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A mild and efficient method for the methoxymethylation and acetylation of alcohols promoted by benzyltriphenylphosphonium tribromide

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Abstract

A mild and efficient method for the conversion of alcohols to their corresponding methoxymethyl ethers and acetates using benzyltriphenylphosphonium tribromide (BTPTB) as catalyst is described. All reactions were performed under completely heterogeneous reaction conditions in good to high yields.

Keywords: Benzyltriphenylphosphonium tribromide; Alcohols; Methoxymethylation; Acetylation; Heterogeneous reaction conditions

Methoxymethyl ethers, as important and stable derivatives of alcohols, are frequently prepared by the alkylation of alcohols with excess amounts of chloromethylether (CME) in alkaline solution [1]. In spite of the applicability of this method, the potent carcinogenic properties of CME [2], is considered as an important reason to encourage organic chemists to use formaldehyde dimethoxy acetal (FDMA), as an inexpensive and commercially available reagent, instead of this reagent. Even though handling of FDMA is easy and use of this reagent needs no special precautions, the low methoxymethylating power is the main drawback for the application of FDMA. To improve the methoxymethylating power of FDMA, a variety of catalysts have been reported of them scandium trifluoromethane sulfonate [3], bismuth triflate [4], phenylsulfonic acid functionalized mesoporous silica [5], silica sulfuric acid [6], $Al(HSO_4)_3$ [7], P_2O_5 [8], *p*-toluenesulfonic acid [9], expensive graphite [10], Nafion-H [11], $MoO_2(acac)_2$ [12] and $FeCl_3$ dispersed on molecular sieves 3A [13] are examples. Although these methods are an improvement, most of them suffer from disadvantages such as long reaction times, harsh reaction conditions, use of toxic or expensive reagents, tedious work-up and un-applicability in the methoxymethylation of tertiary alcohols.

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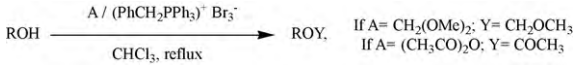
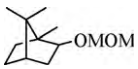
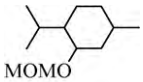
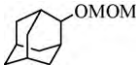
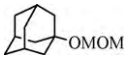
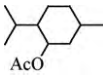


Scheme 1.

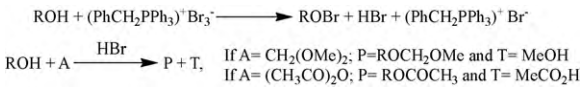
1. Experimental

Chemicals were purchased from Merck, Fluka, and Aldrich Chemical Companies. Products were separated and identified by the comparison of their mp, IR, NMR, and bp with those reported for the authentic samples, and also by

Table 1
Methoxymethylation and acetylation of alcohols catalyzed by BTPTB[a,b,c,d].

Entry	Product	Time (min)	Yield (%)
1	4-$ClC_6H_4CH_2OMOM$	17	96
2	2-$BrC_6H_4CH_2OMOM$	23	92
3	3,4-$Cl_2C_6H_3CH_2OMOM$	25	95
4	4-$Me_2CHC_6H_4CH_2OMOM$	13	90
5	4-$Me_3CC_6H_4CH_2OMOM$	25	95
6	$PhCH(OMOM)CH_3$	45	92
7	$Ph_2CH(OMOM)$	90	80
8	$PhCH_2CH_2OMOM$	23	95
9	$PhCH_2CH_2CH_2OMOM$	10	90
10	$PhCH(Me)CH_2OMOM$	35	90
11		55	92
12		25	90
13		40	95
14		40	92
15	4-$ClC_6H_4CH_2OMOM$	60	0[e]
16	4-$ClC_6H_4CH_2OAc$	10	90
17	2-$ClC_6H_4CH_2OAc$	12	90
18	2,4-$Cl_2C_6H_3CH_2OAc$	8	85
19	2-$MeC_6H_4CH_2OAc$	7	92
20	4-$Me_2CHC_6H_4CH_2OAc$	7	85
21	4-$NO_2C_6H_4CH_2OAc$	25	90
22	2-$NO_2C_6H_4CH_2OAc$	55	85
23	$C_6H_5CH(OAc)Me$	15	85
24	$PhCH_2CH_2CH_2OAc$	8	85
25	$PhCH(Me)CH_2OAc$	8	90
26		13	87
27		18	90
28	2-Adamantanyl acetate	5	85
29	$PhCH_2C(OAc)Me_2$	60	60
30	1-Adamantanyl acetate	15	92

[a] NMR spectroscopy.
[b] Isolated yields.
[c] Methoxymethylation was performed in the presence of 0.1 mmol of BTPTB.
[d] Acetylation was performed in the presence of 0.05 mmol of BTPTB.
[e] Reaction was performed in the absence of BTPTB.



Scheme 2.

regeneration of the corresponding alcohols. All yields refer to the isolated products. ^{1}H NMR spectra were recorded on JNM-EX 90A or Bruker-DRX MH2 NMR spectrometers.

1.1. General procedure

A mixture of the substrate (1 mmol), Ac_2O (2 mmol, 0.21 g) and/or FDMA (3 mmol, 0.228 g) and BTPTB [0.05 mmol, 0.03 g (used for acetylation) or 0.1 mmol, 0.06 g (used for methoxymethylation)] was stirred in refluxing $CHCl_3$ (3 mL). The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated, and Et_2O (5 mL) was added. The mixture was filtered and the solid residue was washed with Et_2O (5 mL). The filtrate was washed with saturated solution of $NaHCO_3$ and H_2O and dried over $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel gave the corresponding acetates and/or methoxymethyl ethers in good to high yields.

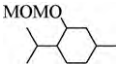
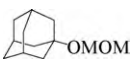
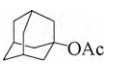
2. Results and discussion

Recently, benzyltriphenylphosphonium tribromide (BTPTB) has been prepared and used as an efficient catalyst in different types of reactions [14–18]. On the basis of these studies and in continuation of our ongoing research program on the development of new methods for functional group transformations [19–23], herein, we wish to report the applicability of BTPTB in the promotion of the methoxymethylation and acetylation of alcohols with FDMA and Ac_2O, respectively. All reactions were performed in $CHCl_3$ at reflux temperature and under completely heterogeneous reaction conditions in excellent yields (Scheme 1 and Table 1).

As shown in Table 1, different types of alcohols, including primary, benzylic, hindered and unhindered secondary and hindered tertiary ones are efficiently converted to their corresponding methoxymethyl ethers and acetates under the selected conditions. It is important to note that the progress of the reaction is so depends to the presence of BTPTB in the reaction mixture, which the reaction did not proceed in the absence of this reagent even after prolonged heating (Table 1, entry15). Also, by-products resulting from the bromination of the starting materials were not observed during the course of the reaction.

In 1987, Kajigaeshi reported that organic ammonium tribromides such as benzyltrimethylammonium tribromide generate HBr and MeOBr in methanol [24]. On the basis of this and obtained results, the mechanism which is shown in Scheme 2, is selected as the most plausible one for the methoxymethylation and acetylation of alcohols catalyzed by BTPTB.

Table 2
Comparison of some of the results obtained by our method (1) with some of those reported by $Sc(OTf)_3$ (2) [3], $Bi(OTf)_3$ (3) [4], $Al(HSO_4)_3$ (4) [7], *N*,*N*-dichloro-4-methylbenzenesulphonimide (5) [25], and 3-nitrobenzeneboronic acid (6) [26].

Entry	Product	Time (h)/yield (%)					
		1	2	3	4	5	6
1	PhCH(OMOM)Me	0.75/92	–	2/95	3/88	–	–
2		0.42/90	7/80	4/85	17.5/85	–	–
3		0.67/92	7/77	–	8.5/75	–	–
4	4-$NO_2C_6H_4CH_2OAc$	0.42/90	–	–	–	48/97	12/94
5		0.25/92	–	–	–	13/97	16/89

To illustrate the efficiency of the proposed method, Table 2 compares some of the results with some of those reported in the literature [3,4,7,25,26].

In conclusion, we developed an efficient and high yielding method for the methoxymethylation and acetylation of alcohols. Relatively short reaction times, high efficiency, heterogeneous reaction conditions, and easy work-up are among the other advantages of this method, which make this procedure a useful and attractive addition to the available methods.

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