

Heteropolyacid-catalyzed synthesis of chloromethyl methyl ether

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Abstract—An efficient (in terms of experiment and time) synthetic procedure for chloromethyl methyl ether (MOM-Cl) is described using heteropolyacids as catalysts.

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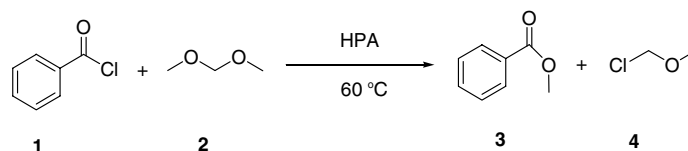
Protection of one functional group in the presence of other groups is an essential task for the synthesis of multi-functional molecules. Methoxymethyl ethers are commonly employed for the protection of alcohols in the synthesis of natural products.¹ These are stable to a variety of commonly used reagents, such as strong alkali, Grignard reagents, butyllithium, lithium aluminium hydride, etc. and are readily removed by mild acid treatment. The commonly employed method for the preparation of methoxymethyl ethers is based on the reaction of the corresponding alkoxide anions with chloromethyl methyl ether (MOM-Cl).² Since MOM-Cl is an excellent electrophile it readily reacts with enolates³ and other carbanions⁴ and thus serves as a convenient one-carbon synthon. Although chloromethyl methyl ether itself is a suspected mild carcinogen, commercial preparations of this reagent often contain significant amounts of the more toxic and carcinogenic bis(chloromethyl) ether. To overcome this limitation, several alternative methods have been developed. A few reports based on dimethoxymethane, a relatively inexpensive reagent, have appeared in the literature.⁵ However, many of these methods suffer from using expensive reagents, high temperatures and slow reaction rates. Many thermally unstable or acid sensitive alcohols are not amenable to the formation of MOM ethers by these routes. For example, the vigorous conditions employed are not suitable for the preparation of sensitive cephalosporins.⁶ It is always difficult to mono-protect 1,3-diols. When

unsymmetrical diols are used, the most hindered alcohol is protected, in contrast to normal methods, which are expected to protect the least hindered alcohol. Diols capable of forming stannyl derivatives can be efficiently mono-protected using MOM-Cl.⁷

Heteropolyacids (HPAs), due to their unique physico-chemical properties, are widely used as homogeneous and heterogeneous acid and oxidation catalysts. They have found industrial applications in several processes.⁸ Many heteropoly compounds have very high solubility in polar solvents and fairly high thermal stability in the solid state. They are also of great interest as model systems for studying fundamental problems of catalysis. HPAs with the Keggin structure constitute the most extensively studied and important class of polyoxometallates. Keggin-type HPAs have played an important role in catalysis. The Keggin-type HPAs, typically represented by the formula $H_{8-x}[X^xM_{12}O_{40}]$, where X is the heteroatom (e.g. P^{5+} or Si^{4+}), x the oxidation state, and M is the addenda atom (usually Mo^{6+} or W^{6+}), are the most important examples especially $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$ or $H_4SiW_{12}O_{40}$. Their significant higher Brønsted acidity, compared with the acidity of traditional mineral acid catalysts, is of great importance for catalysis. Heteropolyacids are promising solid acids and can replace environmentally harmful liquid acid catalysts such as H_2SO_4 .^{8c-e} Solid HPAs possess a discrete ionic structure comprising fairly mobile structural units of heteropoly anions and counter ions. The structure is frequently preserved upon substitution or oxidation/reduction and has extremely high proton mobility and a 'pseudoliquid phase'. $H_3PW_{12}O_{40}$, $H_4SiW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ hydrates were procured from Aldrich

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Scheme 1. Synthesis of MOM-Cl using heteropoly acid catalysts.

or Merck. The acidic salt $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$ was prepared by employing the method reported in the literature.⁹ All the catalysts were pretreated at 250 °C for 3 h and stored in a desiccator over P_2O_5 prior to use.

In the present study, a modified procedure for synthesizing MOM-Cl **4** is reported in which the reagents benzoyl chloride **1** and dimethoxymethane **2** were used as starting materials employing HPAs and their salts as catalysts (Scheme 1). The results of our studies show that $\text{H}_3\text{PW}_{12}\text{O}_{40}$, $\text{H}_4\text{SiW}_{12}\text{O}_{40}$, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ and $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$ were efficient catalysts for the synthesis of MOM-Cl under solvent-free conditions.

Solid acid catalysts are harmless to the environment with respect to corrosiveness, safety, quantity of waste generated and separability. In heteropoly anions, the negative charge is spread over much larger anions than those formed from mineral acids and hence the electrostatic interaction between the proton and anion is much less for HPAs than for mineral acids. An additional important factor is possibly the dynamic delocalizability of the charge. The change in the electronic charge caused by deprotonation can be spread over the entire polyanionic unit.

In the original method¹⁰ in which HCl, formalin and methanol were used as reagents to produce MOM-Cl, bis(chloromethyl) ether was obtained as a by-product. Purification of the product from this reaction required difficult and time consuming fractional distillation. In order to overcome this, several preparative methods were developed using methoxyacetic acid¹¹ or dimethoxymethane.¹² Later, Linderman et al. reported a cost effective route for the synthesis of MOM-Cl by examining several acid chlorides. They selected hexanoyl chloride as the acid chloride of choice and the procedure afforded MOM-Cl at a material cost of \$10.60/mol.¹³ Although the chloromethyl methyl ether was obtained in reasonable yield without the formation of bis(chloromethyl) ether, the process was expensive. An alternative preparation of chloromethyl methyl ether was reported by Reggielin et al. by reacting benzoyl chloride and dimethoxymethane in the presence of sulfuric acid as catalyst.¹⁴ Although MOM-Cl was obtained, which saved 80% of the chemical costs compared to the previous procedures, the method required a long reaction time, nearly 64 h. Thus we have developed a simple and fast procedure for MOM-Cl production using heteropolyacids as catalyst to overcome these drawbacks.

When solid HPAs are used for liquid phase reactions, variable reaction media would be present even if the major portion of the catalyst was present as a solid in

Table 1. Effect of various heteropolyacids in the synthesis of MOM-Cl^a

Entry	Catalyst	Yield ^b (%)	TOF ^c (h ⁻¹)
1	$\text{H}_3\text{PW}_{12}\text{O}_{40}$	79	26
2	$\text{H}_4\text{SiW}_{12}\text{O}_{40}$	66	16
3	$\text{H}_3\text{PMo}_{12}\text{O}_{40}$	59	12
4	$\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$	58	21

^a Reaction conditions: benzoyl chloride/dimethoxymethane (1:1). All the reactions were carried out for 4 h in the presence of 1.5 g of HPA catalyst.

^b Isolated yield.

^c TOF: moles of MOM-Cl produced per mol of catalyst per hour.

the system. For example, the reaction medium may change with the polarity of the solvents, substrates and the type of heteropoly compounds. Pure HPAs when used as heterogeneous catalysts are hindered by their low specific surface area and high solubility values in polar reaction systems, which thus results in catalyst separation problems. Thus in order to bring the reaction medium into the heterogeneous phase, the Cs salt of the heteropolyacid has been employed as the catalyst. Salts of HPA were prepared by partially exchanging protons of the parent HPA with large cations, such as Cs^+ . Some of the partially exchanged monovalent salts showed high catalytic activity for a number of redox and acid-catalyzed reactions. In particular, the $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$ salt was also found to be more active. The Cs^+ salt of $\text{H}_3\text{PW}_{12}\text{O}_{40}$ acts heterogeneously in both polar and non-polar media and can be easily separated from the heterogeneous systems by filtration and can be reused. In Table 1, the catalytic activities of $\text{H}_3\text{PW}_{12}\text{O}_{40}$, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$, $\text{H}_4\text{SiW}_{12}\text{O}_{40}$ and $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$ are compared. The highest yield was obtained when $\text{H}_3\text{PW}_{12}\text{O}_{40}$ was employed as the catalyst. The isolated yield in this case was 79% whereas in the case of the Cs salt, the yield obtained was 58%. It also showed a better turn over frequency (TOF), compared to $\text{H}_3\text{PW}_{12}\text{O}_{40}$. When $\text{H}_3\text{PW}_{12}\text{O}_{40}$, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ and $\text{H}_4\text{SiW}_{12}\text{O}_{40}$ were used as catalysts, the reaction proceeded in homogeneous solution. On the other hand, $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$ is virtually insoluble and exerted a surface type catalysis. That is, the reaction proceeded smoothly in the heterogeneous phase and the catalyst could be separated easily after completion of the reaction. The results of this study show that $\text{H}_3\text{PW}_{12}\text{O}_{40}$ is an effective catalyst for this purpose having the highest acidity compared to the other catalysts studied.

MOM-Cl was obtained in excellent yield. After 4 h of reaction, the conversion remained almost constant. Thus, we have reported the yields at equilibrium conditions, that is, after 4 h of reaction. Compared to the

H₂SO₄ catalyzed reaction¹⁴ (in this case a 64 h reaction time was required), the turn over frequencies are considerably higher for the HPA catalyzed reactions. As HPA is an active catalyst with higher Brønsted acidity, the same synthetic procedure can be employed for the synthesis of other chloro alkyl ethers. For example, diethoxymethane when employed in this reaction instead of dimethoxymethane gave chloromethyl ethyl ether was obtained (yield 78%).

Typical experimental procedure

CAUTION: The reaction should be carried out in an efficient hood due to the acute toxicity and carcinogenicity of the chloromethyl methyl ether. To ensure gas tightness, PTFE-sleeves were used on all glass connections. Benzoyl chloride **1** (9.686 g, 68.9 mmol), dimethoxymethane **2** (5.236 g, 68.9 mmol) and H₃PW₁₂O₄₀ (1.50 g, 0.52 mmol) were taken in a 50 mL two necked round bottomed flask. The mixture was stirred under N₂ and heated in an oil bath, thermostated at 60–65 °C for 4 h. The reaction was conveniently monitored by ¹H NMR. The integrals of the product MOM-Cl signals (δ = 3.52 and 5.46 ppm) were compared with those of dimethoxymethane (δ = 3.34 and 4.56 ppm). After cooling to room temperature, the mixture was distilled at 130 °C. After discarding a small amount of the fore-run, MOM-Cl (chloromethyl methyl ether) was collected (4.38 g, 79%). The purity, especially the absence of the bis(chloromethyl) ether in the crude or distilled product was validated by ¹H NMR spectroscopy (absence of a CH₂ signal at 5.56 ppm). The product contained only a small amount of dimethoxymethane (0.1%). In the reaction where diethoxymethane was employed as the acetal the product, chloromethyl ethyl ether showed ¹H NMR signals at δ 5.5 (s, 2H), 3.8 (q, 2H), 1.3 (t, 3H).

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