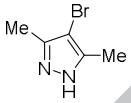
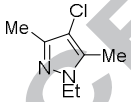
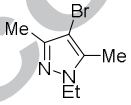
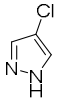
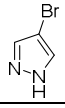


One of the first applications of this mixture was Dieter's report on the oxidation of α,β-enones and alkenes to prepare 2-haloenones and vicinal dihalides.[10] When used with ammonium bromide in the presence of olefins, Oxone affords vicinal bromohydrins and dibromides (Scheme 1a).[11] Similarly, aromatic methyl ketones are α-halogenated using Oxone and sodium halide salts where it was noted that electron rich heterocyclic systems such as pyrroles afforded ring halogenation in preference to α-halogenation at the ketone (Scheme 1b),[12] however a systematic study of this aspect was not reported. Oxone has also been used with halide salts in electrophilic aromatic substitutions of electron rich benzenes[13] and pyrimidines[14] (Scheme 1c) but we are unaware of its use in the halogenation of pyrazoles. Herein, we report our findings using Oxone/NaX as a method for electrophilic pyrazole halogenation (Scheme 1d).

Halogenations were performed with the reaction exposed to the atmosphere. Treating a suspension of the pyrazole substrate in water with sodium halide and Oxone resulted in a mildly exothermic reaction which was followed by stirring at ambient temperature. Reaction conditions were first screened on 3,5-dimethylpyrazole with one-half equivalent of Oxone (corresponding to 1 equivalent of the active oxidant, $KHSO_5$) and two equivalents of NaCl or NaBr. Sodium halide stoichiometry was briefly explored using 1, 1.5, 2, and 5 equivalents of NaBr with the best results obtained using 2 equivalents. Reactions worked well on 1 mmol to 5 mmol scales, and order of addition did not noticeably affect the outcome.

The results of several halogenations performed in water are summarized in Table 1, with reactions producing good yields comparable with NXS halogenation methods.[4c-e] Notably, both chlorination and bromination afforded similar yields. Most reactions were complete within one hour, with the time necessary to reach full conversion related to the electronics of the heterocycle.

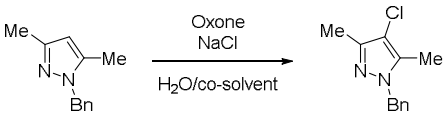
Table 1. Pyrazole halogenation reactions performed in water[a]

Entry	Product	Time (h)	Yield (%)[b]
1		1	93
2		1	93
3		1	84
4		2	74
5		2.5	74
6		4.5	73 (80)[c]

[a]Unless otherwise noted, reactions were carried out using 1-7 mmol pyrazole substrate, 2 equiv. NaX, and 0.5 equiv. Oxone (corresponding to 1 equiv. $KHSO_5$).
[b]Isolated yield following recrystallization or by silica gel column chromatography
[c]Reaction was scaled up to 30 mmol with a 48 hour reaction time, giving good purity without recrystallization

Previously published methods for pyrazole halogenations in water typically involve low molecular weight N-H pyrazoles and/or N-Aryl pyrazoles. We were curious if more hydrophobic alkylated pyrazoles could be efficiently halogenated using the NaX/Oxone method. Not surprisingly, as hydrophobicity of the pyrazoles increased, conversions and yields decreased or the reactions proved irreproducible due to the heterogeneous nature of the reaction mixture. To overcome this problem, a series of co-solvents was screened in the chlorination of 1-benzyl-3,5-dimethyl-1*H*-pyrazole using a 70:30 water to co-solvent ratio and rapid stirring for 1 hour (Table 2). Both miscible (entries 2-4) and immiscible solvents (entries 5-7) were used, and in each case there was an increase in the amount of product obtained relative to the reaction with no co-solvent. Clean products and high conversions were obtained for acetonitrile (entry 2), acetone (entry 3), tetrahydrofuran (entry 4) and ethyl acetate (entry 7) as co-solvents. Dichloromethane and toluene (entries 5 & 6) both led to lower conversions and more complex product mixtures. Ethyl acetate was thus chosen as the preferred co-solvent due to its lower cost, availability, and safety profile compared to acetone, acetonitrile and tetrahydrofuran.[15] In addition, the resulting biphasic mixture was more easily manipulated during workup and isolation of product. Given that the ethyl acetate co-solvent results in a biphasic mixture, an additional experiment was attempted with slower stirring (entry 8). Not surprisingly, the reaction resulted in lower conversions and yields which underscores the importance of vigorously mixing the biphasic solution.

Table 2. Solvent studies[a]



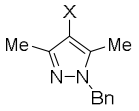
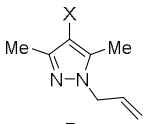
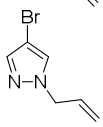
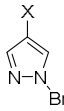
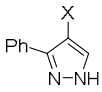
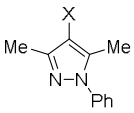
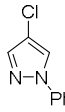
Entry	Co-solvent	Conversion (%)[b]	Isolated yield (%)[c]
1	none[d]	63	44
2	CH_3CN	95	81
3	acetone	94	81
4	THF	92	79
5	DCM	73	48
6	PhMe	79	57
7	EtOAc	>96	93
8	EtOAc[e]	50	41

[a]Unless otherwise noted all reactions involved 1 equiv. of pyrazole substrate, 2 equiv. of NaCl, 0.5 equiv. of Oxone, 0.7 mL of H_2O, 0.3 mL of co-solvent and vigorous stirring >1000 rpm for 1 h.
[b]Determined by ^1H NMR
[c]Yield obtained after purification by silica gel column chromatography
[d]1 mL of H_2O
[e]Reaction run with moderate stirring at ca 350 rpm

With the optimal co-solvent selected, a series of pyrazoles was treated with Oxone and sodium halide salts in a water/ethyl acetate mixture (Table 3). Most reactions gave highly pure products demonstrating the method's tolerance to alkene and aryl functional groups. In particular, the alkene double bond in 1-allyl-3,5-dimethylpyrazole was not halogenated in the chlorination or bromination reactions to any significant extent (Table 3, entries 3 & 4). This is in contrast to 1-allylpyrazole which did halogenate the pyrazole 4-position, but led to inseparable mixtures of over-halogenation products (entry 5). Halogenation of 3,5-dimethyl-1-phenylpyrazole (Table 3, entries 10 & 11) required three additions of 0.35 equivalents of Oxone added over a period of 20 hours due to the formation of byproducts under standard reaction conditions.

Halogenation of electron poor pyrazoles such as diethyl 3,5-pyrazoledicarboxylate afforded low conversions and yields, even under forcing conditions at reflux. This is unsurprising given the presumed electrophilic aromatic substitution mechanism. Additionally, attempts to apply this method to other heterocycles including imidazoles and indoles have been unsuccessful to date.

Table 3. Pyrazole halogenation reactions performed in water/EtOAc[a]

Entry	Product	Time (h)	Yield (%)[b]
1 (X=Cl)		1	93
2 (X=Br)		1	71
3 (X=Cl)		2	77
4 (X=Br)		5	74
5		3	-[c]
6 (X=Cl)		2	73
7 (X=Br)		1	89
8 (X=Cl)		1	77
9 (X=Br)		1	73
10 (X=Cl)		20	78[d]
11 (X=Br)		24	86[d]
12		1	46

[a]Unless otherwise noted, reactions were carried out using 1 equiv. pyrazole substrate, 2 equiv. NaX, and 0.5 equiv. Oxone (corresponding to 1 equiv. $KHSO_5$).

[b]Isolated yield following recrystallization or by silica gel column chromatography

[c]Halogenated product was obtained in low yield with inseparable overhalogenation byproducts.

[d]Three portions of 0.35 equiv. Oxone added over 20 h.

In summary, an operationally simple and efficient method of pyrazole halogenation using Oxone and NaX in water has been developed. The reaction works well for a variety of electron rich N-H, N-alkyl, and N-aryl pyrazoles.

Acknowledgements

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Supplementary Data

Supplementary data (general experimental information, characterization data, ^{1}H and ^{13}C NMR Spectra of new compounds) is available free of charge at

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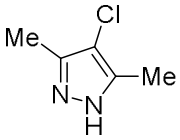
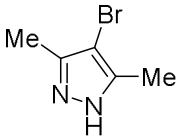
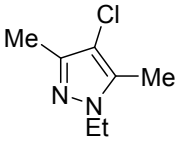
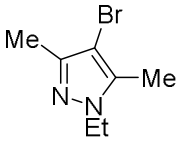
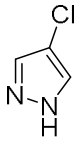
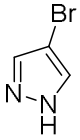
Table 1. Pyrazole halogenation reactions performed in water[a]

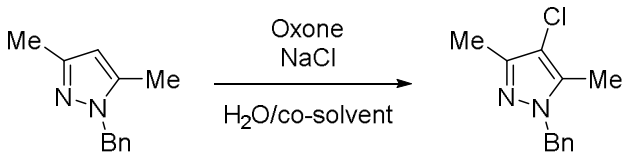
Entry	Product	Time (h)	Yield (%)[b]
1		1	93
2		1	93
3		1	84
4		2	74
5		2.5	74
6		4.5	73 (80)[c]

[a]Unless otherwise noted, reactions were carried out using 1-7 mmol pyrazole substrate, 2 equiv. NaX, and 0.5 equiv. Oxone (corresponding to 1 equiv. KHSO5)

[b]Isolated yield following recrystallization or by silica gel column chromatography

[c]Reaction was scaled up to 30 mmol with a 48 hour reaction time, giving pure product without recrystallization

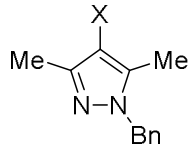
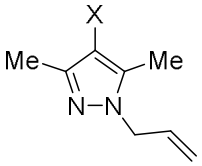
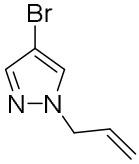
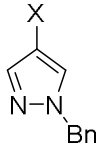
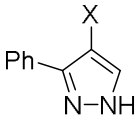
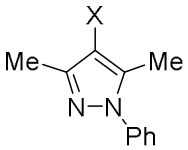
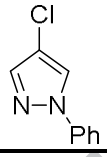
Table 2. Solvent studies[a]



Entry	Co-solvent	Conversion (%)[b]	Isolated yield (%)[c]
1	None	63	44
2	CH_3CN	95	81
3	acetone	94	81
4	THF	92	79
5	CH_2Cl_2	73	48
6	toluene	79	57
7	EtOAc	>96	93
8	EtoAc[e]	50	41

[a]Unless otherwise noted all reactions involved 1 equiv. of pyrazole substrate, 2 equiv. of NaCl, 0.5 equiv. of Oxone, 0.7 mL of H_2O, 0.3 mL of co-solvent and vigorous stirring >1000 rpm for 1 h.
[b]Determined by ^1H NMR
[c]Yield obtained after purification by silica gel column chromatography
[d]1 mL of H_2O
[e]Reaction run with moderate stirring at ca. 350 rpm

Table 3. Pyrazole halogenation reactions performed in water/EtOAc[a]

Entry	Product	Time (h)	Yield (%)[b]
1 (X = Cl) 2 (X = Br)		1 1	93 71
3 (X = Cl) 4 (X = Br)		2 5	77 74
5		3	-[c]
6 (X = Cl) 7 (X = Br)		2 1	73 89
8 (X = Cl) 9 (X = Br)		1 1	77 73
10 (X = Cl) 11 (X = Br)		20 24	78[d] 86[d]
12		1	46

[a]Unless otherwise noted, reactions were carried out using 2 equiv. NaX, and 0.5 equiv. Oxone (corresponding to 1 equiv. $KHSO_5$)

[b]Isolated yield following recrystallization or by silica gel column chromatography

[c]Halogenated product was obtained in low yield with inseparable overhalogenation byproducts.

[d]Three portions of 0.35 equiv. Oxone added over 20 h.

A mild halogenation of pyrazoles using sodium halide salts and Oxone

Kathryn L. Olsen, Matthew R. Jensen, James A. MacKay*

Highlights

- An operationally simple pyrazole halogenation is reported.
- Reagents are safe and the method avoids organic byproducts.
- Reactions are performed in water under ambient conditions.
- Halogenation yields are high for a series of 9 different substrates.