SHORT PAPER

J. Chem. Research (S),
2002, 188–189

TiO_2/SO_4^{2-}, an efficient catalyst for the methoxymethylation of alcohols

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Methoxymethylation of primary and secondary alcohols with dimethoxymethane has afforded the corresponding methoxymethyl ethers in good to high yields in the presence of TiO_2/SO_4^{2-} solid superacid.

Keywords: TiO_2/SO_4^{2-}, methoxymethylation of alcohols

The protection of the hydroxy group as methoxymethyl ether is a commonly used transformation in organic synthesis.[1] It is stable to a variety of commonly used reagents such as strong bases, Grignard reagents, diborane, catalytic hydrogenation, butyllithium and lithium aluminium hydride and is readily removed by acid treatment.[2] In general, methoxymethyl ethers are prepared by protic or Lewis acid catalysed reaction of alcohols with chloromethyl methyl ether[3,4] or dimethoxymethane.[5-14] However, the direct alkylation of an alcohol using chloromethyl methyl ether is restricted due to the reagent being highly carcinogenic. In order to overcome this limitation, a number of alternative methods have been introduced. Acid catalysed condensation of dimethoxymethane with alcohol is widely used for the preparation of methoxymethyl ether. The catalysts for this kind of reaction are *p*-toluenesulfonic acid,[5] Nafion-H,[6] lithium bromide/*p*-toluenesulfonic acid,[7] phosphorous pentoxide,[8] iodotrimethylsilane,[9] molybdenyl(VI) acetyacetone[10] and anhydrous iron(III) chloride.[11] These methods have their own merit and shortcomings. Some methods are not very satisfactory due to drawbacks such as low yields, long reaction time, tedious workup, corrosivity, and effluent pollution and the catalysts are expensive, and non-recoverable. In recent years, a number of catalysts have been employed for this kind of reaction to improve yields, decrease reaction time and eliminate other drawbacks. Such catalysts as Envircoat EPZG^R,[12] K10 montmorillite clay[13] and expansive graphite[14] have been employed as catalysts for this purpose to obtain relatively better results.

$$\mathrm{ROH} + \mathrm{H_3COCH_2OCH_3} \xrightarrow[\text{Reflux,4-9h}]{\substack{TiO_2/SO_4^{2-}\\ CHCl_3\\ 77–95\%}} \mathrm{ROCH_2OCH_3} + \mathrm{CH_3OH}$$

1 **2** **3**

Scheme 1

TiO_2/SO_4^{2-} solid superacid has been used as an efficient catalyst for a variety of organic reactions.[15-18] It is superior to halogenous solid superacid and other liquid acids in terms of green chemistry since it is efficient, non-pollutive, noncorressive and has high activity in the temperature range 773–873K. TiO_2/SO_4^{2-} solid superacid has a greater specific surface area than titanium dioxide, alumino silicate and zeolites and it also exhibits both Brönsted and Lewis acid characteristics,[19] so it has been widely studied in the fields of hydrocaracking of paraffins, dehydration of alcohols, esterification, alkylation of olefins, photochemical catalysis and protection of aldehydes, ketones and alcohols. Herein we wish to report an easy, efficient and practical procedure for the synthesis of methoxymethyl ethers by condensation of alcohols with dimethoxymethane catalysed by TiO_2/SO_4^{2-}solid superacid in the refluxing temperature of dimethoxymethane or $CHCl_3$. The results are summarised in Table 1.

As shown in Table 1, a series of alcohols were methoxymethylated with dimethoxymethane in the presence of TiO_2/SO_4^{2-} solid superacid. Both primary and secondary alcohols were smoothly converted into methoxymethyl ethers. Moreover, primary alcohols can be easily converted into corresponding methoxymethyl ethers (entries 1, 4, 5, 6 and 7) in excellent yields. Dimethoxymethane is employed both as reagent and solvent. Secondary alcohols, show lower reactivity, therefore, chloroform is used as solvent to raise the refluxing temperature. However, tertiary alcohols afford dehydration or rearrangement products instead of the expected methoxymethyl ethers under these conditions.

The catalyst was filtered off after the reaction, washed with dichloromethane and dried at 110^0C for 1h. It was used five times for synthesis of methoxymethane ether **3d** without any significant decrease in activity. When we tried to use it again, the catalyst was not as at efficient as the beginning mainly because of absorption of organics on the solid surface of the acid causing loss of active centres and decrease of the effective surface. Moreover, the SO_4^{2-}on the catalyst was lost in the washing procedure that was also disadvantageous at high temperature, the organics were burned up and the catalyst was activated, so that it could be reused more times.

In conclusion, the protection of alcohols was achieved effectively by condensation of alcohols and dimethoxymethane to form methoxymethyl ethers by use of TiO_2/SO_4^2 solid superacid as the catalyst. This method has the benefits of operational simplicity, high yields and short reaction time. It is non-corrosive, non-pollutive and employs a reusable catalyst.

Experimental

The catalyst TiO_2/SO_4^{2-} solid superacid was prepared according to our reported method.[15,16] Liquid alcohols were purified by distillation prior to use. Melting points were uncorrected. ^{1}H NMR spectra were measured on a Bruker AC-80 (80MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. The products were identified by ^{1}H NMR spectra and comparison of their melting boiling points with literature values.

General procedure for preparation of methoxymethyl ethers ***3***: A mixture of alcohol **1** (10 mmol), dimethoxymethane **2** (30 mmol) and TiO_2/SO_4^{2-}(200mg) was stirred at refluxing temperature (41^0C) for

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Synthesis of methoxymethyl ethers from alcohols catalyzed by TiO_2/SO_4^{2-}

Entry	Alcohols	Solvent/time /h	Yield[a] /%	B.p./Torr or M.p./^{0}C Found	Reported	Partial ^{1}H NMR Spectral data δ (ppm)
1	1-Butanol **1a**	none/8	92	86–88/15	87/15[12]	3.40 (t, 2H, RCH_2O), 4.50 (s, 2H, OCH_2O), 3.27 (s, 3H, OCH_3)
2	2-Butanol **1b**	$CHCl_3$/9	85	78–80/20	80/20[12]	3.42–3.58 (m, 1H, RCH_2O), 3.45 (s, 2H, OCH_2O), 3.27 (s, 3H, OCH_3)
3	(+)Menthol **1c**	$CHCl_3$/9	95	93–94/10	94/10[12]	3.40–3.61 (m, 1H, cyclohexy-H), 4.48 (s, 2H, OCH_2O), 3.32 l (s, 3H, OCH_3)
4	1-Octanol **1d**	None/9	95	97–99/15	97/15[12]	3.40 (t, 2H, RCH_2O), 4.49 (s, 2H,OCH_2O), 3.25 (s,3H, OCH_3)
5	2-Chloroethanol **1e**	None/4	94	36–38/15	38/15[12]	3.65 (t, 2H, RCH_2O), 4.59 (s, 2H, OCH_2O), 3.32 (s, 3H, OCH_3)
6	Tetrahydrofurfuryl alcohol **1f**	None/6	94	75–77/20	75/20[12]	3.50 (d, 2H, RCH_2O), 4.60 (s, 2H, OCH_2O), 3.30 (s, 3H, OCH_3)
7	Benzyl alcohol **1g**	$CHCl_3$/6	92	94–96/20	75/5[12]	4.59 (s, 2H, $ArCH_2O$), 4.71 (s, 2H, OCH_2O), 3.40 (s, 3H, OCH_3)
8	2-Phenyl-ethanol **1h**	$CHCl_3$/8	87	92–94/15	93/15[12]	3.80 (t, 2H, RCH_2O), 4.70 (s, 2H, OCH_2O), 3.32 (s, 3H, OCH_3)
9	Cyclohexanol **1i**	$CHCl_3$/8	90	68–70/15	32–34/1.6[6]	3.37–3.60 (m, 1H, cyclohexy-H), 4.50 (s, 2H, OCH_2O), 3.30 (s, 3H, OCH_3)
10	Cholesterol **1j**	$CHCl_3$/8	77	77–78	78[12]	3.45–3.55 (m, 1H, cyclohexy-H), 4.66 (s, 2H, OCH_2O), 3.37 (s, 3H, OCH_3)

[a] Yields refer to isolated products.

the length of time as indicated in Table 1. For the reactions, solvent $CHCl_3$ (10ml) was also added at the same time. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, the catalyst was filtered off and washed with ether (2×10ml), The solvent and unreacted dimethoxymethane were evaporated by rotary evaporator under reduced pressure. The crude product was purified by distillation under vacuum or by column chromatography on silica gel using petroleum ether as eluent to afford the pure product **3**.

The project was supported by National Natural Science Foundation of China (29872011 and 29572039), Educational Ministry of China, Educational Department of Hebei Province (990104), Science and Technology Commission of Hebei Province.

Received 10 July 2001; accepted 27 October 2001
Paper 01/964

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