Organic Process Research & Development **2002**, *6,* 190–191

A Simple and Efficient Iodination of Alcohols on Polymer-Supported Triphenylphosphine

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Abstract:

A simple, mild, and high-yielding procedure for the iodination of allylic, benzylic, and other primary alcohols using a combination of iodine and imidazole on polymer-supported triphenyl phosphine is described.

Organic halides are indispensable intermediates in organic synthesis, and their transformations to useful compounds are well documented in the literature.[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 the frequently encountered transformation in organic synthesis.[2] Among the halides, iodides are the most reactive, and in some cases, iodides show unique reactivity.[3]

In continuation of our studies on the C−C bond-forming radical reactions of halides,[4] we were in need of a variety of organic halides, especially iodides. A number of methods for the transformation of alcohols into alkyl iodides using a variety of reagent systems such as BF_3-Et_2O/NaI,[5,6] P_4/I_2,[7] Cl_2SO-DMF/KI,[8] MgI_2,[9] HI,[10] $ClSiMe_3$/NaI,[11] R_3PI_2-Et_2O, or C_6H_6/HMPA[12] and gas-phase reactions using KI in the presence of phase-transfer catalysts[13] are reported in the literature. The reported procedures suffer from one or the other drawbacks such as low yields,[14] long reaction times,[15] drastic reaction conditions and tedious work-up[13] procedure. Moreover, in all these reports, the product has to be purified by column chromatography. The most recent reports in these lines are also not devoid of limitations such as long reaction time, refluxing temperature (CH_3CN), or chromatographic purification of the product.[16,17] Although some scant reports using polymer-supported triphenyl phosphine−iodine complex[18] have been reported for the conversion of some α-amino acids[19] and sugars[20] into the corresponding iodides, no work directed towards the synthesis of organic iodides from alcohols using the $Ph_3P{-}I_2$ complex on polymer support has been reported.[21] We now investigated a novel iodination method using iodine, imidazole, and polymer-supported triphenylphosphine in anhydrous dichloromethane, which transforms the alcohols into iodides. We first tried this reagent system on benzyl alcohol, which afforded benzyl iodide in 97% yield within 15 min at room temperature. Subsequent scrutiny showed that the reagent system is suitable for a variety of alcohols and culminated into a simple and mild procedure for the conversion of alcohols into iodides; the latter was obtained in pure form by simple filtration.[22] Thus, benzylic, allylic, and primary alcohols undergo smooth transformation to the corresponding iodides in excellent yields at room temperature.[23]

Among the various solvents tried, dichloromethane was found to be the solvent of choice.[24] The products were isolated after filtration of the polymer-bound phosphine oxide

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(22) In the case of certain aliphatic alcohols (entries 15 and 16) showing low reactivity, filtration of the reaction mixture through a small plug of silicagel was necessary to get pure product. The purity of the products was determined by ^1H NMR or GC analysis and was found to be greater than 95%.

10.1021/op010094c CCC: $22.00 © 2002 American Chemical Society
Published on Web 01/25/2002

and subsequent aqueous work-up of the filtrate. In almost all cases we studied, pure compounds were obtained without chromatographic purification.[22] The reaction works well with ortho, meta, para, and multisubstituted benzylic systems (See entries 2−13 in the table) containing electron-donating or -withdrawing substituents in excellent yields. It also works well for allylic systems (entries 14−16) and simple alcohols (entries 17−19). The latter examples will be useful in natural product synthesis, where such conversions are usually carried out by a two-step process consisting of transformation of the alcohol to mesylate followed by displacing the mesyl group with iodide.[25,26]

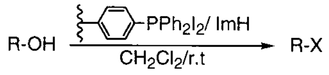
To test the scope and limitations of this methodology, we applied the reaction conditions to secondary alcohols. In such cases, the reaction was found to be slow, and chromatographic purification of the product was necessary to obtain pure compounds. Alternatively, an unsupported Ph_3P/I_2/imidazole reagent system is suggested for such transformations (Table 1, entry 20).

Next, we tried to employ this reagent system in bromination by replacing the iodine with bromine. Although the reaction took more time for its completion, it gave the required bromide in excellent yield (entry 21), showing that the methodology is equally good for bromination. For chlorination, *N*−chlorosuccinimide (NCS) was used instead of Cl_2 and afforded the chloride in high yield after slightly longer reaction time (entry 22).

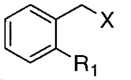
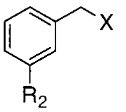
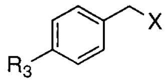
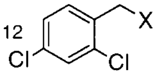
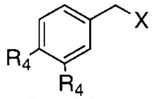
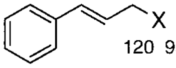
Finally, we tried a 23 mmol scale-up of the iodination reaction. Thus, the alcohol **10** (23 mmol) on treatment with iodine (30 mmol) and imidazole (30 mmol) using 10 g (30 mmol) of polymer-supported triphenylphosphine in dichloromethane (150 mL) gave the corresponding iodide in almost quantitative yield (98%) after work-up. Since the reaction was found to be mildly exothermic, during scale-up, the reaction was initially cooled using a water bath to avoid any possible temperature rise.

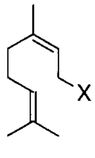
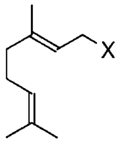
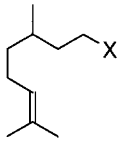
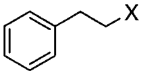
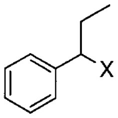
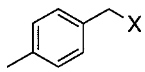
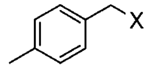
In conclusion, we have demonstrated a simple, general, mild, and high-yielding iodination procedure applicable to allylic, benzylic, and other primary alcohols using a combination of polymer-supported Ph_3P, imidazole, and iodine in dichloromethane at room temperature. The method is amenable to scale-up. Moreover, the methodology is extendable to bromination and chlorination of alcohols by replacing I_2 with Br_2 and NCS, respectively. It is well documented in the literature[27,28] that the polymer-supported phosphine oxide formed in the reaction can be reduced to the original phosphine without much loss of activity by trichlorosilane using the procedure of Regen and Lee.[28]

Table 1. **Iodination of alcohols using polymer-supported $Ph_3P/I_2/ImH$**



R = allylic, benzylic or other 1° group
X = I, Br, Cl

Entry	Substrate (X = OH)	Time (Min)	Product (X = I) Yield(%)
1	 R_1 = H	15	97
2	R_1 = CH_3	15	95
3	R_1 = Br	15	95
4	R_1 = OCH_3	15	96
5	R_1 = CH_2X	15	92
6	 R_2 = OCH_3	15	96
7	R_2 = Br	15	97
8	R_2 = NO_2	15	98
9	R_2 = CN	15	98
10	 R_3 = CH_3	15	97
11	R_3 = OCH_3	15	92
12		15	97
13	 R_4 = OCH_3	15	95
14		120	95

Entry	Substrate (X = OH)	Time (Min)	Product (X = I[a,b]) Yield(%)[c]
15		120	91[d]
16		120	88[d]
17		45	93
18	$CH_3(CH_2)_9X$	90	91
19		30	96
20		15	93[e,f]
21		30	96
22		[g]	90[f]

[a] For entry 21, X = Br; Br_2 was used instead of I_2. [b] For entry 22, X = Cl; NCS was used instead of ImH/I_2. [c] Isolated yield. [d] Filtered through a small plug of silica. [e] Unsupported Ph_3P/ImH/I_2 was used. [f] Purified by column chromatography. [g] The reaction mixture was stirred for 24 hours.

The present study represents a very useful methodology for iodination of alcohols of the type shown. The simplicity of this approach combined with the applicability to a wide variety of alcohols and the avoidance of chromatographic purification of the product makes it more attractive.

Acknowledgment

G.A. thanks the Japan Society for the Promotion of Science (JSPS) for financial support.

Received for review October 8, 2001.

OP010094C

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(23) Typical procedure: To a suspension of polystyryldiphenyl phosphine (1.3 mmol) in anhydrous dichloromethane (10 mL) at room temperature was added imidazole (1.3 mmol) and iodine (1.3 mmol) and stirred for approximately 5 min. The alcohol (1 mmol) was then added to the reaction mixture and stirred at the same temperature. After the complete conversion of the alcohol (monitored by TLC), the reaction mixture was filtered and washed with moist CH_2Cl_2. The filtrate was then sequentially washed with aqueous thiosulfate solution and water, dried by the use of anhydrous sodium sulfate, and concentrated to obtain the iodide.[29] For scale-up reactions, it is necessary to cool the reaction using a water bath to avoid any rapid temperature rise.

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(29) All compounds described are reported in the literature and are characterized by spectroscopic data.