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A Simple, Efficient, and General Method for the Conversion of Alcohols into Alkyl Iodides by a $CeCl_3{\cdot}7H_2O$/NaI System in Acetonitrile

Milena Di Deo, Enrico Marcantoni,* and Elisabetta Torregiani

Dipartimento di Scienze Chimiche, via S. Agostino 1, I-62032 Camerino (MC), Italy

Giuseppe Bartoli,* Maria Cristina Bellucci, Marcella Bosco, and Letizia Sambri

Dipartimento di Chimica Organica "A. Mangini", v.le Risorgimento 4, I-40136 Bologna, Italy

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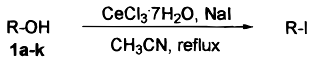
Introduction

The halogen-containing compounds are very useful intermediates in organic synthesis.[1] They react with nucleophiles such as amines or alkoxides to give the corresponding substituted products and are lithiated to introduce electrophiles via a halogen−lithium exchange reaction.[2] The most common precursors to alkyl halides are alcohols, and their conversion into halides is one of most frequently used functional group transformation reactions.[3] Although alkyl iodides are less stable than chlorides and bromides and iodine is the most expensive of the common halogens, they are far more reactive than the other corresponding halogens, and in some cases iodides are the only reactive halides.[4]

Recently, the first preparation method for the conversion of alkanes into their corresponding iodo compounds has been developed in Germany using a multiphase system.[5] The method is selective for tertiary over secondary positions, and no primary C−H activation occurs. Widespread, the iodo compounds can be obtained by the halogen exchange process,[6] considering that the conversion of alcohols to alkyl chloride is one of the most frequently used functional group transformation reactions.[7] However, the iodide products are contaminated with significant amounts of the chloride, which could not be easily removed. Thus, an efficient and general conversion of an alcohol to the corresponding iodide is of importance. A number of synthetic methods have been developed during the past two decades.[8] Of these methods, the treatment with triphenylphosphine, iodine, and imidazole in toluene[9] is the most general and convenient. However, analogously to other methods, it suffers from some drawbacks, which include use of toxic and/or hazardous materials, expensive or commercially nonavailable reagents, long reaction time, low yields, drastic reaction conditions, and tedious workup procedure. As such, mild and efficient methods that can be used to promote the transformation of hydroxyl groups into iodides are of increasing importance to overcome such difficulties.

Scheme 1



Recently cerium(III) chloride has emerged as a Lewis acid imparting high regio- and chemoselectivity in various chemical transformations,[10] since this compound is a very cheap, nontoxic, and water-tolerant reagent.[11] One of the remarkable features of $CeCl_3$ is its efficient activity in combination with sodium iodide.[12] Thus, we considered $CeCl_3$ to be an ideal Lewis acid for effecting one-pot conversion of a hydroxy group into an iodo group. In the present paper, we report an exceedingly mild preparation of iodides from alcohols by the use of a $CeCl_3{\cdot}7H_2O$/NaI system in acetonitrile (Scheme 1).

Results and Discussion

Benzyl alcohol (**1i**) was examined as a model substrate as a ca. 0.1 M solution in acetonitrile containing 1.5 equiv of $CeCl_3{\cdot}7H_2O$ and 1.2 equiv of NaI. Although the reaction was inefficient at room temperature, complete conversion was obtained after 20 h at reflux temperature. Encouraged by this result, several alcohols as substrate for iodination were studied in an effort to elucidate the scope and limitations of this reaction. The results are summarized in Table 1.

First, we have tested whether the electronic properties of the aromatic group in several benzyl alcohols can influence the transformation. We have observed that the

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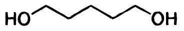
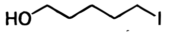
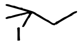
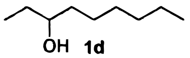
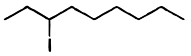
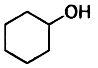
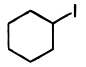
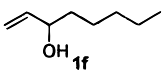
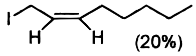
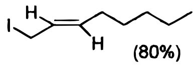
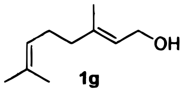
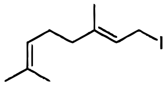
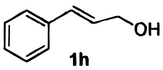
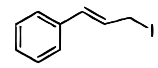
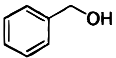
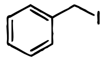
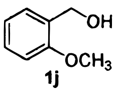
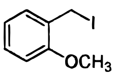
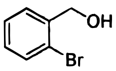
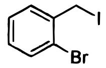
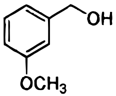
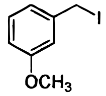
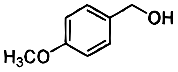
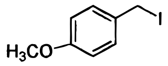
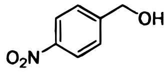
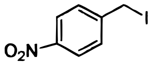
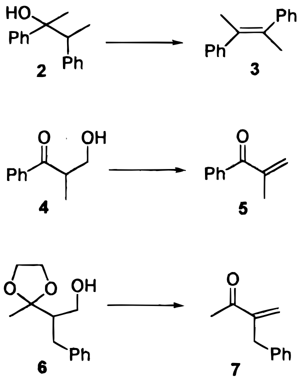
Table 1. Conversion of Alkyl Alcohols into Alkyl Iodides by $CeCl_3·7H_2O$ and NaI in Acetonitrile

Entry	Alchol[b]	Time	Iodide[c]	Yield (%)
1	$C_9H_{19}CH_2OH$ **1a**	48 h	$C_9H_{19}CH_2I$	85
2	 **1b**	48 h		83
3	 **1c**	16 h		89
4		96 h		85
5	 **1e**	96 h		79
6	 **1f**	20 h	 (20%)  (80%)	92
7	 **1g**	15 h		90
8	 **1h**	17 h		93
9	 **1i**	20 h		90
10	 **1j**	28 h		80
11	 **1k**	21 h		93
12	 **1l**	20 h		89
13	 **1m**	13 h		91
14	 **1n**	36 h		69

[a] All reactions were carried out at reflux temperature under an air atmosphere on a 200 mg scale of alcohols with alcohols/$CeCl_3·7H_2O$ (1:1.5) and alcohols/NaI (1:1.2). Yields refer to those of pure isolated products by column chromatography. [b] All starting materials were commercially available or were prepared by conventional methods. [c] All compounds prepared showed physical and spectral (IR, NMR) data in accordance with their expected structure.

reaction can be affected by the electronic properties of the aromatic ring, and there is acceleration by an electron-donating group (Table 1, entry 13). Indeed, while no difference in reactivity was observed when performing the substitution with electron-donating or electron-withdrawing substituents at the *ortho* and *meta* positions (Table 1, entries 10−12), the reaction of benzyl alcohol with an electron-donating group at the *para* position was faster than the one with the hydrogen substituent (Table 1, entry 9). Certainly, the substitution of the electron-withdrawing group onto the aromatic ring retards the transformation (Table 1, entry 14). It has been observed, moreover, that in the case of primary alcohols the conversion into corresponding iodides, more drastic conditions and longer times are necessary (Table 1, entries 1 and 2). The absence of competing elimination during the reaction was proved by recovery of 2-iodo-2-methylbutane almost quantitatively from the reaction of neopentyl alcohol (Table 1, entry 3). This result can be rationally explained by skeletal migration. Likewise, secondary alcohols such as cyclohexanol and 3-nonanol were also converted into the corresponding alkyl iodides (entries 4 and 5). Alkyl iodides of rearranged carbon skeleton were not detected, and our procedure presents

Scheme 2

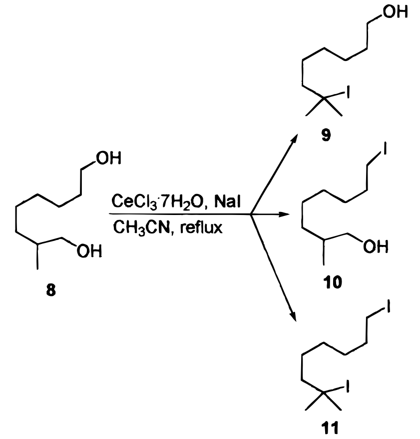


a striking contrast to the reactions of hydrogen iodide[13] with 2-alkanols to produce 2-iodoalkanes because of the competing reduction of alkyl iodide to the alkane.[14]

The reaction of tertiary alcohols presents, instead, the problem of the competing elimination. When 2,3-diphenylbutan-2-ol **2**[15] (Scheme 2) was reacted with the $CeCl_3\cdot7H_2O$/NaI system in refluxing acetonitrile, only alkene **3**[16] was detected in the reaction mixture because of the dehydration of alcohol. Likewise, a β-hydroxy carbonyl compound (**4**) was transformed into the corresponding α,β-unsaturated derivative via dehydration.[17] Interestingly, the reaction of dehydration also occurred when the carbonyl moiety was protected as 1,3-dioxolane (**6**). Very probably the cleavage of acetal[11d] is faster than hydroxyl substitution, and the β-hydroxy ketone intermediate immediately gives the corresponding α,β-unsaturated ketone; nonformation of iodo compound was observed. Analogously to the acetal group, our precedent results[12] have shown that other common functional groups such as trialkylsilyl (R_3Si), methoxymethyl (MOM), and *p*-methoxybenzyl (PMB) are incompatible with the $CeCl_3\cdot7H_2O$/NaI system. On the other hand, we observed that other functional groups, such as tetrahydropyranyl (THP), nitro, and ester functions, are stable under our reaction conditions.

Furthermore, sensitivity to the steric situation around the carbinyl carbon was also observed in the reaction of a primary diol (Scheme 3). Thus, 2-methyl-1,8-octanediol (**8**)[18] gave 7-iodo-7-methyloctan-1-ol (**9**), the product obtained by reaction at the hydroxy group that can generate after rearrangement to the more stable carbocation, in 85% yield, along with 14% of regioisomer (**10**) and 1% of diiodide (**11**).

Scheme 3



The same strategy applied to allylic alcohols led to allylic iodides, nonavailable from commercial sources because of rapid decomposition during storage. Furthermore, it has been observed that the attack of the iodide ion does not involve allylic rearrangement (Table 1, entries 7 and 8). These displacement reactions progressed with retention of stereochemistry without formation of the corresponding Z-isomer. The reaction is believed to proceed via the formation of an intermediate π-allylic cation that takes the more stable E-configuration, followed by attack of the iodide ion. On the other hand, displacement of allylic alcohols containing a terminal double bond gave allylic iodides accompained by allyl rearrangement (Table 1, entry 6). In contrast to our observation, no allylic rearrangement is involved in the displacement reactions using sodium iodide/boron trifluoride etherate.[8b] It is worthwhile to note that if a carbon−carbon triple bond is present in the alcohol substrate, no selectivity was obtained, and the multiple bond was also attacked.

For the mechanism of this transformation of alcohols into iodo compounds we believe that the Lewis acid $CeCl_3$ would give the coordination to alcohol oxygen to form a complexed species that acts as an excellent leaving group. The nucleophilic attack of soft iodide ion to cationic species obtained by dehydration of an oxonium ion intermediate leads to the iodide product.

In conclusion, the present study shows that our procedure may represent a valuable alternative to all of the reagents reported in the literature, to our knowledge, for the conversion of alcohols into iodides. The simplicity of this approach, the low cost of reagents, and the ease of use display the attractiveness of the present method for a wide variety of alcohols. Moreover, the fact that the $CeCl_3\cdot7H_2O$/NaI system is optimal with regard to economic and ecological considerations allows us to believe that this method will find many useful applications in organic synthesis. Further regioselectivity and chemoselectivity in iodination, as well as bromination, using this type of reaction is currently being investigated in our laboratories.

Experimental Section

General Methods. General experimental details are provided as Supporting Information.

Representative Procedure for the Conversion of Benzyl Alcohol to Benzyl Iodide (Table 1, entry 9). To a stirred suspension of benzyl alcohol (**1i**; 0.108 g, 1 mmol) and sodium iodide (0.18 g, 1.2 mmol) in acetonitrile (10 mL) was added cerium(III) chloride heptahydrate (0.56 g, 1.5 mmol), and the resulting mixture was stirred for 20 h at reflux. The reaction progress was monitored by withdrawing aliquots, which were analyzed by GLC, and the products were identified by GC−MS.

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(18) **Preparation of 2-methyl-1,8-octanediol (8):** The DIBAL-H reduction of ϵ-caprolactone followed by Wittig reaction with triethyl 2-phosphono propionate afforded ethyl 8-hydroxy-2-methyl-2-octenoate in 90% yield (two steps). The ester was hydrogenated (Pd/C) and reduced by DIBAL-H to give **8** in 78% yield (two steps).

The reaction mixture was diluted with ether and treated with 0.5 N HCl (15 mL). The organic layer was separated, and the aqueous layer was extracted with ether (4 × 25 mL). The combined organic layers were washed twice with aqueous saturated $NaHCO_3$ solution and saturated NaCl solution and dried over anhydrous Na_2SO_4. The extracts were then concentrated under reduced pressure and the residue chromatographed on a silica gel column (eluent, hexanes–ethyl acetate, 95:5) to give 0.196 g (90% yield) of the corresponding iodide.

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Supporting Information Available: Experimental procedures and spectral data for iodo compounds, not reported previously, designated by their entries in Table 1. This material is available free of charge via the Internet http://pubs.acs.org.

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