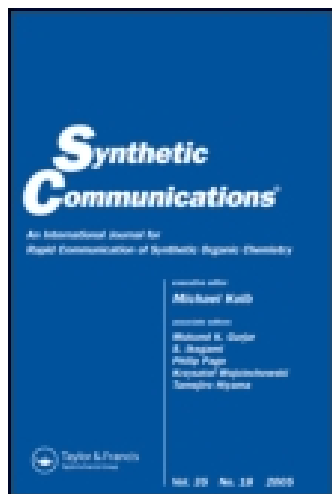


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## Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

### Halide Exchange: Preparation of Alkyl Chlorides

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Published online: 21 Aug 2006.

To cite this article: Jean-François Peyrat, Bruno Figadère & André Cavé (1996) Halide Exchange: Preparation of Alkyl Chlorides, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 26:24, 4563-4567, DOI: [10.1080/00397919608004780](https://doi.org/10.1080/00397919608004780)

To link to this article: <http://dx.doi.org/10.1080/00397919608004780>

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## HALIDE EXCHANGE : PREPARATION OF ALKYL CHLORIDES

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**ABSTRACT:** Primary alkyl bromides can be quantitatively converted into the corresponding chlorides under very mild reaction conditions. The neutral conditions required for such bromide displacements allow the presence of other functions on the substrate.

The halide exchange, sometimes named Finkelstein reaction, generally allows the preparation of iodides from the corresponding chlorides or bromides. It is an equilibrium which can be shifted by taking advantage of the difference of solubility in acetone of the sodium salts<sup>1a,b</sup>. However, for the preparation of primary alkyl chlorides, the corresponding iodides must be treated by HCl in HNO<sub>3</sub><sup>2</sup>, or the bromide heated in a sealed tube at 110 °C in a benzene-water (1:4) solution in the presence of polystyrene ion exchange resin for 240 h<sup>3</sup>. Both procedures are quite drastic and exclude functionalized substrates which could be acidic sensitive or thermic labile. In this letter, we wish to report our findings concerning a mild and efficient preparation of chlorides from the corresponding bromides in neutral conditions. Indeed, we found that when 1-bromoundecane was treated for 1 hour with one equivalent of trimethylsilyl chloride in DMF at 90 °C in

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the presence of two equivalents of imidazole, the corresponding 1-chloroundecane was quantitatively obtained<sup>4</sup> (equation 1).

We then studied the reaction conditions, and the results are summarized in table 1.

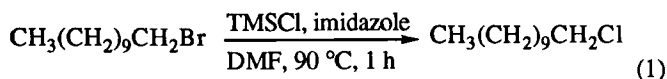


Table 1

entry	R <sub>3</sub> SiCl	imidazole	temperature (°C)	RCH <sub>2</sub> Cl/RCH <sub>2</sub> Br <sup>a</sup>	
				2.5 h	24 h
1	TMSCl (1.3 eq.)	2 eq.	r. t.	32:68	76:23
2	TBDMSCl (1.3 eq.)	2 eq.	r. t.	24:76	63:37
3	TBDMSCl (1.3 eq.)	-	r. t.	09:91	33:67
4	TBDMSCl (1.3 eq.)	2 eq.	60	86:14	100:0
5	TMSCl (1.3 eq.)	2 eq.	80	90:10 (1 h)	
6	TMSCl (1.3 eq.)	2 eq.	90	100:0 (1 h)	

a) ratios are obtained by gc

This study shows clearly that a trialkylsilyl chloride, in the presence of imidazole and in DMF, allows the displacement of a bromine atom by chloride. Furthermore, this study shows that TBDMSCl can be used in lieu of TMSCl, even though the reaction is slightly slower with TBDMSCl (entries 1,2). The presence of imidazole is crucial since in the lack of this reagent the conversion is extremely slow (entries 2,3). The role of imidazole is still not completely understood, and further experiments are needed to rationalize this effect. Finally the temperature factor is dramatic since at 60 °C the reaction is total after 24 h with TBDMSCl, and in only 1 h at 90 °C with TMSCl (entries 4-6).

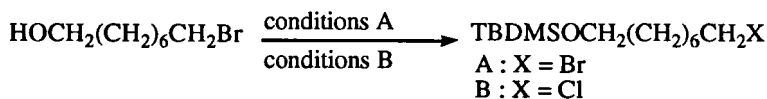
Using the best reaction conditions<sup>6</sup> (1 eq. of TMSCl in DMF at 90 °C for 1 h in the presence of 2 eq. of imidazole) several bromides were converted into their corresponding chloro derivatives in high yields (Table 2).

These results show that the reaction is quite general since primary alkyl bromides are converted into their corresponding chlorides<sup>5</sup>, and when a bromoalcohol is treated then the corresponding chloro- trialkylsilyl ether is obtained in good yield (entries 1-3).

Table 2

entry	RCH <sub>2</sub> Br	RCH <sub>2</sub> Cl	yield (%)
1	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> Br	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> Cl	94
2	Br(CH <sub>2</sub> ) <sub>7</sub> OH	Cl(CH <sub>2</sub> ) <sub>7</sub> OSiMe <sub>3</sub>	90
3	Br(CH <sub>2</sub> ) <sub>7</sub> CO <sub>2</sub> Me	Cl(CH <sub>2</sub> ) <sub>7</sub> CO <sub>2</sub> Me	99

Influence of the solvent is shown by the example below. When we treated 8-bromo-1-octanol with 2.5 eq. of TBDMSCl and 2.5 eq. of imidazole in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 48 h, the 8-bromo-1-*t*-butyldimethylsilyloxyoctane was obtained in quantitative yield<sup>5</sup>. Whereas when the same reaction was carried out with 1.3 eq. of TBDMSCl and 2 eq. imidazole in DMF for 48 h, then the corresponding 8-chloro-1-*t*-butyldimethylsilyloxyoctane was now obtained in quantitative yield<sup>5</sup> (equation 2).



conditions A: TBDMSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, 48 h, r.t.  
conditions B: TBDMSCl, imidazole, DMF, 48 h, r.t.

(2)

In conclusion, this methodology for the preparation of alkyl chlorides presents many advantages over the existing alternative methods. The mildness and absence of acidic or basic treatment of such a reaction allows the preparation of functionalized chlorides, as well as the possibility to prepare compounds labeled with isotopic chloride atoms.

### Acknowledgements

We wish to thank the Ligue Nationale contre le Cancer for a fellowship for J.-F. P.

### References and notes

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- 5 All new compounds gave satisfactory analytical data ( $^1\text{H}$ ,  $^{13}\text{C}$  NMR, gc, mass spectrometry).
- 6 Typical reaction conditions: 1-bromoundecane (0.200 g,  $9.042 \cdot 10^{-4}$  mol.) with imidazole (0.123 g, 2 eq.) was stirred in DMF (0.150 mL) under nitrogen, and  $\text{TMSCl}$  (1.3 eq.) was added. The reaction mixture is heated at

90 °C for 1h, and then after cooling at room temperature, the reaction mixture was filtered off on a cake of silica gel. 1-chloroundecane (0.170g) was then obtained in quantitative yield.

(Received in the UK 5.6.96)