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Conversion of alcohols to bromides using a fluorous phosphine

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Abstract—Reaction of alcohols with the fluorous phosphine–carbon tetrabromide complex in toluene or in a two-phase toluene-FC-72 system afforded the corresponding bromides in good yields. The fluorous-phosphine oxide is readily separated by liquid–liquid extraction, providing an alternative to the homogeneous triphenylphosphine–carbon tetrachloride conversion, as well as to the polymer-supported phosphine method. The fluorous phosphine oxide could be reduced and the product reused.
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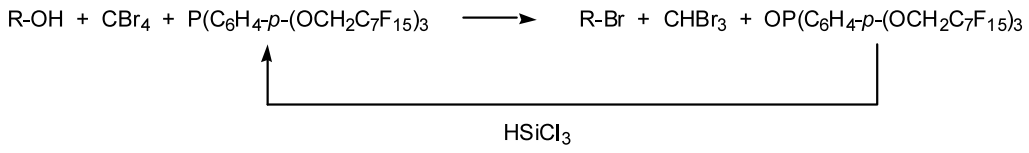
The conversion of alcohols to halides is a well-documented transformation.[1] One of the most widely used reagents is the triphenylphosphine–carbon tetrabromide complex.[2] However, one of the main drawbacks of this reagent is the formation of a stoichiometric amount of triphenylphosphine oxide; the work-up of the reaction is sometimes problematic due to the difficulty in completely removing this oxide from the reaction products. Different approaches have been developed in order to circumvent this problem and to find new technologies for cleaner synthesis of bromides. One solution is the use of polymer-supported triphenylphosphine.[3] Recently Pollastri et al. used diphos as the phosphine;[4] performing the reaction in THF allowed the complete conversion of the alcohol to the corresponding bromide, with the subsequent precipitation of the diphos oxide which was readily removed by simple filtration.

Since the pioneering work of Horvath and Rabai in 1994,[5] fluorous biphasic chemistry has found many applications in the field of catalysis, as well as in organic chemistry. This is due mainly to the easy purification or removal of fluorous compounds by a simple liquid–liquid extraction or a liquid–solid separation. Among the most recent reagents used in organic synthesis are fluorous tin hydrides,[6] fluorous allyltin reagents,[7] fluorous organoselenium reagents,[8] fluorous phosphines,[9] fluorous DEAD reagents,[10] as well as fluorous-protecting groups.[11]

Following our interest in the use of fluorous phosphines as reagents for cleaner synthesis,[9c] we present in this communication their application in the conversion of alcohols to bromides using the fluorous triphenylphosphine–carbon tetrabromide system in stoichiometric amounts (Scheme 1). In order to show the usefulness of this methodology, the reaction of various alcohols with CBr_4 in the presence of tris[4-(1*H*,1*H*-perfluorooctyloxyphenyl)]phosphine[12] was performed in a monophasic system using toluene as the solvent, and in the biphasic system toluene-FC-72 (FC-72 being a mixture of fluorous hexanes). As a reference, the reaction was also performed in toluene using CBr_4/PPh_3 using exactly the same conditions. Some results using typical alcohols are shown in Table 1. We chose toluene as the non-fluorous solvent since the highest conversion of octanol to octyl bromide with PPh_3/CBr_4 was obtained



Scheme 1.

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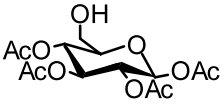
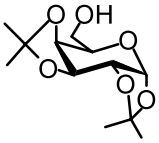
Table 1. Conversion of alcohols to bromides using CBr_4–fluorous triphenylphosphine[a]

Entry	Alcohol	Toluene		Toluene/FC-72	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1	*n*-C_7H_{15}-CH_2OH	4 (4)[b]	75 (81)[b]	4	79
2	$C_6H_{13}CHOHCH_3$	4 (4)[b]	54 (60)[b]	4	100
3	$(C_2H_5)_3COH$	7 (7)[b]	56 (62)[b]	7	59
4		4 (4)[b]	100 (100)[b]	4	100
5		7 (7)[b]	53 (71)[b]	7	76
6		7 (7)[b]	48 (61)[b]	7	40

[a] Conversion determined by GC for entries 1-4 and by ^1H and ^{13}C NMR for entries 5-6. [b] Time and conversion using PPh_3 as the phosphine.

using this solvent: 60, 32 and 53% conversions were observed using toluene, acetonitrile, and diethyl ether (reflux, 4 h), respectively.

The results contained in Table 1 indicated that bromination occurred efficiently at 50°C using toluene or the two-phase toluene-FC-72 as the solvent.[13] The conversion of a primary alcohol such as octanol (entry 1), or a tertiary alcohol such as triethylcarbinol (entry 3), to the corresponding bromide was the same, whatever the conditions used. The conversion obtained using the fluorous phosphine in toluene or in the two-phase system toluene-FC-72 competed well with the usual reagent PPh_3–CBr_4 in toluene. Surprisingly, the conversion of octan-2-ol (entry 2) was almost quantitative using the biphasic system, but only 54 and 60% in toluene using the fluorous and the non-fluorous phosphine, respectively.

Bromination of (*R*)-menthol (entry 4) afforded the corresponding bromide quantitatively, whatever the conditions used. This bromide exhibited a specific rotation of approximately $[\alpha]_D^{25} = +60$ (*c* 1.2, C_2H_5OH), corresponding to the (*S*)-enantiomer;[14] as expected the bromination occurred with complete inversion of configuration.

This bromination procedure was also extended to two carbohydrates, namely 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (entry 5) and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (entry 6). The corresponding bromides were obtained, although in moderate yields, possibly due to the lower accessibility of the hydroxyl function at position C-6 of these carbohydrates.

As expected, the advantage of this methodology is the very easy separation of the fluorous phosphine oxide from the reaction products. At the end of the reaction, the mixture was cooled and extracted twice with FC-72. Evaporation of the fluorous solvent gave more than 85% of the starting phosphine oxide which was readily reduced quantitatively to the fluorous phosphine,[12] and so could be reused. It is to be noted that no traces of phosphine oxide could be detected in the bromide, by NMR.

In conclusion, bromination of alcohols using fluorous phosphine-CBr_4 as the reagent can be easily performed in toluene or in a two-phase toluene-FC-72 system. This method offers a very attractive procedure for the separation of the resulting bromide from the phosphine oxide by a simple liquid–liquid extraction, and is an alternative to the standard triphenylphosphine–carbon tetrabromide conversion, as well as to the polymer supported phosphine reagents. This fluorous phosphine oxide could also be recycled, after reduction.

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13. *Experimental procedure*: In a Schlenk tube under argon containing toluene (6 mL) or a 1:1 toluene/FC-72 mixture (4 mL), were added tris[4-(1*H*,1*H*-perfluorooctyl-oxyphenyl)]phosphine (400 mg, 0.28 mmol), and CBr_4 (94 mg, 0.28 mmol). To this solution was added the alcohol (0.28 mmol), and the mixture was stirred at 50°C for the desired time. The solution was cooled to rt, and the fluorous-phosphine oxide was extracted with FC-72 (4×2 mL). Evaporation of the hydrocarbon phase gave the bromide, and evaporation of the fluorous phase gave the fluorous–phosphine oxide.
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