

Facile conversion of alcohols into their bromides and iodides by *N*-bromo and *N*-iodosaccharins/triphenylphosphine under neutral conditions

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Abstract—*N*-Bromo and *N*-iodosaccharins in the presence of triphenylphosphine convert alcohols into the corresponding bromides and iodides in good to excellent yields at room temperature under neutral conditions.

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1. Introduction

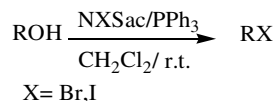
Organic halides are indispensable intermediates in organic synthesis, and their transformations to useful compounds are well documented in the literature.¹ They are often used in carbon–carbon bond formation via radical or substitution reactions.² In addition, they serve as intermediates in a wide variety of reactions and rearrangements.³ The most common and cheap precursors of alkyl halides are alcohols. The Mitsunobu reaction⁴ has been widely applied for the conversion of alcohols into the corresponding halides.⁵ The key compound in this reaction is diethyl azodicarboxylate (DEAD), which is used in combination with Ph₃P. DEAD is potentially an explosive compound and expensive. It irritates mucous membranes and is toxic. It may also cause cancer or mutation. For these reasons, the production and uses of DEAD are rather limited. In addition, the workup and purification of the product using this reaction is a tedious and time-consuming process.⁶ In order to modify this method, other reagent systems such as triphenylphosphine in combination with bromine,⁷ carbon-tetrahalides,⁸ 4-methyl-1,2,4-triazolidine-3,5-dione (MTAD),⁹ 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TAPCO)¹⁰ and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)¹¹ or tributylphosphine in combination with 1,1'-(azodicarbonyl)dipiperidine (ADDP)¹² have been introduced. Tributylphosphine is stable, but pyrophoric being spontaneously inflammable in air and is incompatible with

oxidizing agents and moisture sensitive compound.¹³ *N*-Halosuccinimides in combination with Ph₃P in DMF have also been used for this purpose.¹⁴

Saccharin is a cheap and easily available compound, used as a sweetening agent in the food and drug industries.¹⁵

A search of the literature showed that *N*-halosaccharins have been used as oxidants¹⁶ and as halogenating agents for alkenes, activated aromatic compounds, enol acetates, 1,3-diones, etc.¹⁷ *N*-Halosaccharins, which are simply prepared by halogenation of saccharin,¹⁸ are more electrophilic than, for example, *N*-halosuccinimides.^{18a,19} Therefore, it would be expected that the interaction of Ph₃P with *N*-halosaccharins would generate phosphonium halides as reactive phosphonium species in Mitsunobu reactions.

We report that *N*-bromosaccharin and *N*-iodosaccharin in combination with Ph₃P are highly reactive reagents for the conversion of hydroxyl compounds to the corresponding bromides and iodides using CH₂Cl₂ as the solvent at room temperature under neutral conditions (Scheme 1).



Scheme 1.

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Table 1. Conversion of alcohols into their bromides and iodides with NXSac/PPh₃

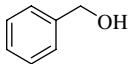
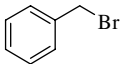
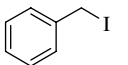
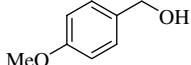
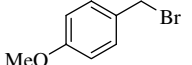
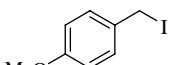
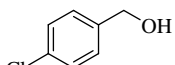
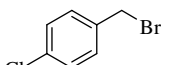
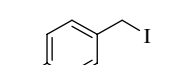
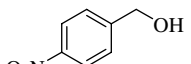
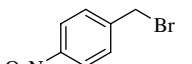
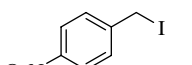
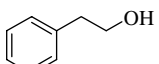
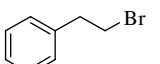
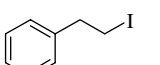
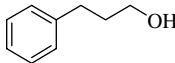
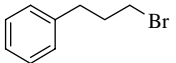
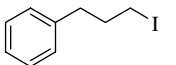
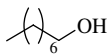
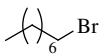
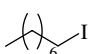

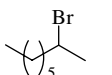
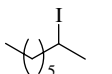

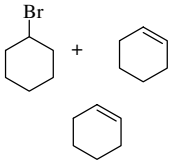
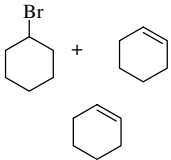
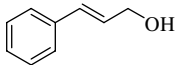
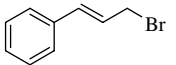
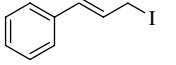
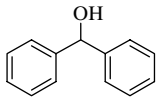
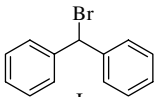
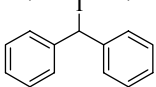



Entry	Alcohol	Product	Time (min)	Yield ^a (%)
1			Immediately	90
			15	90
2			Immediately	92
			5	90
3			5	87
			60	90
4			10	91
			60	85 ^b
5			15	92
			30	95
6			25	87
			35	90
7			15	92
			120	86
8			30	93
			5 h	90
9			10	45+55 ^c
			Immediately	100 ^{c,d}
10			35	90
			40	90

Table 1 (continued)

Entry	Alcohol	Product	Time (min)	Yield ^a (%)
11			75	90
			120	80 ^b
12			175	85 ^b
			270	80 ^b

^a Isolated yield.

^b Reaction performed in CH₃CN under reflux.

^c Determined by GC.

^d Reaction with NIS/PPh₃.

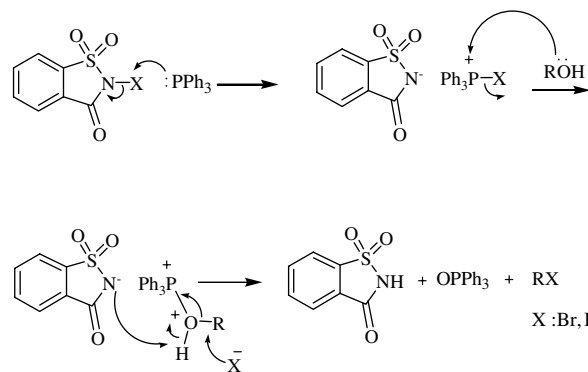
In order to optimize the reaction conditions, we first examined the effect of different ratios of *N*-bromo- and *N*-iodosaccharins/triphenylphosphine in CH₂Cl₂ at room temperature for the conversion of *n*-octanol as a model compound to *n*-octyl bromide and *n*-octyl iodide. We found that the optimized molar ratio for the quantitative conversion (GC) of *n*-octanol to *n*-octyl bromide was 1/2/2 (*n*-octanol/*N*-bromosuccinimide/PPh₃) and for the iodination of *n*-octanol to *n*-octyl iodide was 1/2.5/2.5. This method is general and can be easily applied for the conversion of primary, secondary, tertiary, benzylic and allylic alcohols to their halides using the optimized ratios of *N*-halosaccharins and Ph₃P (Table 1). Although, the ability of *N*-bromosaccharin to oxidize alcohols¹⁶ has been demonstrated, in all the cases we studied, no oxidation products were observed.

We found that when cyclohexanol reacted with NBSac/PPh₃, in addition to the formation of cyclohexyl bromide in 45% yield cyclohexene was also produced in 55% yield (GC) at room temperature (Table 1, entry 9). In the case of NISac/PPh₃, cyclohexene (GC) was produced as the sole product under similar reaction conditions.

The reaction works well for benzylic alcohols substituted with electron-donating or -withdrawing groups giving the corresponding halides in excellent yields at room temperature in CH₂Cl₂ (Table 1, entries 1–4). However, reactions of benzyl alcohols substituted with electron-donating groups were faster. We found that the bromination and iodination of 1-adamantol did not proceed well in CH₂Cl₂ even under reflux. However, in refluxing CH₃CN, the reaction proceeded smoothly and the corresponding bromide and iodide were isolated in 85% and 80% yields, respectively (Table 1, entry 12).

A reaction pathway is proposed (Scheme 2).

In order to show the selectivity of the method, we studied the selected bromination of different alcohols



Scheme 2.

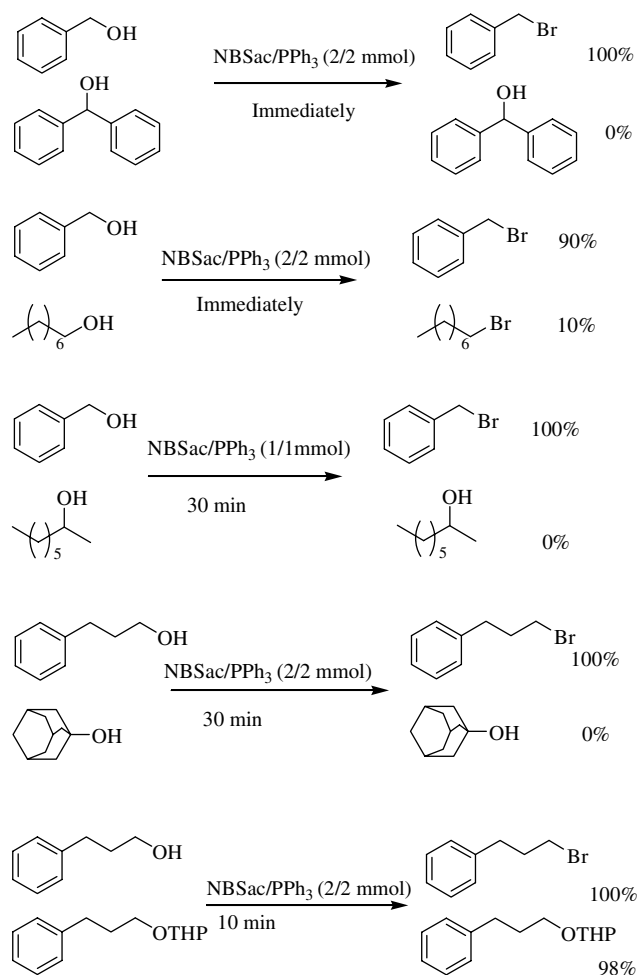
in binary mixtures (Scheme 3, entries 1–4). A tetrahydropyranyl ether (Scheme 3, entry 5) was stable under the reaction conditions.

In conclusion, we have introduced a new reagent system for the conversion of alcohols to the corresponding bromides and iodides under mild and neutral conditions. We have also shown the selective bromination of different alcohols in binary systems.

2. Experimental

2.1. Benzyl bromides from benzyl alcohol using NBSac/PPh₃: typical procedure

To a mixture of NBSac (0.522 g, 2 mmol) and PPh₃ (0.521 g, 2 mmol) in dry CH₂Cl₂ (25 mL) was added benzyl alcohol (0.11 g, 1 mmol) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (Table 1, entry 1), the solvent was evaporated. Column chromatography of the crude mixture on silica gel using hexane/EtOAc (1/5) gave the desired bromide in 0.15 g, 90% yield.



Scheme 3.

2.2. Benzyl iodides from benzyl alcohol using NISac/PPH₃: typical procedure

To a mixture of NISac (0.79 g, 2.5 mmol) and PPh₃ (0.65 g, 2.5 mmol) in dry CH₂Cl₂ (25 mL) was added benzyl alcohol (0.11 g, 1 mmol) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (Table 1, entry 1), the solvent was evaporated. Column chromatography of the crude mixture on silica gel using hexane/EtOAc (1/5) gave the desired iodide in 0.19 g, 90% yield.

Acknowledgement

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