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Communication

Catalytic etherification of hydroxyl compounds to methyl ethers with 1,2-dimethoxyethane

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1,2-Dimethoxyethane is explored for the first time as etherification agent for the acid-catalyzed synthesis of methylethers from biomass-derived hydroxyl compounds. H₃PW₁₂O₄₀ catalyst can provide the formation of isosorbide methylethers with 80% GC yield from isosorbide. The acid catalyst type and acid amount are of critical importance in improving etherification reactivities of hydroxyl groups with 1,2-dimethoxyethane.

With declining reserves of readily accessible fossil energy, efficient conversion of biomass into fuels and chemicals has come into the research spotlight worldwide.¹ The biomass polymers, such as cellulose and hemicellulose, usually contain numerous hydroxyl groups. Therefore, various strategies have been developed to functionalize hydroxyl groups for efficient utilization of biomass.²

Especially, catalytic methylation of hydroxyl groups in biomass-derived platform chemicals, such as glucose,³ glycerol,⁴ isosorbide⁵ and 5-hydroxymethylfurfural,⁶ has been recognized as a common and significant approach. These methyl ether products of considerable interest, by themselves or as key chemical intermediates, are extensively applied as green solvents, biofuels or oxygenated additives, surfactants, and biopolymers.⁷ Several methylating agents with corresponding catalysts have been explored for etherification of hydroxyl groups. Highly toxic methylating agents, such as dimethyl sulfate and methyl halides, have been commonly used for methylation reaction in the presence of strong base as catalyst over the past decades.⁸ Dimethyl carbonate, due to its low toxicity, has been widely employed nowadays as a substitute methylating agent catalyzed by base.⁹ Nevertheless, considering its molecular structure and the reaction pathway, stoichiometric amount of CO₂ is inevitably formed. Recently, methanol as an alternative agent has been reported to convert hydroxyl compounds to monoethers using acid as catalyst.¹⁰ However, the consecutive etherification of hydroxyl groups in polyols with methanol can be prevented by water formed due to equilibrium restrictions.¹¹ Therefore, it is desirable to develop a new environmental benign etherification agent which could be efficient and facile for the synthesis of methyl ethers from mono- and dihydroxyl compounds. Interestingly, 1,2-dimethoxyethane (DMET), as an important chemical, holds the potential to serve as an efficient etherification agent for the synthesis of methyl ethers because of its relatively high boiling point (85 °C), low toxicity and easy availability.¹²

In this work, DMET is explored for the first time as etherification agent for the acid-catalyzed synthesis of methyl ethers from biomass-derived alcohols. The aliphatic alcohols (*n*-butanol and *n*-hexanol) and isohexides (isosorbide, isomannide and isoidide) with two hydroxyl groups were chosen as model compounds. The synthesis in good yields of methyl ethers can be performed by reaction of the alcohols with DMET at 150 °C in the presence of heteropolyacid as catalyst.



Scheme 1 Etherification of isosorbide with DMET catalyzed by acid.

The reaction of hydroxyl groups in isosorbide with DMET took place at 150 °C in the presence of acid catalyst. Typically, three predominant methyl ether products of isosorbide were observed including dimethyl isosorbide, 5-*O*-monomethyl isosorbide and 2-*O*-monomethyl isosorbide due to the different configurations of hydroxyl groups (Scheme 1). Pure dimethyl isosorbide, 2-*O*-monomethyl isosorbide and 5-*O*-monomethyl isosorbide were sequentially achieved by separating reaction mixture through silica-gel column chromatography. They were identified by NMR spectroscopy, data shown in experimental section.

The introduction of different acid catalysts lead to obvious changes in the catalytic results, as shown in Fig. 1. Surprisingly, H₂SO₄ was inert for the etherification reaction with a low conversion of isosorbide (below 1%) under our reaction conditions. However, when ion-exchange resins bearing SO₃H groups were employed as catalysts, the isosorbide conversions were increased to 6%, 6% and 34%, for Amberlyst-70, Amberlyst-15 and Nafion-H, respectively. Interestingly, heteropolyacids including 12-tungstosilicic acid (H₄SiW₁₂O₄₀) and 12-tungstophosphoric acid (H₃PW₁₂O₄₀) exhibited superior activities with the isosorbide conversions of 80% and 87%, respectively. Furthermore, the mono- and dimethyl ethers of isosorbide were achieved in excellent total GC yields up to 76% by using H₃PW₁₂O₄₀ as catalyst. Noticeably, H₃PW₁₂O₄₀ provides the highest yield of dimethyl isosorbide among the acid catalysts with the same acid amount. Acid strength is correlated with the type of acid catalyst. It has been reported that acid strength of these catalysts is in the order H₃PW₁₂O₄₀ > H₄SiW₁₂O₄₀ > Nafion-H > Amberlyst-15 ≈ Amberlyst-70 > H₂SO₄.¹³ The acid

strength order of these tested catalysts is consistent with the order of their activities for the etherification of isosorbide. Therefore, the acid strength of the catalysts plays a vital role in the etherification of isosorbide with DMET.

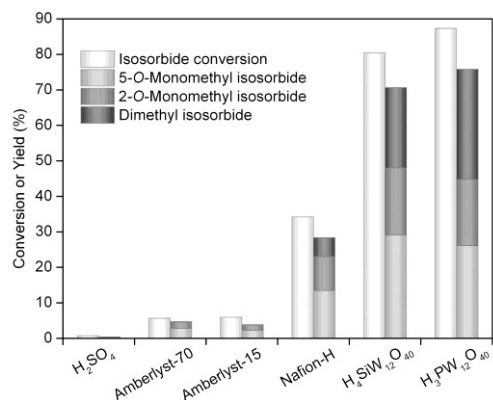


Fig. 1 Catalytic performances of different acid catalysts for the etherification reaction of isosorbide with DMET. Reaction conditions: Isosorbide (2 mmol), acid catalyst (0.077 mmol H⁺), DMET (43 mmol), 150 °C, 60 min.

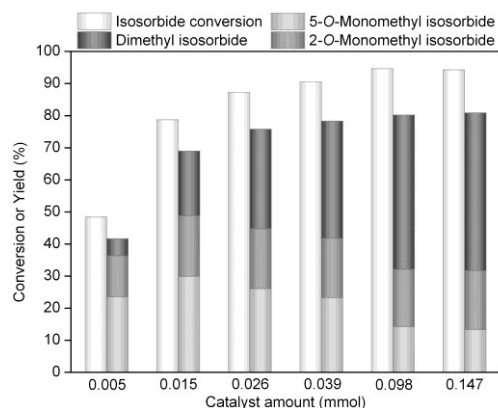


Fig. 2 Effect of acid amount on the etherification reaction of isosorbide with DMET. Reaction conditions: Isosorbide (2 mmol), DMET (43 mmol), H₃PW₁₂O₄₀, 150 °C, 60 min.

The acid amount is expected to influence etherification of isosorbide with DMET. Detailed study was performed to evaluate the effect of acid amount of H₃PW₁₂O₄₀ on its catalytic behaviors (Fig. 2). Both the conversion of isosorbide and the total yields of isosorbide methyl ethers increased with increasing the acid amount of H₃PW₁₂O₄₀ from 0.005 to 0.098 mmol. Furthermore, the formation of dimethyl isosorbide increased with an increase in acid amount, while the total formation of monomethyl ethers first increased and then decreased. The total yields of isosorbide methyl ethers were up to 80% including 48% yield of dimethyl isosorbide at the acid amount of 0.098 mmol. Further increasing the acid amount to 0.147 mmol, no more increase was observed in both isosorbide conversion and yields of etherified products. Therefore, the increase in the acid amount of H₃PW₁₂O₄₀ could enhance the etherification activities of hydroxyl groups in isosorbide and favor the further etherification of the second hydroxyl group towards dimethyl isosorbide.

To gain further insights into the reaction of isosorbide with DMET, experiments were conducted with H₃PW₁₂O₄₀ as catalyst for different reaction time (Fig. 3). Isosorbide as starting material

was consumed rapidly in the initial 30 min, and then slowly reduced with further prolonged reaction time. The yields of both 5- and 2-*O*-monomethyl isosorbide ethers increased significantly and reached 29% and 19% in the first 60 min of reaction, respectively. With prolonging reaction time, the yield of 5-*O*-monomethyl isosorbide decreased apparently while the yield of 2-*O*-monomethyl isosorbide slightly decreased. Meanwhile, the yield of dimethyl isosorbide was gradually increased with increasing reaction time. A slight decrease in the total yields of isosorbide methyl ethers was noted as reaction time prolonged to 600 min. The different changing trends for isosorbide methyl ethers indicate that the etherification of two hydroxyl groups in isosorbide takes place sequentially, namely via the isosorbide monomethyl ethers towards the formation of dimethyl isosorbide. Additionally, the recyclability of the catalyst, H₃PW₁₂O₄₀, was attempted in the same reaction. After reaction, hexane was added into the reaction mixture to recover the catalyst. As shown in Fig. S1 (ESI[†]), although the isosorbide conversion decreased over three cycles, yields for monomethyl ethers of isosorbide remained. The loss in reactivity of the recovered catalyst might be caused by leaching of H₃PW₁₂O₄₀ in DMET.

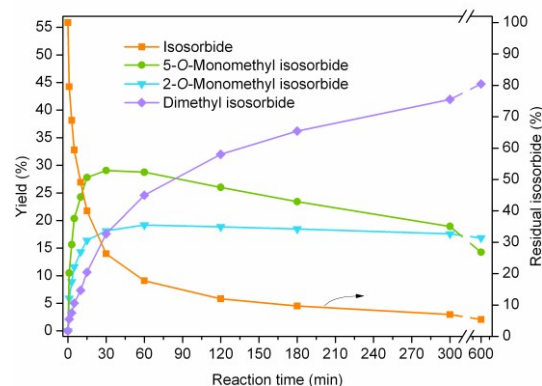


Fig. 3 Time course of the etherification reaction of isosorbide with DMET catalyzed by H₃PW₁₂O₄₀. Reaction conditions: Isosorbide (2 mmol), H₃PW₁₂O₄₀ (0.019 mmol), DMET (43 mmol), 150 °C.

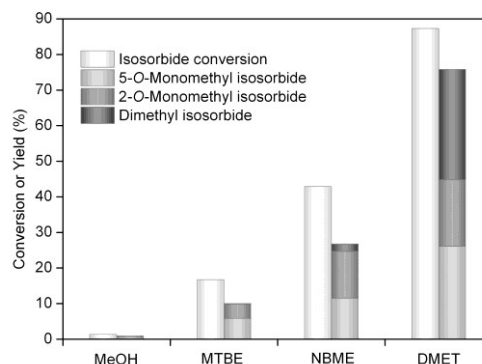






Fig. 4 Catalytic results for the etherification reaction of isosorbide with different etherification agents (MTBE: methyl *tert*-butyl ether, NBME: *n*-butyl methyl ether, DMET: 1,2-dimethoxyethane). Reaction conditions: Isosorbide (2 mmol), H₃PW₁₂O₄₀ (0.026 mmol), etherification agent (4.5 mL), 150 °C, 60min.

To verify the efficiency of DMET, several reagents with methoxy substituent were investigated during the etherification of isosorbide (Fig. 4). When methanol was used, only 1% isosorbide

was converted towards traces of isosorbide monoethers, indicating that methanol was inactive under our reaction condition. Methyl *tert*-butyl ether (MTBE) provided a 17% conversion of isosorbide with 10% yields of isosorbide methyl ethers. However, the etherified products with *tert*-butyl substituent were meanwhile formed with 5% yields (Table S1, entry 2, ESI†). Similarly, *n*-butyl methyl ether (NBME) as etherification agent afforded a 43% conversion of isosorbide with 27% yields of isosorbide methyl ethers as well as 11% yields of other isosorbide-derived ethers with butyl substituent (Fig. 4 and Table S1, entry 3, ESI†). Hence, the complexity of product mixture hinders MTBE and NBME as etherification agents. Notably, DMET exhibits the most promising results with a 87% conversion and 76% yields of isosorbide methyl ethers among etherification agents examined. Isosorbide-derived ethers with methoxyethyl group were formed in low yields of 3% (Table S1, entry 4, ESI†). To further verify the utility of DMET as etherification agent, the reaction mixture was isolated by using silica-gel column chromatograph to sequentially obtain dimethyl isosorbide (20% isolated yield), 2-*O*-monomethyl isosorbide (18% isolated yield), and 5-*O*-monomethyl isosorbide (28% isolated yield). Additionally, it has been reported DMET may be obtained renewably by oxidative coupling of dimethyl ether, which can be directly synthesized from biomass syngas.¹⁴ This enables the future synthesis of isosorbide methyl ethers exclusively from renewable feedstocks. Therefore, DMET can be employed as efficient etherification agent to achieve the selective formation of isosorbide methyl ethers.

To broaden the potential scope of this approach with DMET, several biomass-derived diols and aliphatic alcohols were chosen as alternative reactants catalyzed by H₃PW₁₂O₄₀ (Table 1). Both isomannide and isoidide, with similar structures to isosorbide, exhibit good results (Table 1, entries 1 and 2). Furthermore, the etherification approach is also feasible for the reaction of aliphatic alcohols with DMET (Table 1, entries 3 and 4). Thus, the hydroxyl groups in alcohols exhibited here present satisfying reactivities with DMET and achieved the corresponding methyl ethers in high yields.

Table 1 Etherification reactions of alcohols with 1,2-dimethoxyethane^a

Entry	Substrate	Structure	Conversion (%)	GC yield of methyl ether (%)
1	Isomannide		89	75 (38) ^b
2	Isoidide		72	61 (13) ^b
3	<i>n</i> -Butanol		100	66
4	<i>n</i> -Hexanol		98	70

^a Reaction conditions: Alcohol (2 mmol), H₃PW₁₂O₄₀ (0.026 mmol), DMET (43 mmol), 150 °C, 60 min. ^b GC yields of corresponding dimethylated ethers of isomannide and isoidide.

To gain further insights into the reaction pathway for the etherification of hydroxyl groups with DMET, byproducts were further analyzed by GC-MS during the isosorbide conversion. 2-Methoxyethanol was observed as a major byproduct (Fig. S2, ESI†). It indicates 2-methoxyethanol can be formed as the accompanying byproduct in the etherification of hydroxyl groups with DMET. Additionally, other byproducts were also detected (Fig. S3–S8, ESI†), including dimethyl ether, oligomers of DMET (di- and triglyme) and diethylene glycol monomethyl

ether, which could be mainly formed by self-condensation side-reactions of DMET. Hence, it indicates that methyl group in the etherified products may be directly provided by DMET leaving 2-methoxyethanol as the accompanying byproduct of the etherification reaction (Scheme S1, ESI†).

Furthermore, only three isosorbide methyl ethers were formed by the etherification of isosorbide with DMET based on their NMR spectral data shown in experimental section. It suggests that all isosorbide-derived methyl ethers can preserve their configurations in our synthetic method, which could be ascribed to the rigid structure of isosorbide. It also indicates that hydroxyl groups in isosorbide can function as nucleophilic group during the etherification of isosorbide with DMET.

Conclusions

1,2-Dimethoxyethane was explored for the first time as etherification agent for the acid-catalyzed synthesis of methyl ethers from biomass-derived hydroxyl compounds. The etherification activities of hydroxyl groups in isosorbide with DMET strongly depend on the type of acid catalyst and the acid amount. The successful exploration of DMET as etherification agent opens up a new etherification approach to functionalize hydroxyl groups in alcohols. It also provides an efficient route towards the synthesis of methyl ethers from the readily accessible ether.

Experimental section

General information: All chemicals employed here were commercially supplied with analytical grade purity unless otherwise specified. NMR spectra (¹H and ¹³C) were recorded on a Bruker AVANCE III 400 (MHz) spectrometer (¹H at 400 MHz, ¹³C at 101 MHz) in CDCl₃ with tetramethylsilane (TMS) as internal standard. Gas chromatography (GC) analysis was conducted using an Agilent 7890 GC equipped with a flame ionization detector (FID) and a HP-INNOWAX capillary column (30 m × 0.32 mm × 0.25 μm). Gas chromatography-mass spectrometry (GC-MS) analysis was carried out using an Agilent 7890A GC/5975C MS with a HP-5MS capillary column (30.0 m × 0.25 mm × 0.25 μm) and electrospray ionization (ESI) mode. Column chromatography was conducted on silica-gel (200-300 mesh).

General procedure for the reaction of isosorbide with DMET: The catalytic etherification of isosorbide with DMET was performed in a 20 mL stainless steel autoclave reactor equipped with a manometer, automatic temperature controller and a magnetic stirring bar. In a typical experiment, isosorbide (2 mmol), DMET (43 mmol) and the given amount of acid catalyst were charged into the reactor. Then, the sealed reactor was heated to 150 °C with stirring (900 rpm) for the desired reaction time under autogenous pressure. After reaction, the autoclave was cooled down. The reaction mixtures were neutralized with triethylamine prior to GC analysis. Reaction products were ascertained by GC-MS and by comparison with the GC retention times of the corresponding authentic samples.

The catalytic results exhibited here were either in terms of conversion or in terms of yields towards desired methyl ethers, which were determined by GC internal standard method using

naphthalene as internal standard. All results were calculated based on the initial amount of isosorbide. The conversion of isosorbide and the yields of monoether (2-*O* and 5-*O*-monomethyl isosorbide) and diether (dimethyl isosorbide) products, expressed as mol%, were determined as below.

$$\text{Conversion} = \left(1 - \frac{\text{moles of unreacted isosorbide}}{\text{moles of initial isosorbide}}\right) \times 100\%$$

$$\text{Monoether yield} = \left(\frac{\text{moles of formed monoether}}{\text{moles of initial isosorbide}}\right) \times 100\%$$

$$\text{Diether yield} = \left(\frac{\text{moles of formed diether}}{\text{moles of initial isosorbide}}\right) \times 100\%$$

Separation of the isosorbide methyl ethers: At the end of the reaction, with the addition of hexane, the reaction mixtures were separated into two layers after centrifugation. The transparent organic layer was collected, concentrated with a rotary evaporator, and distilled under vacuum. Then, the enriched distillation fractions were subjected to silica-gel column chromatography eluted with a gradient mixture of petroleum ether/acetone (15/1 to 5/1, v/v). Thus, isosorbide methyl ethers were isolated as pure compounds.

2-*O*-Monomethyl isosorbide: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.60 (t, $J = 5.0$ Hz, 1H), 4.47 (d, $J = 4.5$ Hz, 1H), 4.33–4.24 (m, 1H), 4.05 (d, $J = 9.9$ Hz, 1H), 3.92 (d, $J = 3.8$ Hz, 1H), 3.90–3.81 (m, 2H), 3.58 (dd, $J = 9.5$ Hz, $J = 5.6$ Hz, 1H), 3.39 (s, 3H), 2.68 (d, $J = 6.7$ Hz, 1H) ppm. $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 85.94, 85.77, 82.04, 73.95, 73.32, 72.54, 57.53 ppm. ESI-MS (m/z): 160 (M^+).

5-*O*-Monomethyl isosorbide: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.73 (t, $J = 4.1$ Hz, 1H), 4.46 (d, $J = 4.2$ Hz, 1H), 4.32 (d, $J = 2.8$ Hz, 1H), 4.03–3.90 (m, 4H), 3.58 (t, $J = 10.8$ Hz, 1H), 3.48 (s, 3H), 2.18 (s, 1H) ppm. $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 88.69, 82.11, 80.09, 77.07, 76.22, 70.26, 58.60 ppm. ESI-MS (m/z): 160 (M^+).

Dimethyl isosorbide: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.66 (t, $J = 4.3$ Hz, 1H), 4.52 (d, $J = 4.3$ Hz, 1H), 4.04–3.90 (m, 4H), 3.89–3.85 (m, 1H), 3.65–3.54 (m, 1H), 3.47 (s, 3H), 3.38 (s, 3H) ppm. $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 86.23, 86.21, 82.11, 80.22, 73.35, 70.07, 58.56, 57.50 ppm. ESI-MS (m/z): 174 (M^+). All spectral features of isosorbide methyl ethers correspond to those reported in the literature.⁵ See ESI† for more experimental details.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details; additional table, scheme and figures; copies of NMR, GC and MS spectra. See DOI: 10.1039/b000000x/

- (a) R. J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres and J. G. de Vries, *Chem. Rev.*, 2013, **113**, 1499; (b) Y. L. Wang, W. P. Deng, B. J. Wang, Q. H. Zhang, X. Y. Wan, Z. C. Tang, Y. Wang, C. Zhu, Z. X. Cao, G. C. Wang and H. L. Wan, *Nat. Commun.*, 2013, **4**.
- (a) P. Che, F. Lu, J. Zhang, Y. Huang, X. Nie, J. Gao and J. Xu, *Bioresour. Technol.*, 2012, **119**, 433; (b) I. Sádaba, Y. Y. Gorbanev, S. Kegnaes, S. S. R. Putluru, R. W. Berg and A. Riisager, *ChemCatChem*, 2013, **5**, 284; (c) J. Y. Cai, H. Ma, J. J. Zhang, Q. Song, Z. T. Du, Y. Z. Huang and J. Xu, *Chem. - Eur. J.*, 2013, **19**, 14215; (d) M. Rose, K. Thenert, R. Pfitzenreuter and R. Palkovits, *Catal. Sci. Technol.*, 2013, **3**, 938; (e) J. Li, L. Liu, Y. Liu, M. Li, Y. Zhu, H. Liu, Y. Kou, J. Zhang, Y. Han and D. Ma, *Energy Environ. Sci.*, 2014, **7**, 393.
- W. P. Deng, M. Liu, Q. H. Zhang, X. S. Tan and Y. Wang, *Chem. Commun.*, 2010, **46**, 2668.
- M. Sutter, W. Dayoub, E. Mđay, Y. Raoul and M. Lemaire, *ChemCatChem*, 2013, **5**, 2893.
- P. Tundo, F. Aricò G. Gauthier, L. Rossi, A. E. Rosamilia, H. S. Bevinakatti, R. L. Sievert and C. P. Newman, *ChemSusChem*, 2010, **3**, 566.
- H. Zhu, Q. Cao, C. H. Li and X. D. Mu, *Carbohydr. Res.*, 2011, **346**, 2016.
- (a) M. Rose and R. Palkovits, *ChemSusChem*, 2012, **5**, 167; (b) J. I. Garcia, H. Garcia-Marin and E. Pires, *Green Chem.*, 2014, **16**, 1007; (c) M. J. Climent, A. Corma and S. Iborra, *Green Chem.*, 2014, **16**, 516.
- M. Selva and A. Perosa, *Green Chem.*, 2008, **10**, 457.
- P. Tundo, S. Memoli, D. Herault and K. Hill, *Green Chem.*, 2004, **6**, 609.
- G. A. Kraus and T. Guney, *Green Chem.*, 2012, **14**, 1593.
- J. A. Melero, G. Vicente, M. Paniagua, G. Morales and P. Muñoz, *Bioresour. Technol.*, 2012, **103**, 142.
- (a) M. Adinolfi, A. Iadonisi, A. Ravidà and M. Schiattarella, *Tetrahedron Lett.*, 2004, **45**, 4485; (b) Y.-C. Lu, D. G. Kwabi, K. P. C. Yao, J. R. Harding, J. Zhou, L. Zuin and Y. Shao-Horn, *Energy Environ. Sci.*, 2011, **4**, 2999.
- G. D. Yadav and J. J. Nair, *Microporous Mesoporous Mater.*, 1999, **33**, 1.
- (a) G. Liu, Q. Zhang, Y. Han, N. Tsubaki and Y. Tan, *Green Chem.*, 2013, **15**, 1501; (b) Y. Lv, T. Wang, C. Wu, L. Ma and Y. Zhou, *Biotechnol. Adv.*, 2009, **27**, 551.