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Poly(*N* -bromo-*N*-ethyl-benzene-1,3-disulfonamide), *N,N,N′,N′*-Tetrabromobenzene-1,3-disulfonamide as New Efficient Reagents for Conversion of Alcohols to THP Ethers and Aldehydes to Oxazoline Compounds

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This paper is concerned with an easy preparation of THP ethers from primary, secondary and tertiary alcohols and oxazoline compounds from various aldehydes using poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide), *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide [TBBDA] as new and efficient reagents under ambient conditions without over-oxidation.

Keywords: Oxazolines, THP ethers, Ambient conditions, TBBDA, PBBS

INTRODUCTION

The protection of hydroxyl groups is of paramount importance in multi-step organic synthesis. THP ethers are the most useful protective groups in multi-stage synthesis because they are stable under neutral and basic conditions, and resistant to oxidizing and reducing agents [1]. THP groups are also the protective groups of choice in peptide, nucleotide, carbohydrate, and steroid chemistry [2]. Several reagents have been developed as catalysts for the formation of THP ethers from alcohols and 3,4-dihydro-2H-pyran (DHP). These include *p*-TsOH [3], $Fe(ClO_4)_3$ [4], $La(NO_3)_3.6H_2O$ [5], $CuSO_4.5H_2O$ [6], $AlCl_3.6H_2O$ [7], $CaCl_2$ [8], $Al(HSO_4)_3$ [9], $LiBF_4$ [10], $In(OTf)_3$ [11], Nafion-H [12], heteropolyacids [13], Lithium perchlorate-diethyl ether [14] and NBS [15].

2-Oxazolines have attracted considerable attention because they are present in a wide variety of biologically active natural products [16]. The substructural units of oxazoline heterocycle exist in a variety of naturally-occurring iron chelators [17a], cytotoxic cyclic peptides [17b] and antimitotic [17c] and neuroprotective agents [17d]. Several methods for the synthesis of 2-oxazolines from carboxylic acids [18], esters [19], nitriles [20] hydroxy amides [21], aldehydes [22], and olefins [23], have been reported previousely. The literature survey, however, has revealed that there are only few methods for the direct one-pot conversion of aldehydes to 2-substituted oxazolines.

Recently, the *N*-bromosuccinimide and pyridinium hydrobromide perbromide [24], have been reported for oxidative conversion of aldehydes to corresponding 2-substituted oxazolines. Although all of these methods afford 2-oxazolines in good yields, some of them suffer from drawbacks such as difficulty in multistep manipulation [25,26], utilization of toxic reagents [27], high reactin temperature (200-220 °C) [27c], higher stoichiometric use of reagents [22,24], and stringent reaction parameters with occasional low yields of the products.

EXPERIMENTAL

General Procedure for Protection of Alcohols Using TBBDA and PBBS in the Presence of Solvents

To a magnetically stirred solution of benzyl alcohol (1 mmol) and DHP (1.1 mmol), *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide TBBDA (0.1 g, 0.19 mmol) or PBBS [28] (0.1 g) and CH_2Cl_2 was added, and the mixture was stirred

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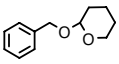
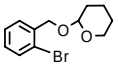
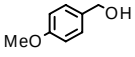
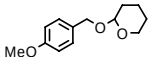
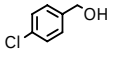
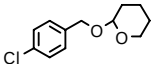
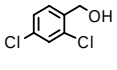
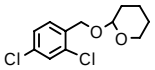
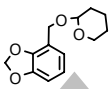
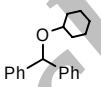
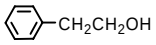
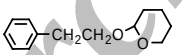
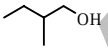
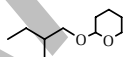
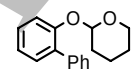
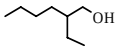
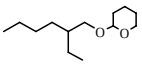
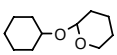
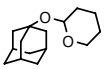
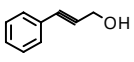
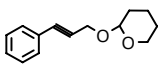
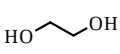
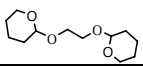
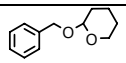
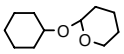
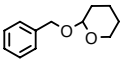
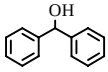
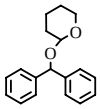
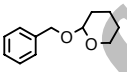
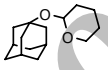
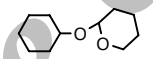
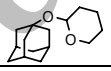
until the complete disappearance of starting material (as monitored by TLC). After the completion of the reaction, reagents were removed by simple filtration. Evaporation of the solvent under reduced pressure gave the almost pure THP ethers. Further purification using column chromatography *n*-hexane/acetone (9:2) gave the product as a liquid (Table 1).

Table 1. Tetrahydropyranylation of Various Alcohols Catalyzed by TBBDA and PBBS in CH_2Cl_2 and Solvent-Free Conditions at Room Temperature

Entry	Substrate	Product	TBBDA(CH_2Cl_2)		PBBS(CH_2Cl_2)		TBBDA(solvent-free)		PBBS(solvent-free)	
			Time (min)	yield (%)[a]	Time (min)	yield (%)[a]	Time (min)	yield (%)[a]	Time (min)	yield (%)[a]
1			4	95	8	90	4	94	10	92
2			5	93	11	90	6	94	11	91
3			4	96	9	92	3	93	7	94
4			8	90	13	92	10	94	16	94
5			4	94	9	92	6	92	7	91
6			6	93	10	93	6	93	9	90
7			15	92	19	90	12	91	18	91
8			20	93	25	94	18	94	25	92
9			5	92	13	92	5	95	12	93
10			10	92	13	94	13	94	17	91
11			18	85	28	82	15	90	22	88
12			8	91	12	93	8	90	13	92
13			15	93	25	93	17	92	25	91
14			25	93	35	91	25	93	32	92
15			10	90	14	87	12	92	18	90
16			20	91	30	85	17	92	24	90

[a]Products were characterized by their physical properties, comparison with authentic samples, and by spectroscopic methods.

Table 2. Competitive Tetrahydropyranylation of Various Alcohols Catalyzed by TBBDA and PBBS in the Presence of Solvent (CH_2Cl_2) at Room Temperature

Entry	Mixture	Product	Time (min)	Conversion (%)[a]
1			5[b] or 15[c]	80
				20
2			10[b] or 15[c]	100
				0
3			20[b] or 30[c]	90
				10
4			20[b] or 30[c]	80
				20

[a]The conversion was detected by TLC and NMR spectroscopy. [b]The conversion was complied with TBBDA. [c]The conversion was complied with PBBS.

General Procedure for Solvent-Free Protection of Alcohols Using TBBDA and PBBS

Benzyl alcohol (1 mmol), DHP (2 mmol) was added to *N*,*N*,*N'*,*N'*-tetrabromobenzene-1,3-disulfonamide TBBDA (0.1 g, 0.19 mmol) or PBBS (0.1 g) at room temperature, and the mixture was magnetically stirred until complete disappearance of starting material (as monitored by TLC). After the completion of the reaction, CH_2Cl_2 (5 ml) was added, and the reagents were removed by simple filtration. Evaporation of the solvent under reduced pressure gave the almost pure THP ethers. Further purification using column chromatography *n*-hexane/acetone (9:2) gave the product as a liquid (Table 1).

General Procedure for Conversion of Aldehydes to 2-Oxazoline Compounds Using TBBDA and PBBS in the Presence of Solvents

To a mixture of substrate (1 mmol), ethanolamine (1.5 mmol) and CH_3CN (5 ml) or H_2O (5 ml), TBBDA (0.15 g, 0.27 mmol) or PBBS (0.15 g) at room temperature, was added. The mixture was stirred at room temperature for a period of time specified in Table 4. After the completion of the reaction, and evaporation of the solvent under reduced pressure, CH_2Cl_2 (10 ml) was added, and the reagents were removed by simple filtration. Water (20 ml) and CH_2Cl_2 (25 ml) were added. The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the pure product (92-98%).

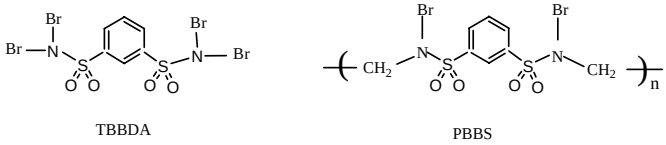
General Procedure for Solvent-Free Conversion of Aldehydes to 2-Oxazoline Compounds Using TBBDA and PBBS

To a mixture of substrate (1 mmol), ethanolamine (1.5 mmol) and TBBDA (0.15 g, 0.27 mmol) or PBBS (0.15 g) at room temperature, was added. The mixture was stirred at room

Table 3. Reaction Times and Yields of the Reaction of Alcohols with DHP Using Various Catalysts

Substrate	Conditions	Reaction time (h)	Yield (%)
p-Methoxybenzyl alcohol	$La(NO_3)_3.6H_2O$	2.5	95[5]
p-Methoxybenzyl alcohol	$CuSO_4.5H_2O$	0.66	89[6]
p-Methoxybenzyl alcohol	NBS	3.5	78[15]
Benzyl alcohol	$La(NO_3)_3.6H_2O$	2.5	95[3]
Benzyl alcohol	Lithium perchlorate in diethyl ether	12	86[14]
Benzyl alcohol	$In(OTf)_3$, 0 ºC	0.5	85[11]
Benzyl alcohol	$CuSO_4.5H_2O$	0.66	91[6]
Benzyl alcohol	Ferric perchlorate	1.5	98[4]
Benzyl alcohol	NBS	2.5	95[15]
Cyclohexanol	Lithium perchlorate in diethyl ether	12	80[14]
Cyclohexanol	$In(OTf)_3$, 0 ºC	0.5	85[11]
Cyclohexanol	Ferric perchlorate	2	94[4]
p-Chlorobenzyl alcohol	$CuSO_4.5H_2O$	0.75	92[6]
Benzhydrol	NBS	9	90[15]
Benzhydrol	Ferric perchlorate	2.5	75[4]

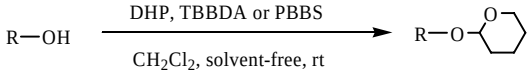
temperature for a period of time specified in Table 4. After the completion of the reaction, CH_2Cl_2 (10 ml) was added to the mixture and reagents were removed by simple filtration. Water (20 ml) and CH_2Cl_2 (25 ml) were added. The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the pure product (87-98%).



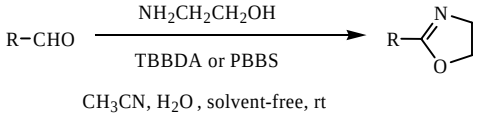
Scheme 1

RESULTS AND DISCUSSION

As part of our ongoing project to study the application of poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] and *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] [28-33] (Scheme 1), which is relatively easy to make [28] in organic synthesis, we now report a mild and efficient method for the conversion of alcohols to THP compounds (Scheme 2). Various aromatic and aliphatic alcohols were tetrahydropyranylated to THP compounds using TBBDA or PBBS in good to high yields under ambient conditions without any by-products.



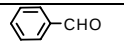
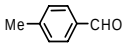
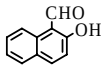
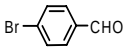
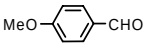
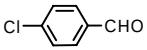
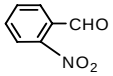
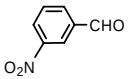
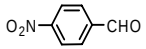
Scheme 2



Scheme 3

The results of oxidation of alcohols to THP ethers are presented in Table 1. As shown in Table 1, primary, secondary

Table 4. TBBDA and PBBS Catalysed Synthesis of Oxazoline Compounds in Solvent-Free and Solvent Conditions

Enty	Substrate	TBBDA(CH_3CN)		PBBS(CH_3CN)		TBBDA(H_2O)		PBBS(H_2O)		TBBDA(solvent -free)		PBBS(solvent-free)	
		Time (min)	yield (%)[a]	Time (min)	yield (%)[a]	Time (min)	yield (%)[a]	Time (min)	yield (%)[a]	Time (min)	yield (%)[a]	Time (min)	yield (%)[a]
1		14	95	18	92	9	98	15	94	5	98	7	94
2		10	96	13	96	6	98	10	95	4	97	10	98
3		38	90	50	86	17	96	30	89	20	89	26	87
4		17	93	26	92	14	95	24	94	15	93	21	93
5		8	97	10	92	3	98	7	98	2	98	5	95
6		16	93	30	94	10	95	21	93	14	95	18	95
7		21	91	24	91	15	96	25	93	10	98	16	92
8		25	90	23	90	15	95	27	92	12	94	15	94
9		17	93	20	90	12	95	17	94	9	97	15	94
10	CH_3CH_2CHO	4	-[b]	6	-[b]	2	-[b]	4	-[b]	2	-[b]	2	-[b]
11	$PhCH_2CH_2CHO$	5	-[b]	8	-[b]	3	-[b]	4	-[b]	4	-[b]	5	-[b]
12	$CH_3(CH_2)_5CHO$	7	-[b]	8	-[b]	4	-[b]	6	-[b]	4	-[b]	4	-[b]

[a]Products were characterized by their physical properties, comparison with authentic samples, and by spectroscopic methods. [b]No reaction.

and tertiary alcohols and phenols were all protected under the said conditions. We also found that sensitive compounds (entries 7, 15), were protected under the above-mentioned conditions without any by-products.

It was also found that *N*,*N*,*N'*,*N'*-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] were efficient reagents for the conversion of aldehydes to oxazoline compounds (Scheme 3) in the presence of 2-amino ethanol under (i) solvent-free, (ii) solvent conditions.

Table 4 represents the treatment of a variety of aldehyds with ethanol amine in the presence of solvent (CH_3CN, H_2O) and solvent-free conditions using TBBDA or PBBS. It is noteworthy that various aromatic aldehydes were converted to oxazolines with high chemoselectivity without over-oxidation of aldehydes to carboxylic acids. However, sevaral attempts to convert aliphatic aldehydes to oxazolines using PBBS or TBBDA under (i) solvent-free, (ii) solvent conditions failed.

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