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Practical and efficient synthesis of *N*-halo compounds

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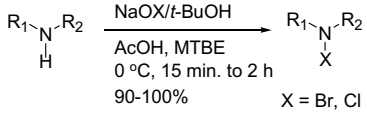
Abstract—A practical and efficient synthesis of *N*-halo compounds is described. Treatment of primary and secondary amines or amides with sodium hypohalite in the presence of *tert*-butanol and acetic acid afforded *N*-halo compounds in 90–100% yield.

N-Halo compounds are versatile reagents and have been employed as potentially reactive intermediates that are widely used in organic synthesis.[1] Numerous methods utilizing an electrophilic halogen source have been studied to achieve the *N*-halogenation of amines and amides.[2] Sodium hypohalites (bleach and NaOBr), *tert*-butyl hypochlorite, and *N*-halo succinimides (NCS and NBS) are the most common reagents used to perform this N–H to N–X oxidation. However, these reagents have several limitations, which curtail their use. NCS and NBS are widely used as *N*-halogenating reagents, but removal of the succinimide by-product is often difficult.[3] Sodium hypochlorite is a safe, inexpensive commodity chemical, although R_2N–H oxidations typically suffer from prolonged reaction times with modest yields. *N*-halogenation with *tert*-butyl hypochlorite generally provides good to excellent yields; however, *tert*-butyl hypochlorite is an expensive, hazardous reagent[2d,4] that is best suited for small scale research applications.

Herein, we present a new and efficient protocol for the preparation of *N*-halo compounds via the in situ generation of *tert*-butyl hypohalite. Organic solutions of amines and amides are treated with aqueous sodium hypohalite (NaOCl or NaOBr) in the presence of *tert*-butanol and acetic acid. Under these biphasic conditions, *tert*-butyl hypohalite is slowly generated in situ with the dropwise addition of the oxidant. The amine or amide in an organic solvent such as EtOAc, IPAc, MTBE or toluene reacts with the organic soluble *tert*-butyl hypohalite to give the desired N–X product (Scheme 1). The N–H oxidation occurs rapidly with amines, and the resulting exotherm is then controlled by the slow addition of sodium hypohalite to avoid the large buildup of *tert*-butyl hypohalite. This feature makes the protocol particularly attractive for industrial scale processing given the low concentration of *tert*-butyl hypohalite at any given time.



Scheme 1.

The scope of this new protocol was investigated and all substrates shown in Table 1 were converted to *N*-halo compounds in high yield. The substrates were dissolved in the organic solvent along with 0.25–1 equiv of *tert*-butanol. Then, 1–1.5 equiv of sodium hypohalite (0.75 M or 0.5 M) and 1–1.5 equiv of acetic acid were added dropwise at 0 °C. Under these conditions, the reaction was typically completed within 15 to 30 min for amines and 1 to 2 h for amides.[5] Secondary amides including sulfomaide (entries 1–5, 17) were oxidized to the corresponding *N*-halo compounds in very high yield. Amine hydrochloride salts (entries 8 and 9, 15 and 16) can be oxidized to the corresponding *N*-chloro and *N*-bromo compounds in the absence of acetic acid. An

Keywords: Amine oxidation; Amide oxidation; *N*-halogenation; Sodium hypohalite; *tert*-Butyl hypohalite.
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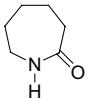
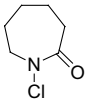
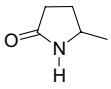
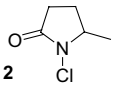
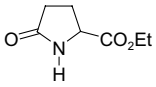
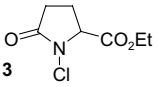
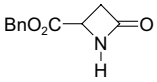
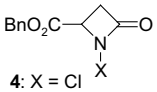
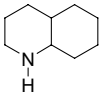
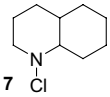
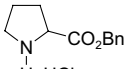
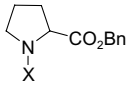
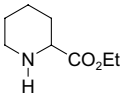
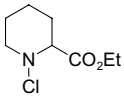
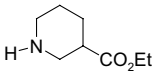
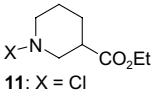
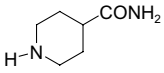
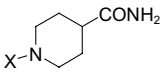
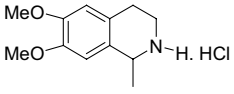
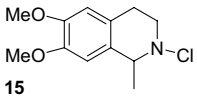
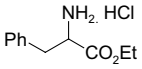
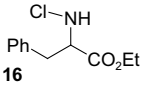
Table 1. Synthesis of *N*-halo compound

Entry	Substrate	Product	NaOX (equiv)[a]	*t*-BuOH (equiv)	AcOH (equiv)	Solvent[b]	reaction time (h)	Yield (%)[c]
1		 **1**	1	1	1	Toluene	2	100
2		 **2**	1	0.5	1	IPAc	1	99
3		 **3**	1	0.5	1	IPAc	1	99
4		 **4**: X = Cl	1.5	0.5	1.5	IPAc	1	100
5		**5**: X = Br	1.5	0.5	1.5	MTBE	1	98
6		 **6**	1	0.5	1	MTBE	0.5	100
7		 **7**	1	0.5	1	MTBE	0.5	100
8			1	1	—	MTBE	0.25	100
9	H. HCl	**8**: X = Cl **9**: X = Br	1	1	—	MTBE	0.5	90
10		 **10**	1	0.5	1	MTBE	0.5	100
11		 **11**: X = Cl	1	0.25	1	MTBE	0.5	100
12		**12**: X = Br	1.2	1	1.2	MTBE	0.5	94
13			1	1	1	EtOAc	0.5	90
14		**13**: X = Cl **14**: X = Br	1	1	1	EtOAc	1	90
15		 **15**	1	0.25	—	IPAc	0.5	100
16		 **16**	1	0.5	—	MTBE	1	96
17		 **17**	1.5	1	1.5	IPAc	0.5	92

[a] Sodium hypochlorite solution (0.75 M) and 0.5 M of sodium hypobromide was used.
[b] IPAc = isopropyl acetate; MTBE = *tert*-butyl methyl ether; EtOAc = ethyl acetate.
[c] Isolated yields were obtained via evaporation of solvents to give desired products which were determined to be >95% pure by ^{1}H NMR.

amino amide (entries 13 and 14) was selectively oxidized at the amine N–H. Finally, a primary amine (entry 16) was selectively monochlorinated in 96% yield. Dichlorinated product was not detected.

In summary, we have developed a practical, efficient and scaleable synthesis for the preparation of a wide range *N*-halo compounds.[6] *tert*-Butyl hypohalite is generated in situ by treatment of sodium hypohalite with *tert*-butanol in the presence of acid. The reaction is carried out under mild conditions and produces *N*-halo compounds in excellent purity and high yield. This method offers an alternative to hazardous *tert*-butyl hypochlorite and should find wide use for the oxidation of amines and amides.

References and notes

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4. Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1995; Vol. 2, p 890.
5. Typical procedure for the preparation of *N*-halo compounds: To a solution of amine or amide (5.0 mmol), *tert*-butanol (0.25–1 equiv) in MTBE was slowly added acetic acid (1–1.5 equiv) and sodium hypohalite (1–1.5 equiv) at −5 to 0 °C at the same time. The resulting solution was aged at 0 °C for 15 min to 2 h. The organic layer was separated, washed with water, and then brine. The organic solution was concentrated to give desired *N*-halo compound in 90–100% yield.
6. All new compounds gave satisfactory analytical and spectral data in accordance to their structures. Selected data for compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.34 (m, 5H), 5.27 (s, 2H), 4.53 (dd, J = 5.9, 2.7 Hz, 1H), 3.40 (dd, J = 13.6, 5.9 Hz, 1H), 3.21 (dd, J = 13.6, 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 164.8, 134.7, 128.9 (2C), 128,8, 128.5 (2C), 68.0, 57.4, 43.4. Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.30 (m, 5H), 5.21 (s, 2H), 4.27 (dd, J = 5.9, 2.7 Hz, 1H), 3.46 (dd, J = 13.3, 5.9 Hz, 1H), 3.29 (dd, J = 13.3, 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.5, 166.0, 134.7, 128.7 (2C), 128.5, 127.0. Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.58 (s, 2H), 4.19 (q, J = 6.6 Hz, 1H), 3.85 (s, 6H), 3.63 (m, 1H), 3.38 (m, 1H), 3.00–2.89 (m, 2H), 1.56 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.0, 147.7, 129.7, 124.5, 111.1, 109.7, 65.3, 56.1, 55.9, 55.3, 27.1, 21.6. Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.19 (m, 3H), 7.12 (br d, J = 7.0 Hz, 2H), 4.62 (d, J = 9.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.89 (td, J = 9.2, 6.8 Hz, 1H), 3.04 (d, J = 6.8 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 135.8, 129.2 (2C), 128.6 (2C), 127.1, 68.4, 61.5, 37.9, 14.1.