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A simple, efficient, and highly selective method for the iodination of alcohols using $ZrCl_4$/NaI

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Abstract—Iodination of primary, secondary, allylic, and benzylic alcohols giving their corresponding iodides was achieved with $ZrCl_4$/NaI in anhydrous CH_3CN with excellent yields and selectivities.

Development of efficient and selective methods for the preparation of halogen-containing compounds, which have extensive applications in organic syntheses, is a worthwhile goal.[1] Halides can be employed in carbon–carbon bond forming reactions.[2] They have also been utilized in nucleophilic reactions for the preparation of amines and ethers and they can be converted into nucleophilic organolithium compounds via halogen–lithium exchange reactions.[3] Among the halides, iodides are the most reactive and in some cases, they show unique reactivity.[4] Iodination of alcohols is the most general protocol for the preparation of alkyl iodides and therefore, this conversion is a frequently encountered transformation in organic synthesis.[5] This transformation is very important in natural product synthesis, where such conversions are usually carried out by a two-step process consisting of transformation of the alcohol to a mesylate followed by displacing the mesyloxy with iodide.[6]

To perform iodination of hydroxyl groups, several methods have been described using a variety of reagent systems such as BF_3–Et_2O/NaI,[7] P_4/I_2,[8] Cl_2SO–DMF/KI,[9] MgI_2,[10] HI,[11] $ClSiMe_3$/NaI,[12] R_3PI_2–Et_2O, or C_6H_6/HMPA,[13] $CeCl_3{\cdot}7H_2O$/NaI,[14] PPh_3/DDQ/$R_4N^+X^-$,[15] KI/$BF_3{\cdot}Et_2O$,[16] PPh_3/DEAD/LiI,[17] and gas-phase reactions using KI in the presence of phase-transfer catalysts,[18] and/or I_2/petroleum ether.[19] NaI/Amberlyst 15 has also been also used for the iodination of a variety of alcohols, except tertiary alcohols in good to excellent yields with some selectivity.[20] Polymer-supported triphenylphosphine/I_2/ImH has also been used for the iodination of benzylic alcohols.[21] However, some of the systems reported suffer from drawbacks such as the presence of hazardous vapor,[7,12,16] danger of explosion (DEAD),[22] low yields,[18,19] long reaction times,[14,19] harsh reaction conditions, non-commercially available materials and tedious work-up procedures.[18] Thus introducing new methods, with higher efficiency and selectivity, less toxicity, which are easier to handle, and using commercially available materials are important. Zirconium salts are known for their low toxicities. For example, the LD_{50} of $ZrCl_4$ supplied orally to rats is $1688\,mg\,Kg^{-1}$.[23] New applications of $ZrCl_4$ in organic synthesis as a catalyst or a reagent were highlighted very recently.[24] We now report that $ZrCl_4$/NaI can be used as an efficient and selective system for the one-pot conversion of structurally diverse alcohols to their iodides with high efficiency and selectivity and with a simple work-up procedure (Scheme 1).

The system works well for the iodination of benzylic alcohols substituted with electron-donating or electron-withdrawing groups in excellent yields. However, the rate of the reaction was faster when the substituted group was an electron-donating group. An allyl alcohol (Table 1, entry 8) was converted into the corresponding

$$\mathrm{ROH} \xrightarrow[\text{anhy. } CH_3CN]{ZrCl_4/NaI} \mathrm{RI}$$

R= alkyl, allyl, benzyl

Scheme 1.

Keywords: Iodination; Zirconium tetrachloride; Alcohols; Sodium iodide.

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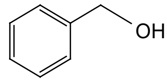
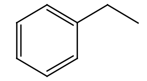
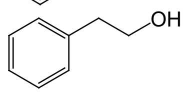
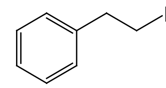
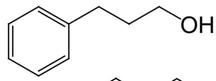
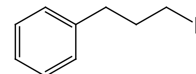
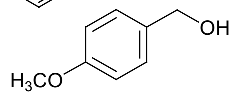
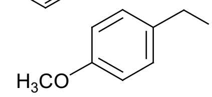
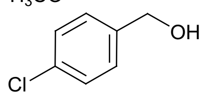
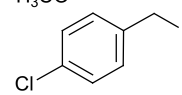
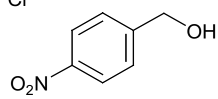
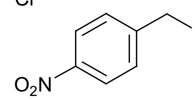
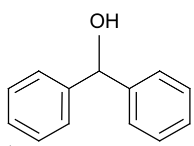
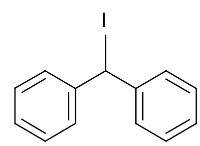
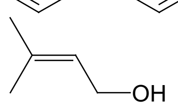
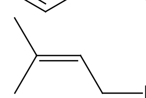
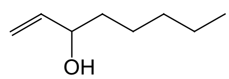
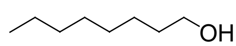
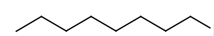
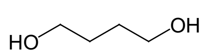
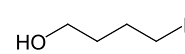
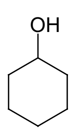
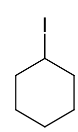
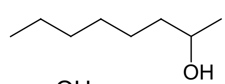
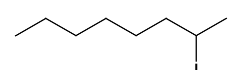
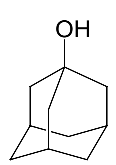
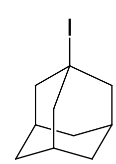
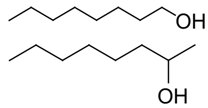
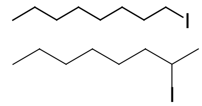
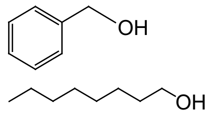
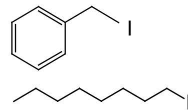
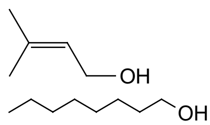
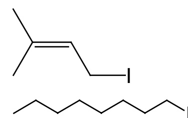
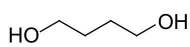
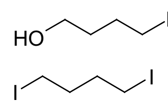
Table 1. Iodination of alcohols using $ZrCl_4$/NaI in anhydrous CH_3CN[a]

Entry	Alcohol	Time (min)[b]	Product[c]	Yield %[d]
1		10		95
2		75		90
3		50		92
4		2		96
5		45		90
6		60		75
7		50		94
8		4		93
9		5		95[e]
10		70		97
11		20		97
12		40		80
13		120		85
14		50		90

[a] The molar ratio of alcohol/NaI/$ZrCl_4$ is 1:1.5:0.5.
[b] All reactions were conducted at reflux except for entries 1, 2, 6, and 7, which were at rt.
[c] All products were identified by spectroscopy and by comparison with known samples.
[d] Yields of isolated products.
[e] *cis* and *trans* isomers not separated.

allylic iodide without rearrangement in high yield, but an allyl alcohol (Table 1, entry 9) with a terminal double bond underwent iodination in an excellent yield but accompanied by allylic rearrangement. The method can be applied easily for the conversion of primary and secondary saturated alcohols into their iodides in excellent yields (Table 1, entries 10–13). We also studied the iodination of 1-adamantanol as an example of a tertiary alcohol. The reaction proceeded smoothly under reflux conditions to give the corresponding iodide in 90% isolated yield (Table 1, entry 14). In order to show the selectivity of the system, a diol (Table 1, entry 11) was converted easily into the mono-iodination product in 97% yield in 20 min, whereas a similar reaction conducted in the presence of $CeCl_3 \cdot 7H_2O$/NaI produced the same product in 83% yield after 48 h.[14] We also tried the reaction of the diol (Table 1, entry11) with excess amounts of $ZrCl_4$ (2 mmol) and NaI (4 mmol) in order

Table 2. $ZrCl_4$/NaI used for selective iodination of different alcohols

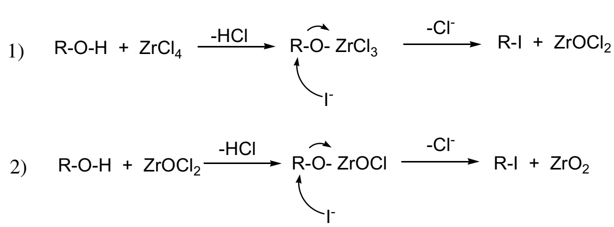
Entry	Alcohols	Products	Time (min)	% Conversion[c]
1[a]			60	85 20
2[b]			10	97 7
3[b]			5	100 15
4[a]			20	100[d] 0

[a] Reactions were conducted at reflux.
[b] Reactions were conducted at room temperature.
[c] GC yield.
[d] ^{1}H NMR yield.

to obtain the corresponding diiodide. However, we observed that a mixture of mono and diiodo compounds were produced after 5h in 70% and 30% yields, respectively.

We have also examined the selectivity of $ZrCl_4$/NaI in several competing reactions between structurally different alcohols. The results for selective iodination reactions are given in Table 2.

It is important to note that the pinkish $ZrCl_4$ should not be used for these reactions. The reactions proceeded sluggishly in the presence of the excess amounts of the pinkish compound. We believe that the pinkish compound is a mixture of $ZrCl_4$, $ZrOCl_2$ and ZrO_2. In these reactions, $ZrCl_4$ is probably converted to ZrO_2 according to the following reaction scheme.



In conclusion, in this study we have introduced a new system for the iodination of structurally diverse alcohols. $ZrCl_4$/NaI conducts the reactions with high yields and selectivity. The low toxicity of $ZrCl_4$, its ease of handling and its commercial availability accompanied with the simple work-up of the reaction mixture are the strong practical points of the presented method.

Typical procedure

To a solution of benzyl alcohol (0.108g, 1mmol) and NaI (0.225g, 1.5mmol) in dry CH_3CN (2mL) was added $ZrCl_4$ (0.116g, 0.5mmol) in several portions (it is very important to note that $ZrCl_4$ with a faint pink hue should not be used).

The mixture was stirred at rt and the progress of the reaction was monitored by TLC or GC. After 10min, the reaction mixture was diluted with ether (10mL) and water (10mL). The organic layer was separated and washed with an aqueous solution of $Na_2S_2O_3$ (10%, 10mL), then H_2O (10mL). The organic layer was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure at rt gave benzyl iodide (0.103g, 95%) of a very high purity.

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