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Efficient and Selective Halogenation of Allylic and Benzylic Alcohols under Mild Conditions

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Summary. A simple, mild, and high yielding procedure for the halogenation of allylic and benzylic alcohols using a combination of $SOCl_2$, benzotriazole, and potassium halides in *DMF* is described. The effectiveness of the protocol is manifested in its selectivity towards allylic and benzylic alcohols whereas other simple alcohols such as primary, secondary, and tertiary are found to be unreactive.

Keywords. Alcohols; Halogenation; Organic fluorides; Bromides; Iodides.

Introduction

Organic halides are indispensable intermediates in organic synthesis and their transformations to useful compounds are well documented [1]. Both organic bromides and iodides are often used in the carbon–carbon bond formation *via* radical or substitution reactions. In addition, they serve as intermediates in a wide variety of reactions and rearrangements. Thus, the conversion of alcohols into the corresponding halides is a very important transformation. The most common precursors to alkyl halides are alcohols and therefore the conversion of alcohols into halides is a frequently encountered transformation in organic synthesis [2]. Among organic halides, iodides are the most reactive, bromides are the moderate reactive, chlorides are less reactive, fluorides are the least reactive, and in some cases, iodides show unique reactivity [3].

As the C–C bond-forming radical reactions of halides are important [4], we were in need of a variety of organic halides. A number of methods for the transformation of alcohols into organic iodides using a variety of reagent systems

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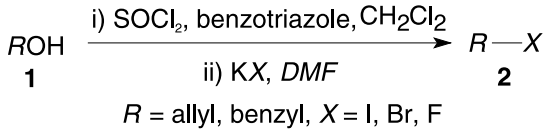


Scheme 1

such as BF_3–Et_2O/NaI [5], P_4–I_2 [6], Cl_2SO–*DMF*/KI [7], MgI_2 [8], HI [9], ClSiMe_3/NaI [10], gas phase reactions using KI in the presence of a phase transfer catalysts [11], and others [12] are available. Organic bromides have been prepared from the corresponding alcohols using various reagents such as HBr/*Ac*OH [13], triphenylphosphine–CBr_4/pyridine [14], *TPP–NBS* [15], *N*,*N*-carbonyldiimidazole-allyl bromide [16], trifluoroacetanhydride–LiBr [17], tetramethyl-Δ-bromoenamine [18], and others [11]. However, very few methods have been reported for the direct conversion of alcohols into the corresponding organic fluorides and some of the reagents known for this transformation are difluorotriphenylphosphorane [19], diethylamino sulfurtrifluoride [20], tetraalkylammonium fluoride [21], and HF/pyridine [22]. The reported procedures for the preparation of organic halides suffer from one or the other drawbacks, such as low yields, long reaction times, use of expensive reagents, drastic reaction conditions, and tedious work-up procedures. We now investigated a novel halogenation method using the inexpensive, safe, and easily available reagent $SOCl_2$–benzotriazole [23], and KI, KBr, or KF in *DMF*, which transforms allylic and benzylic alcohols into the corresponding organic iodides, bromides, and fluorides (Scheme 1).

Results and Discussion

We first tried this reagent system on benzyl alcohol, which afforded benzyl iodide in 97% within 10 minutes at room temperature (entry 1). This reagent system also worked well for the preparation of benzyl bromides and fluorides (entries 2–3). Subsequent scrutiny showed that this reagent system is suitable for a variety of allylic and benzylic alcohols and culminated into a simple and mild procedure for the conversion of alcohols into organic iodides, bromides, and fluorides (entries 4–24). The methodology worked well with *ortho*, *meta*, *para*, and multi-substituted benzylic systems (entries 4–24) containing electron-donating or -withdrawing substituents furnishing excellent yields of products. It also worked well for allylic alcohols (entries 25–27) giving high yields of the corresponding iodides and bromides, whereas fluorides were obtained in poor yields. It was observed that the iodination and bromination reactions were fast as compared to chlorination of allylic and benzylic alcohols. It is important to note that though simple primary, secondary, and tertiary alcohols remain unreacted (entries 34–45), homoallylic secondary and tertiary alcohols (entries 28–33) underwent smooth halogenation under these reaction conditions. Finally we tried a 20 mmol scale-up of the iodination reaction. Thus, 4-chlorobenzyl alcohol furnished the corresponding iodide in almost quantitative yield (99%) after usual work-up.

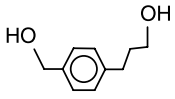
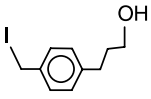
Excellent selectivities were observed during inter- and intra-molecular competition between benzylic and aliphatic alcohols. Thus, during intramolecular

Table 1. Halogenation of alcohols using $SOCl_2$, benzotriazole in CH_2Cl_2, and KI/KBr/KF in *DMF*

Entry	Substrate	Product	Time min (h)	Yield[a] %
1	Benzyl alcohol	Benzyl iodide	10	97
2	Benzyl alcohol	Benzyl bromide	30	99
3	Benzyl alcohol	Benzyl fluoride	(10)	82
4	4-Bromobenzyl alcohol	4-Bromobenzyl iodide	6	96
5	4-Bromobenzyl alcohol	4-Bromobenzyl bromide	13	90
6	4-Bromobenzyl alcohol	4-Bromobenzyl fluoride	(10.5)	62
7	4-Chlorobenzyl alcohol	4-Chlorobenzyl iodide	5	99
8	4-Chlorobenzyl alcohol	4-Chlorobenzyl bromide	16	99
9	4-Chlorobenzyl alcohol	4-Chlorobenzyl fluoride	(10)	70
10	2,4-Dichlorobenzyl alcohol	2,4-Dichlorobenzyl iodide	8	98
11	2,4-Dichlorobenzyl alcohol	2,4-Dichlorobenzyl bromide	5	91
12	2,4-Dichlorobenzyl alcohol	2,4-Dichlorobenzyl fluoride	(9)	71
13	4-Methoxybenzyl alcohol	4-Methoxybenzyl iodide	30	85
14	4-Methoxybenzyl alcohol	4-Methoxybenzyl bromide	50	79
15	4-Methoxybenzyl alcohol	4-Methoxybenzyl fluoride	(12)	78
16	3,4-Methylenedioxybenzyl alcohol	3,4-Methylenedioxybenzyl iodide	6	96
17	3,4-Methylenedioxybenzyl alcohol	3,4-Methylenedioxybenzyl bromide	13	90
18	3,4-Methylenedioxybenzyl alcohol	3,4-Methylenedioxybenzyl fluoride	(10.5)	70
19	6-Chloro-3,4-methylenedioxybenzyl alcohol	6-Chloro-3,4-methylenedioxybenzyl iodide	6	96
20	6-Chloro-3,4-methylenedioxybenzyl alcohol	6-Chloro-3,4-methylenedioxybenzyl bromide	13	90
21	6-Chloro-3,4-methylenedioxybenzyl alcohol	6-Chloro-3,4-methylenedioxybenzyl fluoride	(10.5)	62
22	4-Nitrobenzyl alcohol	4-Nitrobenzyl iodide	45	97
23	4-Nitrobenzyl alcohol	4-Nitrobenzyl bromide	50	91
24	4-Nitrobenzyl alcohol	4-Nitrobenzyl fluoride	(11)	63
25	Cinnamyl alcohol	Cinnamyl iodide	(1)	98
26	Cinnamyl alcohol	Cinnamyl bromide	(4)	92
27	Cinnamyl alcohol	Cinnamyl fluoride	(8)	25
28	4-(4-Chlorophenyl)-4-hydroxy-1-butene	4-(4-Chlorophenyl)-4-iodo-1-butene	(6)	84
29	4-(4-Chlorophenyl)-4-hydroxy-1-butene	4-(4-Chlorophenyl)-4-bromo-1-butene	(8)	81
30	4-(4-Chlorophenyl)-4-hydroxy-1-butene	4-(4-Chlorophenyl)-4-fluoro-1-butene	(18)	23
31	4-(4-Chlorophenyl)-4-hydroxy-1-pentene	4-(4-Chlorophenyl)-4-iodo-1-pentene	(8)	82
32	4-(4-Chlorophenyl)-4-hydroxy-1-pentene	4-(4-Chlorophenyl)-4-bromo-1-pentene	(11)	80
33	4-(4-Chlorophenyl)-4-hydroxy-1-pentene	4-(4-Chlorophenyl)-4-fluoro-1-pentene	(24)	00
34	1-Octanol	1-Iodo octane	(24)	00
35	1-Octanol	1-Bromo octane	(24)	00
36	1-Octanol	1-Fluoro octane	(24)	00
37	2-Isopropyl-5-methylcyclohexanol	2-Isopropyl-5-methyl iodocyclohexane	(24)	00
38	2-Isopropyl-5-methylcyclohexanol	2-Isopropyl-5-methyl bromocyclohexane	(24)	00
39	2-Isopropyl-5-methylcyclohexanol	2-Isopropyl-5-methyl fluorocyclohexane	(24)	00
40	Triphenylmethanol	Triphenyliodomethane	(24)	00
41	Triphenylmethanol	Triphenylbromomethane	(24)	00
42	Triphenylmethanol	Triphenylfluoromethane	(24)	00

(*continued*)

Table 1 (*continued*)

Entry	Substrate	Product	Time min (h)	Yield[a] %
43	1,10-Didecanol	1,10-Diiododecane	(24)	00
44	1,10-Didecanol	1,10-Dibromodecane	(24)	00
45	1,10-Didecanol	1,10-Difluorodecane	(24)	00
46			25	90
47	4-Chlorobenzyl alcohol + 1-Hexanol	4-Chlorobenzyl iodide + 1-Hexanol	5	85 + 97
48	Cinnamyl alcohol + Cyclohexanol	Cinnamyl iodide + Cyclohexanol	(1)	93 + 98

[a] Yields of pure isolated products

competition (entry 46) benzylic alcohol selectively underwent iodination in the presence of aliphatic primary alcohol. Similarly, when a equimolecular mixture of 4-chlorobenzyl alcohol and l-hexanol (entry 47) is subjected to iodination, selectively 4-chlorobenzyl alcohol underwent iodination in excellent yield whereas 1-hexanol remained unreacted. Selective iodination of cinnamyl alcohol in the presence of cyclohexanol (entry 48) was also observed under these reaction conditions. Recently, $SOCl_2$–benzotriazole has been reported [23] as highly efficient reagent for rapid conversion of alcohols into the corresponding chlorides. Therefore, this procedure has been applied for the preparation of bromides, iodides, and fluorides. The alcohols might be first converted into the corresponding chlorides, which further underwent smooth bromination, iodination and flourination with KBr, KI and KF involving SN_2 mechanism.

In conclusion, the present method shows unique selectivity and constitutes a useful alternative to commonly accepted halogenation procedures of alcohols. Moreover, the superiority and flexibility of the protocol lies in its ease of operation and simplicity in work-up. Efficient, and high yielding procedure applicable to allylic, benzylic, and homoallylic alcohols under mild conditions using the inexpensive and easily available reagent system make this simple protocol economically attractive. In addition, this method is amenable to scale-up.

Experimental

IR spectra were recorded on Bomem MB-104 FTIR spectrometer, whereas ^1H NMR were scanned on a AC-300F NMR (300 MHz) instrument using $CDCl_3$ as solvent and *TMS* as internal standard.

Typical Procedure

A mixture of 5 mmol of benzyl alcohol, 5.5 mmol of thionyl chloride, and 5 mmol of benzotriazole in 10 cm^3 of CH_2Cl_2 was stirred for 5 min. Then to this mixture 5 mmol of KI in 10 cm^3 of *DMF* were added and stirring was continued until the reaction was complete (TLC, 10 min). The product was extracted with 3×10 cm^3 of ether, washed with 3×5 cm^3 of aq. sodium thiosulfate (5%), and 3×10 cm^3 of H_2O. The organic layer was dried with Na_2SO_4 and the solvent removed under reduced

pressure to furnish the crude product, which was purified by column chromatography (pet. ether). The products were characterized by IR, NMR, elemental analysis, and comparison with authentic samples.

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