N,N,N',N'-Tetrabromobenzene-1,3-disulfonamide and Poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) as Efficient Catalysts for the Methoxymethylation of Alcohols under Solvent-free Conditions

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Methoxymethylation of a variety of alcohols was performed using formaldehyde dimethyl acetal in the presence of N, N, N', N'-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(N-bromo-N-ethylbenzene-1,3-disulfonamide) [PBBS] as catalysts at room temperature and solvent-free conditions. The methoxymethyl ethers (MOM-ethers) were obtained with good to excellent yields.

Keywords: Alcohols; Formaldehyde dimethyl acetal; TBBDA; PBBS; Solvent-free conditions.

INTRODUCTION

In view of the tremendous versatility of the hydroxyl group in organic synthesis, a wide variety of methods have been developed for the protection of hydroxyl groups.¹ Methoxymethylation of alcohols is an important organic transformation² that is a frequently used protection method in multistep synthesis due to its stable to strong basic media, Grignard reagents, diborane, butyllithium, catalytic hydrogenation and reduction with hydrides. Formaldehyde dimethyl acetal (FDMA) is a stable, cheap, and commercially available compound that can be used for the preparation of methoxymethyl ethers from hydroxyl compounds. However, the activity of FDMA is poor, so a variety of catalysts have been used for activating this reagent, such as P_2O_5 , ³ *p*-toulenesulfonic acid,⁴ Nafion-H,⁵ TMSI,⁶ molybdenum(VI) acetylacetonate,⁷ BF₃,⁸ envirocat,⁹ sulfated zir-

Scheme I

conia,¹⁰ expensive graphite,¹¹ FeCl₃ dispersed on molecular sieves,¹² pyridyl sulfide,¹³ Sc(OTf)₃ and Bi(OTf)₃,¹⁴ silica sulfuric acid,¹⁵ and H₃PMo₁₂O₄₀.xH₂O.¹⁶ However, many of these methods suffer from using expensive reagents, high temperature, strong protic acid conditions or slow reaction rates. Consequently, there is a need to develop alternative reagents for this reaction.

RESULTS AND DISCUSSION

More recently our group has exploited the application of [TBBDA] and [PBBS]¹⁷⁻²⁵ as mild reagents in organic synthesis. Prompted by these results, herein we wish to report a simple, mild and efficient method, for the direct methoxymethylation of alcohols with [TBBDA] and [PBBS] as new catalysts at room temperature and under solvent-free conditions (Scheme I).



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Entry	Substrate	Reagents	Time (h)	Yield ^a (%)
1	ОН	А	1	100
1		В	1.2	95
•	ОН	А	2	65
2	O ₂ N	В	3	60
	СОН	А	1.3	95
3	F	В	2	90
	П ОН	А	1.1	98
4	Br	В	2	95
	СОН	А	2	90
5	LBr	В	2.4	95
	CI	А	2	98
6	СІ	В	2.2	90
7	СОН	А	1.2	100
		В	1.3	90
	СОН	А	1	85
8	н₅со	В	1.1	75
		А	1	95
9	H.C	В	1.3	90
	OH	А	2	75
10		В	2.2	60
11	СН.СН.ОН	А	2	80
11		В	1.45	75
12	~~~_он	A	4	85
		B	4.2	80 80
13	ОН	В	4	80
	~~~~он	Ā	4.1	75
14	Ĺ	В	4.5	60
15		А	3	90
	( ) ₁₃ on	В	2.5	88
16	Г ОН	А	4	-
10		В	5	-
17	<pre></pre>	А	8	-
1/	ci –	В	8	-

Table 1. Methoxymethylation of alcohols with TBBDA (A) and<br/>PBBS (B) under solvent-free conditions

^a All products are known and their spectra as well as physical data have been reported in the literature.

Our experiments show that primary and secondary alcohols can be smoothly converted into the corresponding MOM-ethers in excellent yields. Benzylic alcohols bearing both electron withdrawing groups such as nitro and halogens (Table 1, entries 2-7) and electron releasing groups such as methoxy and methyl (Table 1, entries 8-9) are con-

Table 2.	Comparison of reaction time and yield of our reagents
	with previously published methods

Substrate	Conditions	Time (h)	Yield (%)
Вг	TBBDA PBBSA	1.1 2	98 95
Вг	Sc(OTf) ₃ , CHCl ₃ , reflux	3	98 ¹⁴
Вг	Silica sulfuric acid, CH ₃ CN, RT	2.5	85 ¹⁵
Вг	H ₃ PMo ₁₂ O ₄₀ .xH ₂ O, Solvent-free, RT	3.5	85 ¹⁶
СІОН	TBBDA PBBS	2 2.2	98 95
СІОН	Silica sulfuric acid, CH ₃ CN, RT	0.42	78 ¹⁵
СІ ОН	H ₃ PMo ₁₂ O ₄₀ .xH ₂ O, Solvent-free, RT	4	86 ¹⁶
~~~_он	TBBDA	4	85
ОН	Silica sulfuric acid, CH ₃ CN, RT	4.2 4	65 ¹⁵

verted into the corresponding methoxymethylated products in good to excellent yields. We found that [TBBDA] and [PBBS] can be used for the methoxymethylation of primary and secondary alcohols by formaldehyde dimethyl acetal. During our investigation, we also found that hindered tertiary alcohols such as 1-adamantanol and 2-methyl-2-propanol were methoxymethylated in refluxing CH₃CN with low yields. The results of the conversion of various alcohols are presented in Table 1. Furthermore, our examination showed that this method is not applicable for protection of hydroxyl groups in phenol, and the starting material was recovered.

Since TBBDA and PBBS contain halogen atoms which are attached to nitrogen atoms, it is very probable that these reagents release Br^+ *in situ* which can conduct as an electrophilic species.¹⁷⁻²⁵ Therefore, the mechanism for the reaction can be suggested as follows (Scheme II). The advantages of PBBS and TBBDA over reported reagents in methoxymethylation of 4-bromobenzyl alcohol, 2,4-dichlorobenzyl alcohol, and octanol, are shown in Table 2. In conclusion, the advantages of our method are mild reaction



conditions, high yields, short reaction time, solvent-free conditions, low cost, and uses eco-friendly catalysts.

EXPERIMENTAL

General procedure for methoxymethylation of alcohols using FDMA with TBBDA and PBBS

To a stirred solution of alcohol (1 mmol), dimethoxymethane (10 mmol) was added [TBBDA] (0.15 mmol) or [PBBS] (0.1 g) and the mixture was stirred at room temperature under solvent-free conditions. The progress of the reaction was monitored by TLC (4:1 *n*-hexan/aceton). After completion of the reaction, H₂O (20 mL) was added and the mixture was extracted with CCl₄ (25 mL), and then the organic layer was dried over anhydrous Na₂SO₄ (5 g). The reagent was removed by simple filtration. Evaporation of the solvent under reduced pressure gave the pure product (60-100%).

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