

Molybdatophosphoric acid as a catalyst for the methoxymethylation of alcohols under solvent-free conditions

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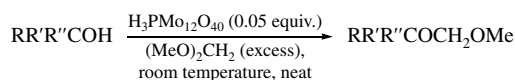
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The methoxymethylation of alcohols was performed using formaldehyde dimethoxy acetal in the presence of $\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$ at room temperature under solvent-free conditions.

Acids are widely used as catalysts in industry.¹ Solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal in chemical processes. On the other hand, any reduction in the amount of liquid acid needed and/or any simplification in handling procedures is required for risk reduction, economic advantage and environment protection.² Heteropoly acids (HPAs) as catalysts for fine organic synthetic processes have been developed.³ They are cheap, reusable, heterogeneous, and easily available catalysts.^{4,5} Heteropoly acids and their salts have received considerable attention as a powerful reaction medium for effecting various organic transformations⁴ such as selective bromination of aromatic compounds, silylation of alcohols, oxidation of aromatic amines to nitro compounds, thioacetalisation and transthiacetalisation reactions, oxidation of hydroxy groups to corresponding carbonyl functions, *gem*-acylation,⁶ and Friedel–Crafts⁷ reactions. Therefore, there are several advantages of HPAs as a catalyst for reactions under green conditions.^{8–10}

Protection of the hydroxyl functional group is an important process in a multi-step synthesis. One of the popular methods for this purpose is to transfer hydroxyl groups of methoxymethyl ethers (MOM ethers). The methoxymethyl protecting group is thus superior to the tetrahydropyranyl group especially in the cases of polyols, because it is easier to distinguish mono-protection from multi-protection and to estimate impurity amounts by NMR spectroscopy.¹¹ Methoxymethylation has usually been done with chloromethyl methyl ether under basic conditions.¹² Formaldehyde dimethoxy acetal (FDMA) is a cheap and commercially available compound that can be used for the preparation of MOM ethers from hydroxyl compounds. Even though the handling of this reagent is easy, its main drawback is its poor methoxymethylating power that needs forceful conditions.¹³ For the activation of FDMA, a variety of catalysts have been reported, but these methods have their own merits and limitations. For example, $\text{MoO}_2(\text{acac})_2$ has been reported as an excellent catalyst for the methoxymethylation of alcohols, but it is not a cheap and commercial catalyst for this purpose.¹⁴ Anhydrous iron(III) chloride dispersed on molecular sieves (3A) was used for the methoxymethylation of primary and secondary alcohols by FDMA at room temperature with excellent yields. However, the above procedure was unsuitable for methoxymethylation of tertiary alcohols.¹⁵ Recently, $\text{Sc}(\text{OTf})_3$ has been used as an effective catalyst for methoxymethylation of alcohols with an excess of FDMA (50 equiv.) in refluxing CHCl_3 .¹⁶ Here, we report a simple and efficient method for the direct methoxymethylation of alcohols with FDMA in the presence of $\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$ as a green catalyst at room temperature and under solvent-free conditions.

Both primary and secondary alcohols can be smoothly converted into the corresponding MOM ethers in excellent yields.



R, R', R'' = Alkyl, Aryl, H

Scheme 1

Secondary alcohols were methoxymethylated faster than primary alcohols under mild conditions. For example, benzhydrol was converted into a corresponding MOM ether in 91% yield with

Table 1 Preparation of MOM ethers from alcohols and formaldehyde dimethoxy acetal in the presence of molybdatophosphoric acid at room temperature and under solvent-free conditions.

Entry	Substrate	Time/h	Yield (%) ^a	Reference ^b
1		3	90	18
2		0.25	10 ^c	18
3		3.5	85	16
4		4	86	16
5		4.5	83	16
6		2.5	87 ^d	16
7		3.25	90	13(b)
8		3	89	13(b)
9		8	80	13(b)
10		5	85	17
11		0.5	91 ^e	17
12		1.5	92	16
13		3.5	90 ^f	17
14		5	75 ^f	13(b)

^aIsolated yield. ^bAll of the isolated products are known compounds and their spectra and physical data have been reported in the literature (see references). ^c85% cinnamaldehyde was identified. ^dAlmost 10% corresponding carbonyl compound was produced. ^eFDMA (2 mmol) was used. ^fReaction conditions: $\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$ (0.05 mmol) was added to a solution of alcohol (1 mmol) and FDMA (30 mmol) in MeCN (3 ml) under reflux conditions.

FDMA (2 equiv.) for 0.5 h (Table 1, entry 11), whereas benzyl alcohol was less reactive and afforded methoxymethyl benzyl ether in 90% yield by FDMA (10 equiv.) for 3 h (Table 1, entry 1). By this protocol,[†] cinnamyl alcohol was oxidised to cinnamaldehyde and only 10% methoxymethyl cinnamyl ether was isolated. We also found that hindered tertiary alcohols such as 1-adamantanol and 1-methyl-2-phenylpropan-2-ol were methoxymethylated in refluxing MeCN with good to excellent yields. In the case of tertiary alcohols, elimination reaction was not observed (Table 1, entries 13 and 14). Furthermore, our examination showed that this method is unsuitable for the protection of hydroxyl groups in phenol because the starting material was recovered intact.

In conclusion, we found that $\text{H}_3\text{PMo}_{12}\text{O}_{40}\cdot x\text{H}_2\text{O}$ can be used for the methoxymethylatoin of primary, secondary and tertiary alcohols by formaldehyde dimethoxy acetal. The advantages of this method are mild reaction conditions, high yields, cheapness and eco-friendly catalyst.

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[†] Molybdatophosphoric acid ($\text{H}_3\text{PMo}_{12}\text{O}_{40}\cdot x\text{H}_2\text{O}$) as a commercially available catalyst was purchased from Merck.

General procedure. $\text{H}_3\text{PMo}_{12}\text{O}_{40}\cdot x\text{H}_2\text{O}$ (0.05 mmol) was added to a mixture of an alcohol (1 mmol) and FDMA (10 mmol) and the mixture was stirred for an appropriate time. After completion of reaction, H_2O (10 ml) was added and the mixture was extracted with CH_2Cl_2 (2×15 ml) and then dried over anhydrous Na_2SO_4 (3 g). The evaporation of the solvent on a rotary evaporator afforded a residue, which was passed through a short pad of silica gel using a mixture of ethyl acetate and *n*-hexane as an eluent to afford a highly pure MOM ether.

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