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1,3-Dichloro-5,5-dimethyl hydantoin and Poly *N,N′*-dibromo-*N*-ethyl naphthyl-2,7-disulfonamide as efficient catalysts for the methoxymethylation of alcohols under solvent-free conditions

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Abstract

Methoxymethylation of a variety of alcohols was performed using formaldehyde dimethyl acetal in the presence of 1,3-dichloro-5,5-dimethyl hydantoin [DCDMH] and Poly *N,N′*-dibromo-*N*-ethyl naphthyl-2,7-disulfonamide [PBNS] as catalysts at room temperature and under solvent-free conditions. Our experiments show that primary and secondary alcohols can be smoothly converted into the corresponding MOM-ethers in excellent yields. The methoxymethyl ethers (MOM-ethers) were obtained with good to excellent yields. 1,3-Dichloro-5,5-dimethyl hydantoin [DCDMH] and Poly *N,N′*-dibromo-*N*-ethyl naphthyl-2,7-disulfonamide [PBNS] effectively catalyzed the methoxymethylation of alcohols with dimethoxymethane at ambient temperature. The notable advantages of this method are mild reaction conditions, high yields, cheapness, safety and eco-friendliness, and recyclability of the catalysts.

Keywords: Methoxymethylation; alcohols; DCDMH; PBNS; 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 transformation [2] that is a frequently used protection method in multistep synthesis due to its stable bond 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 $Sn^{IV}(TPP)(OTf)_2$ [3], $[C_4mim][InCl_4]$ [4], $Sn^{IV}(Br_8TPP)(OTf)_2$ [5], RHA-

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SO_3H [6], molybdenum(VI) acetylacetonate [7], BF_3 [8], envirocat [9], sulfated zirconia [10] expensive graphite [11], $FeCl_3$ dispersed on molecular sieves [12], pyridyl sulfide [13], $Sc(OTf)_3$ and $Bi(OTf)_3$ [14], silica sulfuric acid [15], and $H_3PMo_{12}O_{40}.xH_2O$ [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.

Experimental

General

Chemicals such as alcohols, dimethoxymethane and DCDMH were purchased from Fluka, Merck and Aldrich chemical companies. IR and ^1H NMR spectra were recorded using a Shimadzu Infrared Spectrophotometer FT-IR Model IR Prestige 21 (KBr pellets) and a 90 MHz Jeol FT-NMR spectrometer, respectively. ^1H NMR chemical shifts were measured relative to TMS.

General procedure for methoxymethylation of alcohols using FDMA with [DCDMH] and [PBNS]

[DCDMH] (0.02 mmol, 0.004 g) or [PBNS] (0.05 g) was added to a stirred solution of alcohol (1 mmol) and dimethoxymethane (10 mmol, 0.76 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*-hexane/acetone). After completion of the reaction, H_2O (20 mL) was added and the mixture was extracted with CCl_4 (25 mL), and then the organic layer was dried over anhydrous Na_2SO_4 (5 g). The reagent was removed by simple filtration. Evaporation of the solvent under reduced pressure gave the pure product (60-100%).

Methoxy methyl benzyl ether: IR (Nujol): 3029, 1456, 1377, 1251, 1104, 1070, 874, 843, 694 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 7.17(s, 5H), 4.71 (s, 2H), 4.61(s, 2H), 3.43(s, 3H).

Methoxy methyl 4- nitro-benzyl ether: IR (Nujol): 1606, 1526, 1459, 1377, 1346, 1252, 1153, 1104, 873, 844 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 8.16(d, 2H), 7.40(d, 2H), 4.67(m, 4H), 3.34(s, 3H).

Methoxy methyl 2,4- dichloro-benzyl ether: IR (Nujol): 1591, 1563, 1464, 1377, 1253, 1201, 1142, 1091, 874, 844 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 7.36(m, 3H), 4.71(s, 2H), 4.44(s, 2H), 3.21(s, 3H).

Methoxy methyl 4- methoxy-benzyl ether: IR (Nujol): 1587, 1482, 1444, 1377, 1287, 1254, 1061, 919, 845, 752 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 7.21(d, 2H), 6.92 (d, 2H), 4.65(s, 2H), 4.52(s, 2H), 3.73(s, 3H), 3.56 (s, 3H).

Methoxy methyl 2- phenyl ethyl ether: IR (Nujol): 1606, 1526, 1459, 1377, 1346, 1250, 1150, 1111, 873, 844, 735 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 7.27(s, 5H), 4.60-4.51 (d, 2H), 3.84(t, 2H), 3.30 (s, 3H), 2.86 (t, 2H).

Methoxy methyl 2,4- dibromo-benzyl ether: IR (Nujol): 1591, 1565, 1464, 1253, 1201, 1150, 1100, 1091, 1047, 874, 844, 724 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 7.24 (m, 3H), 4.51 (s, 2H), 4.35 (s, 2H), 3.21 (s, 3H).

Methoxy methyl 4- bromo-benzyl ether: IR (Nujol): 1460, 1376, 1251, 1150, 1104, 1011, 874, 842 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 7.42 (q, 4H), 4.65 (d, 2H), 4.51 (d, 2H), 3.82 (s, 3H).

Methoxy methyl pentyl ether: IR (Nujol): 1459, 1385, 1251, 1120, 1029,

997, 931, 847, 840 cm^{-1}. ^1H NMR (90 MHz, acetone-d_6) δ (ppm): 4.57 (br, 2H), 3.57 (s, 3H), 3.35 (br, 2H), 1.21-0.92 (br, 9H).

Methoxy methyl heptyl ether: IR (Nujol): 1657, 1460, 1377, 1250, 1150, 1097, 840, 746 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 4.70 (s, 2H), 3.51 (t, 2H), 3.35 (s, 3H), 1.31 (br, 10 H), 0.86 (br, 3H).

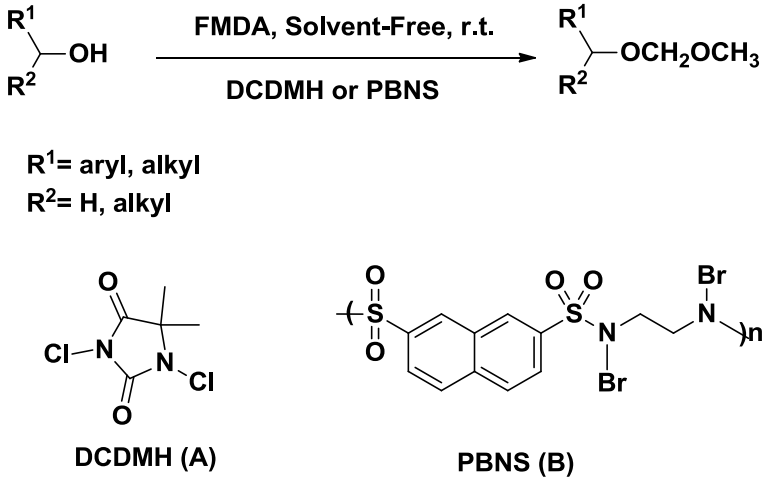
Methoxy methyl adamantyl ether: IR (Nujol): 1462, 1377, 1354, 1304, 1153, 1133, 1093, 1016, 872, 838, 751 cm^{-1}. ^1H NMR (90 MHz, acetone-d_6) δ (ppm): 4.67 (s, 2H), 3.50 (s, 3H), 1.95-1.51 (m, 15 H).

Methoxy methyl thiophyl ether: IR (Nujol): 1463, 1377, 1251, 1224, 1150, 1100, 870, 843, 697 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 7.17 (d, 1H), 6.88 (d, 2H), 4.60 (s, 4H), 3.32 (s, 3H).

Methoxy methyl 2-isopropyl-5-cyclohexyl ether: IR (Nujol): 1591, 1565, 1464, 1377, 1253, 1201, 1120, 1105, 1097, 1091, 874, 844, 724 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 4.74 (s, 2H), 3.31 (s, 3H), 2.36 (m, 14H), 1.85 (s, 9H), 0.65 (s, 9H).

Results and discussion

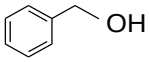
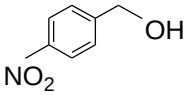
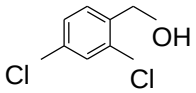
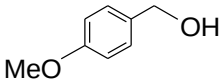
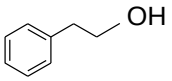
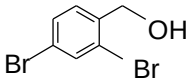
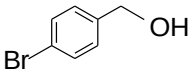
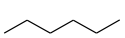
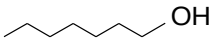
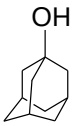
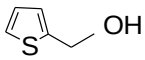
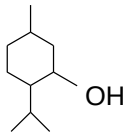
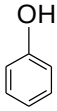
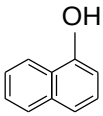
More recently, our group has exploited the application of DCDMH and PBNS [17-19] as mild reagents in organic synthesis. Prompted by these results, herein, we wish to report a simple, mild and efficient method for the direct methoxymethylation of alcohols with [DCDMH] and [PBNS][20] as new catalyst at room temperature and under solvent-free conditions (Scheme 1).



Scheme 1. methoxymethylation of alcohols with [DCDMH] and [PBNS][20] as new catalyst at room temperature and under solvent-free conditions

The results of the reaction have been depicted in Table 1.

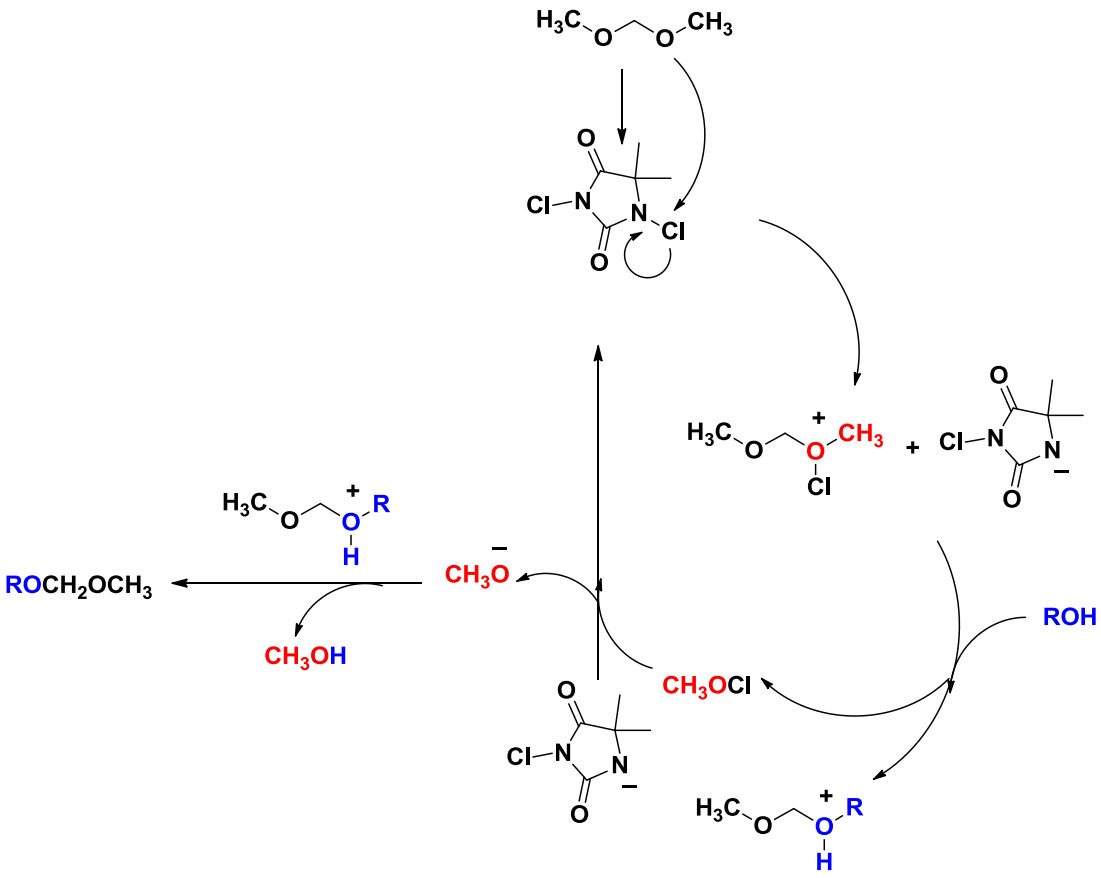
Table 1. Methoxymethylation of alcohols using FDMA with [DCDMH](A) and [PBNS](B)

Entry	Substrate	Time (h)	Yields%[a,b] (A)	Time (h) B	Yields%[a,b] (B)
1		1	90	1	90
2		1.3	83	1.5	85
3		2	95	2.4	90
4		1	93	1.4	90
5		1	80	1.3	90
6		2.1	83	2.2	85
7		1.2	90	1.2	90
8		5	85	5	85
9		8	75	8	75
10		8	70	10	70
11		3	80	3.5	80
12		4	83	4	85
13		-	-	-	-
14		-	-	-	-

[a]Products were characterized by their physical constants, and IR and NMR spectra; [b] Isolated yields; [c]Reaction Conditions: alcohol (1 mmol), FDMA (10 mmol), [DCDMH] (A) (0.02 mmol) or [PBNS] (B) (0.05 g) at r.t..

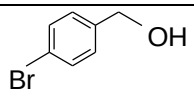
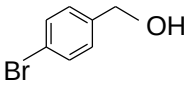
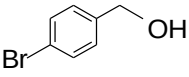
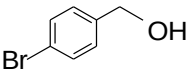
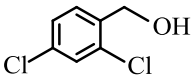
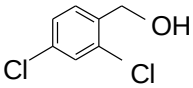
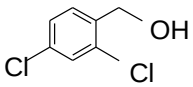
Our experiments show that primary and secondary alcohols can be smoothly converted into the corresponding MOM-ethers in excellent yields. Benzylic alcohols bearing both electron withdrawing groups such as nitro and halogens (Table 1, Entries 2-3-6-7) and electron releasing groups were converted into the corresponding methoxymethylated products in good to excellent yields. We found that [DCDMH] and [PBNS] 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 CH_3CN 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 DCDMH and PBNS contain halogen atoms which are attached to nitrogen atoms, it is very probable that these reagents release Cl^+ or Br^+ in situ which can conduct as an electrophilic species [17-19]. A plausible mechanism is shown in Scheme 2. The advantages of [DCDMH] and [PBNS] over reported reagents in methoxymethylation of 4-bromobenzyl alcohol, 2,4-dichlorobenzyl alcohol are shown in Table 2.



Scheme 2. Proposed mechanism for methoxymethylation of alcohols by DCDMH]

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

Substrate	Conditions	Time (h)	Yields (%)
	DCDMH	1.2	90
	PBNS	1.2	90
	$Sc(OTf)_3$, $CHCl_3$, reflux	3	98[14]
	Silica sulfuric acid, CH_3CN, RT	2.5	85[15]
	$H_3PMo_{12}O_{40}.xH_2O$, Solvent-free, RT	3.5	85[16]
	DCDMH	2	95
	PBNS	2.4	90
	Silica sulfuric acid, CH_3CN, RT	0.42	78[15]
	$H_3PMo_{12}O_{40}.xH_2O$, Solvent-free, RT	4	86[16]

Conclusion

1,3-Dichloro-5,5-dimethyl hydantoin [DCDMH] and Poly *N,N'*-dibromo-*N*-ethyl naphthyl-2,7-disulfonamide [PBNS] effectively catalyzed the methoxymethylation of alcohols with dimethoxymethane at ambient temperature. The notable advantages of this method are mild reaction conditions, high yields, cheapness, safety and eco-friendliness, and recyclability of the catalysts.

Acknowledgements

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