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Halogenation of Primary Alcohols Using a Tetraethylammonium Halide/$[Et_2NSF_2]BF_4$ Combination

Marie-France Pouliot, Olivier Mahé, Jean-Denys Hamel, Justine Desroches, and Jean-François Paquin*

Canada Research Chair in Organic and Medicinal Chemistry, Département de Chimie, Université Laval, 1045 avenue de la Médecine, Québec, QC, Canada G1V 0A6

jean-francois.paquin@chm.ulaval.ca

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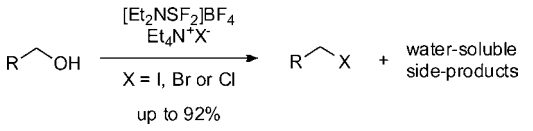
ABSTRACT



The halogenation of primary alcohols is presented. The use of a combination of tetraethylammonium halide and $[Et_2NSF_2]BF_4$ (XtalFluor-E) allows for chlorination and bromination reactions to proceed efficiently (up to 92% yield) with a wide range of alcohols. Iodination reactions are also possible albeit in lower yields.

Primary alkyl chlorides, bromides and iodides are arguably key intermediates in organic synthesis. Indeed, they can be used as electrophiles and converted, by nucleophilic displacement, to various valuable synthons including amines, thiols, or ethers.[1] Alternatively, metal−halogen exchange converts them into nucleophiles that can be used in subsequent reactions.[2] Generally, the alkyl halides are prepared from the corresponding alcohol.[3] This conversion can be accomplished using a two-steps procedure where the alcohol is first converted into a leaving group (generally a sulfonate) followed by nucleophilic displacement with the appropriate halide[1,4] or in a single flask where both steps are performed *in situ*, the latter being generally preferable. Not surprisingly,

(1) Nelson, J. D. In *Practical synthetic organic chemistry: reactions, principles, and techniques*. Caron, S. (Ed.), John Wiley & Sons, Inc., Hoboken, 2011 and references therein.

(2) Rappoport, Z.; Marek, I., Eds. *The Chemistry of Organolithium Compounds*; John Wiley & Sons Ltd.: Chichester, 2004.

(3) In the manufacture of drugs, 22% of functional group interconversions are alcohol to halide, see Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

(4) For a recent application of this sequence in total synthesis, see Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17–46.

(5) Chloration: For selected examples, see (a) Mukaiyama, T.; Shoda, S.-i.; Watanabe, Y. *Chem. Lett.* **1977**, 383–386. (b) Fujisawa, T.; Iida, S.; Sato, T. *Chem. Lett.* **1984**, 1173–1174. (c) Benazza, M.; Uzan, R.; Beaupère, D.; Demailly, G. *Tetrahedron Lett.* **1992**, *33*, 3129–3132. (d) Benazza, M.; Uzan, R.; Beaupère, D. Demailly *Tetrahedron Lett.* **1992**, *33*, 4901–4904. (e) Gomez, L.; Gellibert, F.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 6049–6052. (f) Iranpoor, N.; Firouzabadi, H.; Aghapour, Gh.; Vaez zadeh, A. R. *Tetrahedron* **2002**, *58*, 8689–8693. (g) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553–555. (h) Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 7186–7187. (i) Kelly, B. D.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 13930–13931. (j) Denton, R. M.; An, J.; Adeniran, B. *Chem. Commun.* **2010**, *46*, 3025–3027. (k) Vanos, C. M.; Lambert, T. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 12222–12226. (l) Newman, S. G.; Bryan, C. S.; Perez, D.; Lautens, M. *Synthesis* **2011**, 342–346. (m) Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. *J. Org. Chem.* **2011**, *76*, 6749–6767.

(6) Bromination: For selected examples, see ref 5e−5g, 5m in addition to (a) Roper, K. A.; Lange, H.; Polyzos, A.; Berry, M. B.; Baxendale, I. R.; Ley, S. V. *Beilstein J. Org. Chem.* **2011**, *7*, 1648–1655. (b) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem.* **2011**, *3*, 140–145.

(7) Iodination: For selected examples, see ref 6a, 6b in addition to (a) Jung, M. E.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, *31*, 2659–2662. (b) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247–1251. (c) Lauwers, M.; Regnier, B.; Van Eenoo, M.; Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1979**, *20*, 1801–1804. (d) Vankar, Y. D.; Rao, C. T. *Tetrahedron Lett.* **1985**, *26*, 2717–2720. (e) Martinez, A. G.; Alvarez, R. M.; Vilar, E. T.; Fraile, A. G.; Barnica, J. O.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1987**, *28*, 6441–6442. (f) Fernandez, I.; Garcia, B.; Munoz, S.; Pedro, J. R.; Salud, R. *Synlett* **1993**, 489–490. (g) Joseph, R.; Pallan, P.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1995**, *36*, 609–612. (h) Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 2830–2833. (i) Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *Tetrahedron Lett.* **2001**, *42*, 951–953. (j) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2004**, *45*, 7451–7454. (k) Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* **2004**, 635–638. (l) Hajipour, A. R.; Falahati, A. R.; Ruoho, A. E. *Tetrahedron Lett.* **2006**, *47*, 4191–4196. (m) Ellwood, A. R.; Porter, M. J. *J. Org. Chem.* **2009**, *74*, 7982–7985.

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a wide range of methods for the direct halogenation of alcohols has been reported.[5−7] Perhaps, the most general and mildest system to affect the halogenation of alcohols is the Appel reaction.[1,8] In this approach, Ph_3P is combined with a electrophilic halogen source such as CCl_4, CBr_4 or I_2. This method suffers from two drawbacks: purification issues related to the stoichiometric generation of $Ph_3P{=}O$ along with the low atom economy of the reaction because of the high molecular weight of the reagents which are often used in large excess (> 1.5 equiv).

Diethylaminodifluorosulfinium tetrafluoroborate ($[Et_2NSF_2]BF_4$), XtalFluor-E,[9] has been recently reported as an alternative reagent for the deoxofluorination reaction.[10] In contrast with typical deoxofluorinating agent such as DAST or Deoxofluor, this reagent is fluoride-free. Hence, an external source of fluoride is required for the reaction to proceed. Based on that observation, we wondered if this reagent could, in the presence of other halides, be used as an activating agent[11] for the halogenation of alcohols.[12] Herein, we report the use of a combination of tetraethylammonium halide and XtalFluor-E for the chlorination, bromination and iodination of primary alcohols. In addition, and as opposed to the Appel reaction, this system generates water-soluble side-products, that facilitates purification (Figure 1).

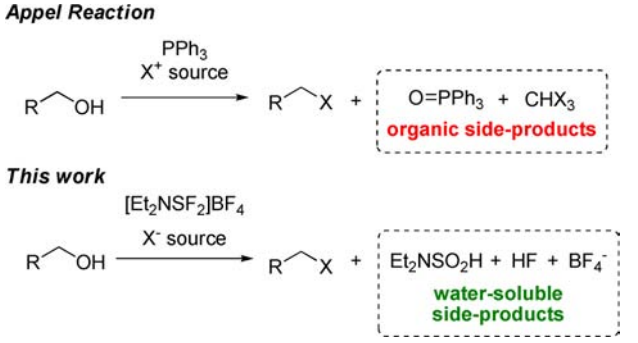
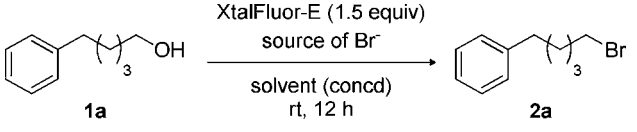


Figure 1. Tetraethylammonium halide/$[Et_2NSF_2]BF_4$ combination as a potential alternative to the Appel reaction.

We first optimized the bromination reaction using 5-phenyl-1-pentanol (**1a**) as the test substrate and selected results are shown in Table 1. Screening of an appropriate solvent was first performed using 1.5 equiv of XtalFluor-E and 2 equiv of tetrabutylammonium bromide (TBAB) as a soluble bromide source at 21 °C for 12 h. Nearly identical yields were obtained in DMF or EtOAc (Table 1, entries 1−2) although with the latter, a significant amount of 5-phenylpentyl acetate (ca. 20%) was also isolated. This side-product likely comes from reaction of the substrate with the solvent. Slightly improved yields were obtained using CH_2Cl_2 and toluene (Table 1, entries 3−4) and both were chosen for further optimization. Increasing the concentration from 0.1 to 0.5 M in CH_2Cl_2 (Table 1, entries 4−6) resulted in an improved yield of 79%. Reducing the amount of XtalFluor-E from 1.5 to 1.2 equiv gave rise to a 90% isolated yield for the desired bromoalkane **2a** (Table 1, entry 7). Performing the reaction under identical condition but using toluene instead of CH_2Cl_2 gave a slightly inferior result (Table 1, entry 8). While the reaction proceeded well with TBAB, we wondered if we could use another bromide source that would have a lower molecular weight since replacing CBr_4 by TBAB only brings a marginal gain (331.63 g/mol vs 322.37 g/mol). Interestingly, using tetraethylammonium bromide (TEAB, MW = 210.16 g/mol), a slightly inferior yet good yield was obtained (Table 1, entry 9). Unfortunately, a low yield was obtained in CH_2Cl_2 and toluene with tetramethylammonium bromide (TMAB, MW = 154.05 g/mol), most likely for solubility reason (Table 1, entries 10−11). Sodium bromide (MW = 102.89 g/mol), not surprisingly, performed poorly as its solubility in CH_2Cl_2 is low (Table 12, entry 12). With these results in hand, we decided to fine-tune the reaction using TEAB as

Table 1. Selected Optimization Results for the Bromination of Alcohol **1a**[a]



1a 2a

entry	source of Br^- (equiv)	solvent (concd in M)	yield (%)[b]
1	TBAB (2)	DMF (0.1)	46
2	TBAB (2)	EtOAc (0.1)	52
3	TBAB (2)	toluene (0.1)	57
4	TBAB (2)	CH_2Cl_2 (0.1)	61
5	TBAB (2)	CH_2Cl_2 (0.25)	70
6	TBAB (2)	CH_2Cl_2 (0.5)	79
7[c]	TBAB (2)	CH_2Cl_2 (0.5)	90
8[e]	TBAB (2)	toluene (0.5)	83
9	TEAB (2)	CH_2Cl_2 (0.5)	81
10	TMAB (2)	CH_2Cl_2 (0.5)	40
11	TMAB (2)	toluene (0.5)	9
12	NaBr (2)	CH_2Cl_2 (0.5)	*ca.* 31[d]
13[e]	TEAB (2)	CH_2Cl_2 (0.5)	74
14	TEAB (1.5)	CH_2Cl_2 (0.5)	89
15	TEAB (1.5)	toluene (0.5)	33
16[e]	**TEAB (1.5)**	**CH_2Cl_2 (0.5)**	**91 (73)**[f]

[a] See the Supporting Information for details of the reaction conditions. [b] Yield of isolated **2a** after purification by flash chromatography. [c] 1.2 equiv of XtalFluor-E was used. [d] Compound **2a** was contaminated with ca. 10% of inseparable and unidentified side-products. [e] Performed in the presence of 2,6-lutidine (3 equiv). [f] Reaction was performed on a 6.46 mmol scale (i.e., 1.06 g of **1a**).

(8) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–811.

(9) The reagent $[Et_2NSF_2]BF_4$ is commercially available under the trademark of XtalFluor-E.

(10) (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; Laflamme, F.; L'Heureux., A. *Org. Lett.* **2009**, *11*, 5050–5053. (b) L'Heureux, A.; Beaulieu, F.; Bennet, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401–3411.

(11) (a) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 988–993. (b) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Tetrahedron Lett.* **2012**, *53*, 4121–4123.

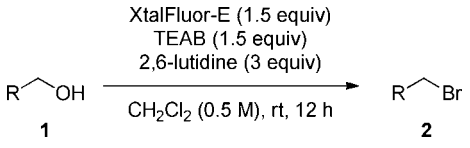
(12) Cochi, A.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2011**, *13*, 4442–4445.

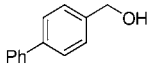
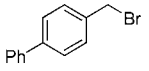
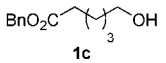
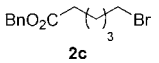
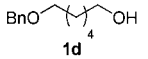
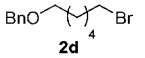
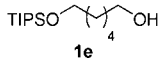
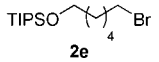
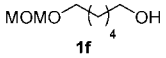
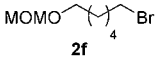
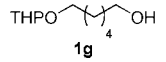
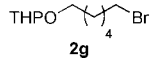
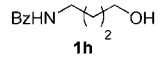
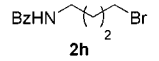
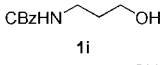
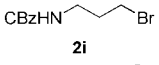
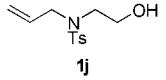
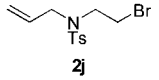
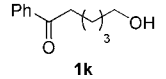
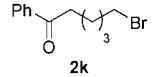
the bromide source. Reducing the amount of XtalFluor-E from 1.5 to 1.2 equiv did not provide this time an increase in yield (Table 1, entry 13) whereas decreasing the amount of TEAB from 2 to 1.5 equiv afforded an excellent yield of 89% (Table 1, entry 14). The same conditions in toluene unfortunately did not perform well for solubility reason. Finally, it was later found that performing the reaction in the presence of 2,6-lutidine (3 equiv) provided cleaner reaction that facilitates purification with slightly improved yield of 91% (Table 1, entry 16).

Using the optimized conditions, we next examined the scope of primary alcohols (Table 2). A benzylic alcohol (**1b**) reacted well providing the corresponding benzylic bromide (Table 2, entry 2) in excellent yield. An ester is well accepted as shown with substrate **1c**. In terms of an alcohol protecting group, a wide range can be used including a benzyl ether (Table 2, entry 4), a TIPS (Table 2, entry 5), a MOM ether (Table 2, entry 6), and a THP (Table 2, entry 7), and good yields were obtained in all cases. Amines can be present when protected with a benzoyl group (Table 2, entry 8), a Cbz (Table 2, entry 9), or a tosylate (Table 2, entry 10). Finally, ketone **1k** was converted into bromide **2k** in good yield. In all cases, ^{1}H and ^{19}F NMR analysis of the crude mixture showed no more than trace amounts (< 3%) of fluorinated products.[10]

We then explored the possibility of realizing chlorination reactions using tetraethylammonium chloride (TEAC). The optimal conditions from the bromination could be transposed directly to the chlorination reaction, and selected results are shown in Table 3. In all cases, good yields were obtained. Interestingly, an unprotected phenol (**1l**) is well tolerated (Table 3, entry 4). In the case of cinnamyl alcohol **1m** (Table 3, entry 5), the secondary chloride that would result from an S_N2' reaction was not observed and only the product originating from an S_N2 reaction was isolated.

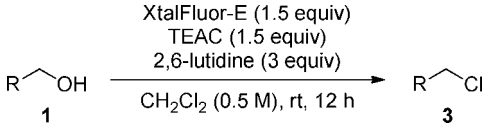
Table 2. Bromination of Various Alcohols[a]

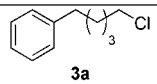
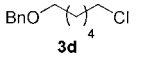
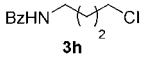
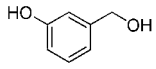
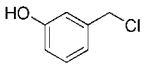
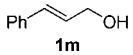
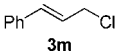


entry	substrate	product	yield (%)[b]
1	**1a**	**2a**	91
2	 **1b**	 **2b**	92
3	 **1c**	 **2c**	75
4	 **1d**	 **2d**	84
5	 **1e**	 **2e**	84
6	 **1f**	 **2f**	67
7	 **1g**	 **2g**	71
8	 **1h**	 **2h**	83
9[c]	 **1i**	 **2i**	70
10	 **1j**	 **2j**	83
11[c]	 **1k**	 **2k**	80

[a] See the Supporting Information for details of the reaction conditions. [b] Yield of isolated **2** after purification by flash chromatography. [c] XtalFluor-E (1 equiv) was used.

Table 3. Chlorination of Primary Alcohols[a]



entry	substrate	product	yield (%)[b]
1	**1a**	 **3a**	85
2	**1d**	 **3d**	82
3	**1h**	 **3h**	81
4	 **1l**	 **3l**	70
5	 **1m**	 **3m**	63[c]

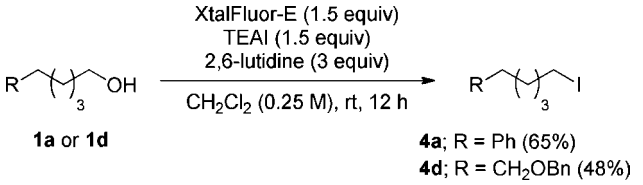
[a] See the Supporting Information for details of the reaction conditions. [b] Yield of isolated **3** after purification by flash chromatography. [c] Crude yield of **3m**.

For the iodination, tetraethylammonium iodide (TEAI) was used as the iodide source. In this case, a more dilute condition (0.25 M) proved to be somewhat beneficial even though only moderate yields were obtained (Scheme 1). In the case of the iodination of **1d**, ca. 30% of the corresponding fluorinated product was also observed by ^{1}H NMR in the crude product along with starting material.

At present, the halogenation is limited to primary alcohols. Indeed, with secondary alcohols as exemplified by 4-phenyl-2-butanol (**5**), the halogenation reaction using various tetraethylammonium halides (TEAX) is slower and, as a result, fluorination becomes somewhat competitive. As a consequence, the secondary halides (**6a**–**c**) are only observed in moderate NMR yields (Scheme 2). In all

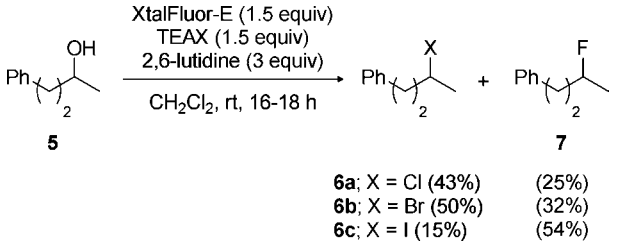
(13) Bromination of *L*-menthol under the standard conditions provided 45% NMR yield of bromination products along with 44% NMR yield of fluorination products. The bromination products consist in a mixture of diastereomers most likely resulting from both inversion and apparent retention (i.e., successive inversions) in a 82/18 ratio. See the Supporting Information for details and ref 6b.

Scheme 1. Iodination of Primary Alcohols



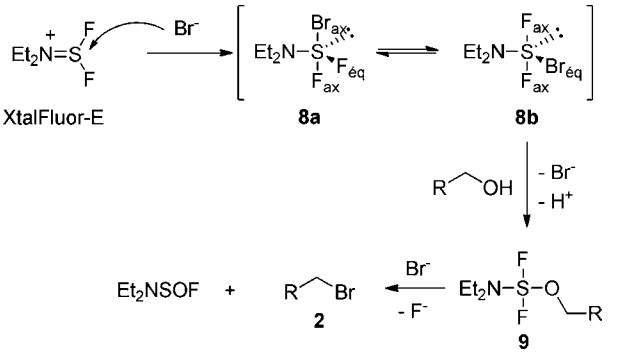
cases, 3-phenyl-2-fluoropropane (**7**) was observed as a major side-product (ca. 25−54%). Further optimization will be necessary to make this transformation synthetically useful.[13]

Scheme 2. NMR Yields for the Halogenation of Secondary Alcohols



In terms of the mechanism, as shown in Scheme 3 for the bromination reaction, we propose that bromide would first react with XtalFluor-E to form diethylaminosulfur bromodifluoride (**8**).[14] Experimentally, a rapid solubilization and color change upon addition of the halide source are observed. Preliminary ^{19}F NMR analysis supports the hypothesis of the reaction of bromide with XtalFluor-E. Indeed, upon addition of 1 equiv of TEAB to a 20 °C solution of XtalFluor-E in $CDCl_3$, disappearance of the ^{19}F signal for the difluorosulfinium moiety (δ 14 ppm) is observed in addition to the appearance of two new signals at 55.6 and 37.7 ppm in a 1:3 ratio. The two resonances could represent the nonequivalent axial and equatorial position for the fluorine atoms in pseudotrigonal bipyramids (**8a** and **8b**).[15] Further NMR experiments will be necessary to further characterize these putative intermediates. Interestingly, this behavior contrasts with the deoxofluorination of alcohols using XtalFluor-E where ^{19}F NMR

Scheme 3. Proposed Mechanism. Counterions (BF_4^- and n-Bu_4N^+) have been omitted for clarity



studies indicated that DAST was not formed upon mixing a 1:1 mixture of XtalFluor-E and $Et_3N\cdot 3HF$,[10b] although other data actually suggest that it may be the case.[16] In any case, the diethylaminosulfur bromodifluoride (**8**) would then react with the alcohol liberating bromide that would perform a nucleophilic substitution of the alkoxy-*N*,*N*-dialkylaminodifluorosulfane (**9**),[17] a key intermediate in the deoxofluorination reaction. This transformation would release the desired alkyl bromide in addition to diethylaminosulfinyl fluoride[18] that would be hydrolyzed upon work-up to form water-soluble *N*,*N*-diethylaminosulfinic acid.

In conclusion, we have described the chlorination, bromination, and iodination reaction of primary alcohols using a combination of tetraethylammonium halide and $[Et_2NSF_2]BF_4$ (XtalFluor-E). The extension of this concept to other nucleophiles is in progress and will be reported in due course.

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Supporting Information Available. Full experimental details and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.