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Methoxymethylation of alcohols catalyzed by sulfated metal oxides

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More acidic sulfated metal oxides (SMO) such as SO_4^{2-}/ZrO_2 and SO_4^{2-}/TiO_2 catalyzed the methoxymethylation of alcohols with dimethoxymethane at ambient temperature to achieve a product yield of greater than 90% within a few hours. The reaction displayed a significant steric effect on the product yield with a preferential order of primary alcohol > secondary alcohol ≫ tertiary alcohol. The observed steric effect might result from the repulsion between the bulky alkyl group in the alcohol and the two methoxy groups in the protonated dimethoxymethane (oxonium ion).

KEY WORDS: methoxymethylation of alcohols; sulfated metal oxides; steric effect.

1. Introduction

Lately, responsible operation and sustainable development have become the emphasis of industrial chemical production in order to minimize the impact on the environment. Therefore, all chemical production processes are required to be optimized with respect to energy efficiency, utilization of nontoxic raw material, and waste reduction. Such production technologies are green production technologies [1]. Paraffin isomerization catalyzed by sulfated metal oxides (SMO) has been the subject of much interest in the petrochemical industry due to the worldwide introduction of reformulated gasoline, which is aimed to reduce air pollution in metropolitan areas. For example, Hosoi and co-workers claimed that the butane isomerization activity of platinum-promoted sulfated zirconia was much higher than that of Pt-promoted molecular sieves but comparable to that of Pt-promoted chlorinated alumina in the low reaction temperature range [2]. The latter catalyst, however, required a continuous addition of toxic and corrosive chlorides to replace those slowly leaching away during the reaction. Therefore, SMO could behave more like green production catalysts than those currently used in the petrochemical industry.

These SMO include oxides of ZrO_2, TiO_2, Fe_2O_3, SnO_2, HfO_2, Al_2O_3, and SiO_2. They are stable and mesoporous solid materials with an acid strength ranging between -12 and -16 on a Hammett indicator scale [3]. Such strong acid strength originates from the electron-withdrawing effect of the sulfate group in SMO. They contain both Brønsted and Lewis acidities and display a comparable or stronger acidity than other well-known solid acids such as heteropolyacids, Nafion-H resins, and zeolites. Nonetheless, there have been very few research results on the application of SMO catalysts in synthetic organic chemistry reported thus far, and their potential in this field has not yet been fully explored.

In view of the tremendous versatility of the hydroxyl group in organic synthesis, many methods have been developed for protecting this group. Methoxymethyl ethers were commonly utilized in protecting alcohols and phenols in natural product synthesis. The reagent employed for methoxymethylation was chloromethyl methyl ether [4,5], which is no longer suitable due to its extreme carcinogenicity. For this reason, the condensation of dimethoxymethane with alcohols was adopted instead:

$$ROH + CH_3OCH_2OCH_3 \rightarrow ROCH_2OCH_3 + CH_3OH.$$

The catalysts reported in the literature for this reaction were Nafion-H resin [6], phosphorus pentoxide [7], expansive graphite [8], Li/Br/p-toluenesulfonic acid [9], $FeCl_3$/molecular sieve 3A [10], iodotrimethylsilane [11], and $MoO_2(acac)_2$ [12]. While some of these catalysts did have their merits, they were not entirely satisfactory with drawbacks such as low product yield, requiring high reaction temperature, containing corrosive halides, tedious aqueous work-up, expensive, and unrecoverable. We found that SMO were excellent catalysts for this reaction. At ambient temperature, the more active SMO catalysts could produce a product yield of >90% within a few hours. The reaction ran smoothly and selectively for most of the alcohols tested. Interestingly, the order of the product yields for methoxymethylation of different types of alcohol was primary alcohol > secondary alcohol ≫ tertiary alcohol, which strongly suggested that a steric effect was operating in this catalytic reaction.

2. Experimental

The sulfated metal oxides were prepared according to the method reported previously [3]. Except for SO_4^{2-}/Al_2O_3, all the SMO were prepared by immersing

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appropriate metal hydroxides into a sulfuric acid solution. The mixture was filtered, dried, and calcined at an appropriate temperature to produce SMO. The calcination temperatures for SMO are the following: 898 K for SO_4^{2-}/ZrO_2, 798 K for SO_4^{2-}/TiO_2, 823 K for SO_4^{2-}/SnO_2, 973 K for SO_4^{2-}/HfO_2, 773 K for SO_4^{2-}/Fe_2O_3, and 823 K for SO_4^{2-}/Al_2O_3. The metal hydroxides were obtained by precipitating their corresponding metal salt solutions with aqueous ammonia (29.5%). The final pHs of the solutions to obtain the metal hydroxides are the following: 9.0 for $Zr(OH)_4$, $Ti(OH)_4$, $Hf(OH)_4$, and $Fe(OH)_3$ and 9.5 for $Sn(OH)_4$. The metal salts used to prepare these SMO were $ZrOCl_2{\cdot}8H_2O$, $Ti[OCH(CH_3)_2]_4$, $SnCl_4{\cdot}5H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$, and $HfCl_4$. SO_4^{2-}/Al_2O_3 was prepared by immersing γ-Al_2O_3 in 1.60 M sulfuric acid solution, followed by calcining at 823 K.

A typical reaction procedure is the following. 10 mmol of alcohol were mixed with excess dimethoxymethane (226 mmol), which serves both as the solvent and methoxymethylation reagent. This mixture was added to 0.50 g of SMO catalyst, which was dried at 723 K for 3 h prior to the reaction, and the combination was reacted with stirring for a specific amount of time at ambient temperature. At the end of the reaction, the mixture was separated from the solid catalyst by filtration, and the filtrate was analyzed by GC with an internal standard method. HP-6890 GC equipped with a HP-5973 mass selective detector (MSD) was used to identify the reaction products. A trace amount of dimethoxymethylated product was observed with this HP-5973 MSD for cyclohexylmethanol, cyclohexanol, and 1-hexanol. IR and NMR were also used to verify the product structure wherever necessary.

3. Results and discussion

The efficiencies of SMO to catalyze the methoxymethylation of alcohols are demonstrated with the data in table 1. It was shown that methoxymethylation of cyclohexylmethanol was more effective over the more acidic SMO catalysts, such as SO_4^{2-}/ZrO_2, SO_4^{2-}/TiO_2, SO_4^{2-}/SnO_2, and SO_4^{2-}/HfO_2 (Ho = −15 to −16), than over those with less acidity, such as SO_4^{2-}/Fe_2O_3 and SO_4^{2-}/Al_2O_3 (Ho = −13 to −14) [3]. The former group of catalysts could produce a product yield of >85% within 3 h at ambient temperature, while the latter catalysts produced less than 48%. The smaller product yield was less likely to be due to the deactivation of the catalyst since the product yield obtained over SO_4^{2-}/Al_2O_3 continued to increase from 27% at 3 h to 57% at 20 h (see also table 1). The catalytic performance of the SMO catalysts was comparable to that of a Nafion resin, which produced a product yield of 87% under our reaction condition, and to others reported in the literature.

Table 1
Methoxymethylation of cyclohexylmethanol over SMO catalysts[a]

Catalyst	Reaction time (h)	Yield of MOM ether (%)
Blank reaction[b]	10	0
SO_4^{2-}/TiO_2	3	90
SO_4^{2-}/ZrO_2	3	93
SO_4^{2-}/HfO_2	3	89
SO_4^{2-}/SnO_2	3	85
SO_4^{2-}/Fe_2O_3	3	48
SO_4^{2-}/Al_2O_3	3	27
SO_4^{2-}/Al_2O_3	20	57
Nafion NR-50	3	87

[a] Reaction took place at ambient temperature using 10 mmol of cyclohexylmethanol, 226 mmol of dimethoxymethane, and 0.5 g of catalyst.
[b] No catalyst was used.

In a previously published paper [13], we performed TPD experiments on SO_4^{2-}/TiO_2 and SO_4^{2-}/Fe_2O_3 to analyze the distribution of the strength and the number of the acid sites in these SMO catalysts. The data are summarized in table 2 and figure 1. A well-defined peak at 808 K and an asymmetric peak at 475 K were observed for SO_4^{2-}/TiO_2. The former was attributed to NH_3 desorption from strong acid sites and the latter to desorption from the weak acid sites. In between these two peaks there was a plateau area (543–723 K) which was attributed to NH_3 desorption from the medium–strong acid sites. A similar distribution of acid sites was found in SO_4^{2-}/Fe_2O_3, except that the peak maximum of strong acid sites in SO_4^{2-}/Fe_2O_3 was located at 713 K and the plateau area (543–623 K) arising from the medium–strong acid site was smaller. The results

Table 2
The distribution of the strength and the number of acid sites in SMO catalysts[a]

Catalyst	Desorption temperature and amount					
	Strong acid site		Medium acid site		Weak acid site	
	Peak temp./range (K)	Amount (μmol/g)	Peak temp./range (K)	Amount (μmol/g)	Peak temp./range (K)	Amount (μmol/g)
SO_4^{2-}/TiO_2	808/723–843	50	–/543–723	51	475/373–543	42
SO_4^{2-}/Fe_2O_3	713/623–793	85	–/543–623	23	475/373–543	35

[a] Data obtained from reference [13].

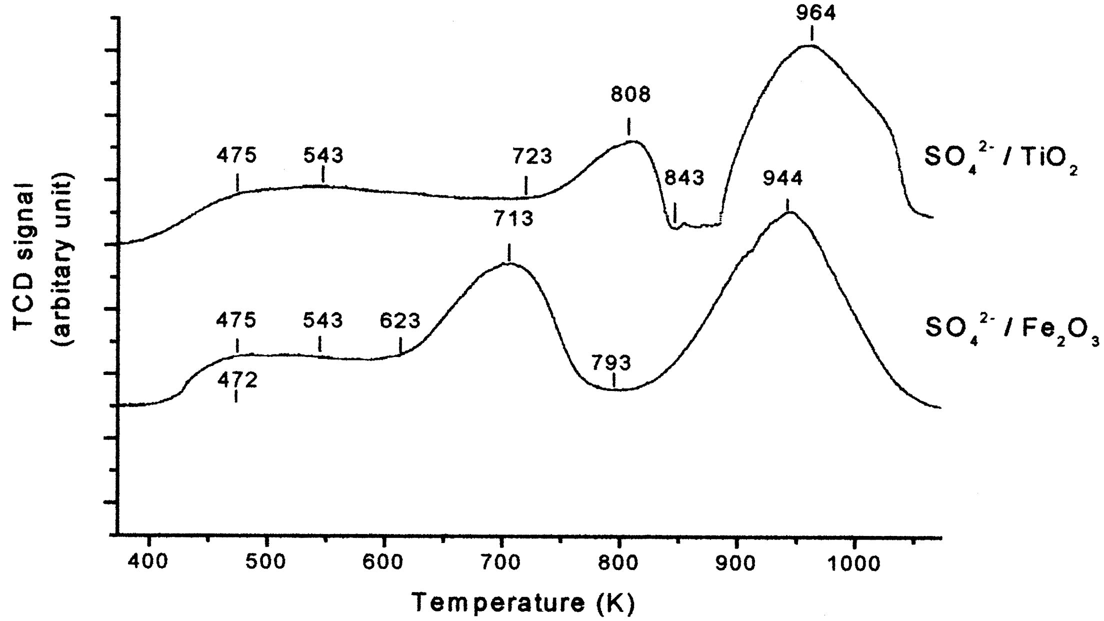
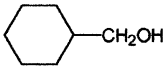
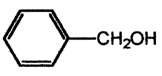
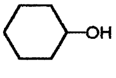
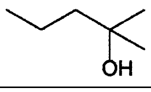


Figure 1. Distribution of the number and strength of acid sites in SMO catalysts measured by NH_3-TPD.

indicated that SO_4^{2-}/Fe_2O_3 contained more strong acid sites than SO_4^{2-}/TiO_2 (85 μmol g^{-1} for SO_4^{2-}/Fe_2O_3 and 50 μmol g^{-1} for SO_4^{2-}/TiO_2) but the sum of the number of medium–strong and strong acid sites was about the same in both catalysts (101 μmol g^{-1} for SO_4^{2-}/TiO_2 and 108 μmol g^{-1} for SO_4^{2-}/Fe_2O_3). However, SO_4^{2-}/TiO_2 obviously possessed a higher acid strength than SO_4^{2-}/Fe_2O_3 as the NH_3 desorption peak maximum of the strong acid sites in the former was located at 808 K, which was much higher than those in the latter (located at 713 K). Therefore, we believed that due to such a difference in the distribution of the acid strength in SMO catalyst, SO_4^{2-}/TiO_2 was able to achieve a higher level of product yield than SO_4^{2-}/Fe_2O_3.

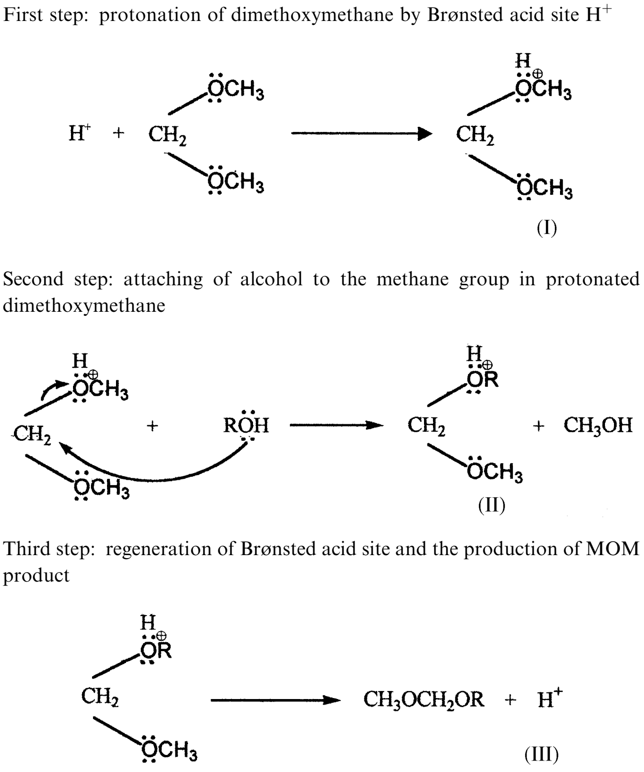
Alcohols with different structural characteristics had also been tested for this reaction utilizing SO_4^{2-}/TiO_2 as the catalyst. Unlike previous reports of the SMO-catalyzed synthesis of cyclic acetals from carbonyl compounds in which both steric and electronic effects played important roles in the reaction [14], only the steric effect was observed in the methoxymethylation of alcohols over SMO catalysts. For example, with increasing steric complexity in the neighborhood of the hydroxyl group in the alcohols (1-hexanol < 2-hexanol < 2-methyl-2-pentanol), the MOM product yield dropped significantly (99% > 80% > 23%, see table 3). As a matter of fact, as long as the hydroxyl group remained unhindered, the MOM product yields were not sensitive to the rest of the molecular structure of alcohols. Therefore, MOM yields for propargyl alcohol and allyl alcohol were about the same irrespective of their degree of unsaturation in their molecular structures (90% *versus* 93%), as were those of cyclohexylmethanol and benzyl alcohol (90% *versus* 91%). Similarly, secondary alcohols such as cyclohexanol and 2-hexanol also gave similar but lower product yields (83% *versus* 80%). On the other hand, the more hindered tertiary alcohols such as 2-methyl-2-pentanol did produce the expected MOM product, but the yield was very low (23%) and a small amount of dehydrated olefinic products was also observed (3%). Interestingly, not only acidic catalysts

Table 3
Methoxymethylation of alcohols over SO_4^{2-}/TiO_2 [a]

Type [b]	Alcohol	Yield of MOM ether (%)
1^0		90
1^0		91
1^0	$1\text{-}C_6H_{13}OH$	99
1^0	$CH_2{=}CHCH_2OH$	93
1^0	$HC{\equiv}CCH_2OH$	90
2^0		83
2^0	$2\text{-}C_6H_{13}OH$	80
3^0		23

[a] Reaction conditions were the same as table 1.

[b] 1^0, 2^0, 3^0 represent primary, secondary, and tertiary alcohols, respectively.


First step: protonation of dimethoxymethane by Brønsted acid site H^+

Second step: attaching of alcohol to the methane group in protonated dimethoxymethane

Third step: regeneration of Brønsted acid site and the production of MOM product

Scheme 1. Reaction mechanism for methoxymethylation of alcohols over SMO catalysts.

such as SMO and Nafion resin but also expansive graphite and iodotrimethylsilane displayed a similar steric selectivity pattern [6,8,11].

These experimental results suggested a possible mechanism for this reaction (depicted in scheme 1). As there was excess dimethoxymethane serving both as the reactant and the solvent, the more reasonable first step in the reaction was the protonation of dimethoxymethane to produce an oxonium ion (I) by the Brønsted acid site in SMO catalysts. The alcohol then attached to the carbon atom of methylene group in the oxonium ion (I) to produce methanol and oxonium ion (II). It was in this second step where the progress of the reaction was affected by the steric bulkiness of the alkyl group in the alcohol. The repulsion between the bulky alkyl group of the alcohol and the two methoxy groups of the oxonium ion (I) produced the observed steric effect, which resulted in the significantly lower MOM product yield in the tertiary alcohol. The mechanism suggested that such a steric effect had more to do with the structural characteristic of the alcohol and dimethoxymethane than with the catalyst itself. This might be the reason why many different types of catalysts displayed a similar steric effect in catalytic activity and selectivity in this methoxymethlation reaction. The final step of the reaction was the decomposition of oxonium ion (II) to produce the MOM product and to regenerate the Brønsted acid site. One of the features of this mechanism was the formation of oxonium ion as the reaction intermediate. Unlike those carbocations having a conjugated double bond in their molecular structures in the synthesis of cyclic acetals from carbonyl compound and ethylene glycol [14], the oxonium ion (II) in this mechanism could not utilize the resonance effect to delocalize the positive charge on the oxygen atom through conjugation to enhance its stability. Therefore, oxonium ion (II) formed from a benzyl alcohol, like that from a saturated cyclohexyl methanol, could not delocalize its positive charge through its benzene ring. As a result, no electronic effect could be observed, and these two compounds, with a similar molecular size and steric effect, produced similar MOM product yields.

4. Conclusions

Mesoporous sulfated metal oxides effectively catalyzed the methoxymethylation of alcohols with dimethoxymethane at ambient temperature. This reaction required strong acid sites and displayed a significant steric effect on the MOM product yields, with a preferential order of primary alcohol > secondary alcohol ≫ tertiary alcohol. Such a steric effect depends more on the steric repulsion between bulky alcohol and dimethoxymethane than on the structure of the catalyst.

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