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N,N,N′,N′-Tetrahalobenzene-1,3-disulfonamide/PPh_3 as an Efficient System for the Preparation of Alkyl Halides

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N,N,N′,N′-Tetrabromobenzene-1,3-disulfonamide (TBBDA)/PPh_3 and *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide (TCBDA)/PPh_3 are two highly reactive reagent systems for the conversion of alcohols corresponding into alkyl chlorides and bromides in moderate to excellent yields in dichloromethane at room temperature under mild and neutral conditions.

Key Words : Alcohol, Alkyl halide, *N,N,N′,N′*-Tetrabromobenzene-1,3-disulfonamide (TBBDA), *N,N,N′,N′*-Tetrachlorobenzene-1,3-disulfonamide (TCBDA), Triphenylphosphine (PPh_3)

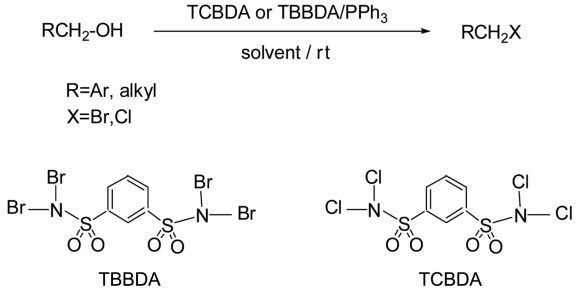
Introduction

The conversion of alcohols to the corresponding alkyl halides is one of the important transformations in organic synthesis. Alkyl halides are versatile synthetically intermediates that can easily be converted into a variety of other functional groups. Alkyl chlorides classically are prepared by the reaction of alcohols with chlorinating agents such as $SOCl_2$, $POCl_3$, PCl_5[1-3] and TCT/DMF[4] or combined systems of PPh_3 with CCl_4,[5] Cl_3CCCl_3,[6] $Cl_3CCOCCl_3$,[7] Cl_3CCN,[8] Cl_3CCONH_2,[9] and TCCA.[10] Similarly, alkyl bromides can be synthesized by using $POBr_3$,[11] PBr_3[12] or combined systems of PPh_3 with bromosaccharin (NBSac),[13] Br_3CCO_2Et,[14] $Br_3CCOCBr_3$,[15] CBr_4[16] and HCl/$ZnCl_2$[17] are used as brominating agents. Some of above mentioned procedures suffer from several drawbacks such as tedious work-up procedure, low yields of products, expensive reagents and catalysts.

Triphenylphosphine is a fairly general reducing agent and its reactions with selected oxidants can lead to the formation of phosphonium intermediates. Phosphorus in these intermediates is positively charged and its reaction as a strong oxophilic reagent in most cases is driven by the formation of thermodynamically favoured triphenylphosphine oxide.[18]

N,N,N′,N′-Tetrabromobenzene-1,3-disulfonamide [TBBDA] and *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide [TCBDA] are efficient halogenating agents.[19m,o] These compounds are effective catalysts and reagents for various organic transformations.[19] Since TBBDA and TCBDA contain halogen atoms which are attached to nitrogen atoms. It is possible they release *in situ* X^+ which can act as an electrophilic species. Therefore, it would be expected that the interaction of PPh_3 with TBBDA or TCBDA generates phosphonium halides as reactive phosphonium species in Mitsunobu reactions.

On this basis and continuing our recent interests in the application of *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide and *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide in organic synthesis,[19] we report that *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide and *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide in combination with PPh_3 are highly reactive media for the conversion of alcoholic compounds to the corresponding alkyl bromides and chlorides in solvent at room temperature under neutral conditions (Scheme 1).



Scheme 1

In order to optimize the reaction conditions, we first examined the effects of different molar ratios of *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide (TBBDA)/triphenylphosphine in CH_3CN as solvent or *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide (TCBDA)/triphenylphosphine in CH_2Cl_2 as solvent at room temperature for the conversion of 4-chlorobenzyl alcohol to 4-chlorobenzyl bromide and 4-chorobenzyl chloride as model reaction. We found that the optimized molar ratio for the conversion of 4-chlorobenzyl alcohol to 4-chlorobenzyl chloride was 1/0.55/2 (4-chlorobenzyl alcohol/TCBDA/PPh_3) and for the bromination of 4-chlorobenzyl alcohol to 4-chlorobenzyl bromide was 1/0.55/2 (4-chorobenzyl alcohol/TBBDA/PPh_3). This method is general and can be easily applied for the conversion of a variety of primary, secondary, benzylic and allylic alcohols to their corresponding alkyl halides using TCBDA and/or TBBDA with PPh_3 (Table 1). Although, the ability of TBBDA to oxidize alcohols has been demonstrated, in all the cases we studied, no oxidation products were observed.[19p]

The reaction works well for benzylic alcohols substituted with electron-donating or electron-withdrawing groups and

Table 1. Conversion of alcohols into their alkyl bromides and alkyl chlorides with TBBDA/PPh_3 and TCBDA /PPh_3

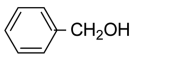
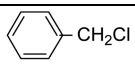
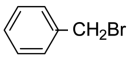
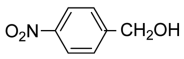
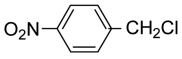
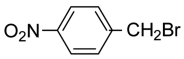
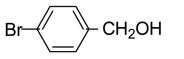
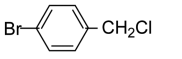
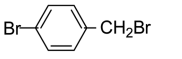
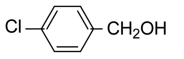
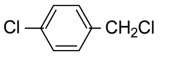
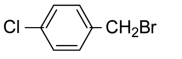
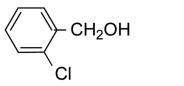
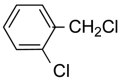
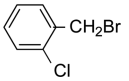
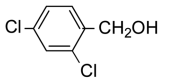
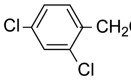
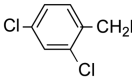
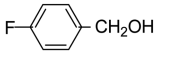
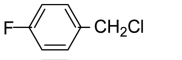
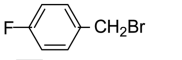
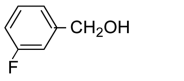
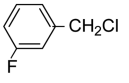
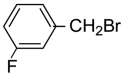
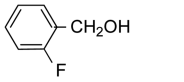
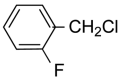
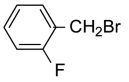
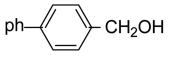
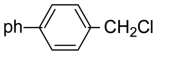
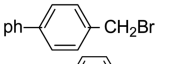
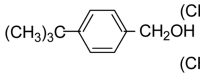
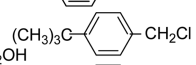
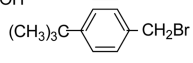
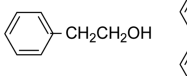
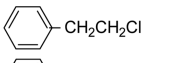
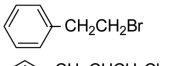
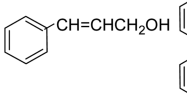
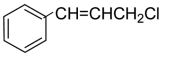
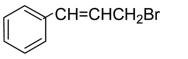
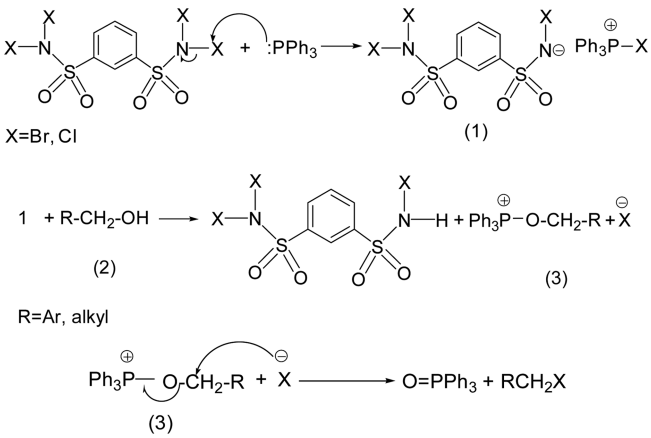
Entry	Substrate	Product[a]	Time (min)	Yield (%)[b]
1			Immediately	90
			Immediately	90
2			Immediately	91
			Immediately	92[d]
3			Immediately	88
			Immediately	93
4			Immediately	90
			Immediately	94
5			Immediately	87
			2 min	92
6			Immediately	93
			2 min	94
7			Immediately	88
			Immediately	90
8			Immediately	91
			Immediately	93
9			Immediately	90
			2 min	91
10			Immediately	92
			2 min	95
11			Immediately	89
			3 min	90
12			Immediately	87
			Immediately	86
13			Immediately	91
			Immediately	90

Table 1. Continued

Entry	Substrate	Product[a]	Time (min)	Yield (%)[b]
14	$CH_3(CH_2)_5CH_2OH$	$CH_3(CH_2)_5CH_2Cl$	Immediately	87
		$CH_3(CH_2)_5CH_2Br$	Immediately	86
15	$CH_3(CH_2)_4CHCH_3$ (OH)	$CH_3(CH_2)_4CHCH_3$ (Cl)	5 min	90
		$CH_3(CH_2)_4CHCH_3$ (Br)	10 min	87
16	ph-CH-ph (OH)	ph-CH-ph (Cl)	5 min	87
		ph-CH-ph (Br)	135 min	93[c]

[a]Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods. [b]Isolated yield after column chromatography. [c]Reaction conditions: alcohol (1 mmol), PPh_3 (2.5 mmol), TBBDA (0.7 mmol), rt. [d]Reaction conditions: alcohol (1 mmol), PPh_3 (3 mmol), TBBDA (0.8 mmol), rt.



Scheme 2

produce the corresponding halides at room temperature with good to excellent yields (Table 1). We found that the bromination of alcohols did not proceed well in CH_2Cl_2. However, this reaction proceeded smoothly in CH_3CN as solvent and the corresponding bromides were isolated with high yields (Table 1).

Proposed mechanism for this transformation proceeds by the activation of the triphenylphosphine by reaction with the *N*-halo compounds, which leads to intermediate 1. Then, nucleophilic attack of alcohol 2 on this intermediate gives intermediate 3. Finally nucleophilic attack of halide anion on intermediate 3 gives alkyl halide and triphenylphosphine oxide (Scheme 2).[13]

In conclusion, TBBDA/PPh_3 and/or TCBDA/PPh_3 are mild and efficient reagent systems for the conversion of alcohols into alkyl chlorides and alkyl bromides. These procedures have same good advantages such as simple work-up, high yields, short reaction times and the occurrence of the reactions at room temperature.

Experimental

General. Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The acetylated products were characterized by comparison of their spectral (IR, ^1H

NMR, and ^{13}C NMR) and physical data with authentic samples.

Typical Procedure for the Synthesis of Alkyl Chlorides: To a stirred mixture of TCBDA (0.55 mmol) and PPh_3 (2 mmol) in dry CH_2Cl_2 (5 mL), alcohol (1 mmol) was added at room temperature. The progress of the reaction monitored by TLC. After completion of the reaction (Table 1), the solvent was evaporated. The crude products were purified by short column chromatography (packed with silica gel, using *n*-hexane/ethyl acetate (8:2) as eluent) to achieve desired alkyl chloride with good to high yields.

Typical Procedure for the Synthesis of Alkyl Bromides: To the mixture of TBBDA (0.55 mmol) and PPh_3 (2 mmol) in dry CH_3CN (5 mL), alcohol (1 mmol) was added at room temperature. The progress of the reaction monitored by TLC. After completion of the reaction (Table 1), the solvent was evaporated. The crude products were purified by short column chromatography (packed with silica gel, using *n*-hexane/ethyl acetate (8:2) as eluent) to achieve desired alkyl bromide with good to excellent yields.

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