Contents lists available at ScienceDirect







journal homepage: www.elsevier.com/locate/mcat

# Molybdenum (VI)-catalyzed dehydrative construction of C–O and C–S bonds formation via etherification and thioetherification of alcohols and thiols



# Rahulkumar Rajmani Singh, Alex Whittington, Radhey S. Srivastava\*

University of Louisiana at Lafayette, Department of Chemistry, Louisiana, LA 70504, USA

ARTICLE INFO	A B S T R A C T
Keywords:	An inexpensive, easily available, environmentally benign, and efficient catalyst molybdenum(VI) dioxo (acet-
Hydroxyl activation	ylacetonate) $_2$ was used for the direct oxo- and thioetherification of alcohol. This method endures selective
Mo catalysis	molybdenum catalyzed dehydrative synthesis of symmetrical ethers from benzylic secondary alcohols as well as unsymmetrical ethers from the reaction of benzylic secondary alcohols with primary alcohol. Furthermore, we
C–O and C–S bond Dehydrative	have been also successful in the synthesis of Aryl thioether by using alcohol and thiols.

### Introduction

The formation of C–O bonds by alkylation and arylation reactions is very important to synthesize ethers and has become a major objective for the construction of pharmaceutically important compounds. The common structural motif of ethers found widespread application in the various synthesis, the common application as solvents on a daily basis. In addition, ethers have numerous important applications such as drug intermediates, fragrances, herbicides, plasticizers, disinfectants, and precursors in polymers [1]. The traditional method for etherification employs alkyl halides and sodium alkoxide, invented by Williamson [2]. This method is not very efficient as it involved a multistep process that requires preparation of toxic halide precursor which can be formed from the corresponding alcohols. Another serious limitation of the Williamson method is producing symmetrical and unsymmetrical ethers by generating inorganic waste [3]. The formation of C-S bonds have been exploited as an important building block for the efficient preparation of naturally occurring products and range of application in pharmaceuticals, biologically active compounds and in agrochemicals [3a-3b]. Nevertheless, like oxo ether, thioethers also can be conventionally synthesized from alkyl halide precursor involving multistep procedures with limited substrate scope [4]. Therefore development of a greener method which reduces the inorganic waste formation was really important aspects of the researcher around the world.

Construction of C–O and C–S bonds by means of substitution of the highly deactivated hydroxyl group of alcohol have found great attention in the past [5,6]. The poor ability of hydroxyl functionality as a leaving group makes exciting to activate hydroxide. Subsequently, hydroxide activation by nucleophilic substitution has been recognized as a key area for green chemistry research (Scheme 1). Dehydration transformation of alcohol into valuable final products have found widespread attention in organic synthesis.

These inadequacies were addressed by the development of the transition-metal-catalyzed synthesis of ethers from diverse functional groups. For instance, previously reported reaction for the synthesis of Aryl ethers derivatives using aryl halides precursors and alcohols in the reaction of Ullmann-type [7] with Pd- and Cu-catalysts, etherification reaction of Mitsunobu-type [8], reductive deoxygenations of esters [6], redox condensation of alcohols via alkoxydiphenylphosphines [7], various alkenes affording corresponding ethers by hydro-etherification reaction consuming alcohols [9], and aryl C-H bonds oxidative etherification are reported [10]. The results of these reactions suffer from the narrow scope and poor atom economy. Therefore, the development of etherification reaction with direct coupling of alcohol is essential which can be atom economical and environmentally compassionate and producing water as the sole byproduct (Scheme 2). Heterogeneous acid or strong Brønsted acid catalysts have been used for the synthesis of ethers in bulk [11]. The synthesis of unsymmetrical

\* Corresponding author. *E-mail address:* rss1805@louisiana.edu (R.S. Srivastava).

https://doi.org/10.1016/j.mcat.2020.110954

Received 18 March 2020; Received in revised form 10 April 2020; Accepted 11 April 2020 2468-8231/@ 2020 Elsevier B.V. All rights reserved.

**Conventional Methods:** 



Scheme 1. Comparison between conventional and catalytic method.

ethers directly from two different alcohols is also realized using transition-metal catalysts [12]. There have been several reports on the transition metal-catalyzed synthesis of oxoether and thioether (Scheme 2) [7–12], but there is still scope for the development of cheaper and greener methods for its synthesis.

Herein, we report a highly selective dehydrative formation of symmetrical and unsymmetrical ethers of two different alcohols which have been not reported yet. The method also works nicely for the synthesis of thioether derivatives using the same standard reaction conditions to afford various substituted thioether derivatives. This catalytic method can tolerate a wide range of alcohols by generating water as a sole byproduct under mild conditions by using cheap and commercially available Mo (VI) catalyst. These reactions proceed via activation of secondary benzylic alcohols to form symmetrical ethers and subsequently unsymmetrical ethers formed in the presence of primary alcohols.

### **Results and discussion**

During optimization, we treated 1-phenyl ethanol 1a with MoO<sub>2</sub>Cl<sub>2</sub> the catalyst in dichloromethane as a solvent at 30 °C, which afforded desired oxoether product 2a in 28% yields with two isomeric form dr the ratio of 1:1, and also a small quantity of styrene 2a' as a byproduct (entry 1). The results excited us to explore other Mo catalytic system

and indeed there was an increase in the yield of the products up to 42% by using  $MoO_2(acac)_2$  in dichloromethane (DCM) at 30 °C (entry 2). By increasing temperature up to 60 °C and changing the solvent from DCM to 1,2 dichloroethane (DCE) we have seen a substantial increase in the yield of the oxoether products up to 61% with  $MoO_2Cl_2$  catalyst (entry 3). Entry 4 shows an increase in the yield up to 82% by using  $MoO_2(acac)_2$  catalyst and DCE as a solvent at 60 °C. Further, we tested various molybdenum catalyst such as  $Mo(CO)_6$ ,  $MoO_3$  and  $(NH_4)_6Mo_7O_{24}.4H_2O$  in entry 5–7 but all in three cases desired oxoether was obtained in small amounts. Changing solvents such as toluene and benzene (entry 8 and 9) respectively but the results were not impressive. These solvents failed to show any improvement in reaction efficiency (Table 1)

Having optimized reaction conditions in hand, we carried out the substrate scope for the oxoethers moieties. These reactions show broad substrate scope with a range of alcohols affording desired ethers in all the cases with good to excellent yield. Results have been presented in Table 2 showing its scope for symmetrical and non-symmetrical ether derivatives. We treated 1-phenyl propanol 1b with MoO<sub>2</sub>(acac)<sub>2</sub> the catalyst in DCE at 60 °C which affords corresponding oxoether 2b in 75% with dr ration of 1:1 (entry 2). Various electron-donating and withdrawing substitution at the para position of phenyl ethanol was also investigated under an optimized reaction condition. Desired products 2c-2e in 81-85% with a good dr ratio (entry 3-5) were observed. Diphenyl carbinol 1f was also a suitable substrate for this catalytic reaction affording the corresponding oxoether products 2f in 92% yield. We have also shown the importance of our catalytic system by synthesizing numerous unsymmetrical oxoether products 2g-2j by treating various aliphatic alcohol such as butanol, hexanol, heptanol and octanol with 1-phenyl ethanol 1a which afforded the corresponding product in 89-93% (entry 7-10).

Under a similar reaction condition, we explored the synthesis of thioethers, and results were pleasing to get desired thioethers **4a** in excellent yield without much loss in the starting materials (Table 3). Oxo ether **2a** was the minor products in this case (< 5%), in the case of diphenyl disulfide **3a'** a small amount of thiol dimer was detected as the result of the dimerization of thiols (< 5%). A relatively very small amount of two byproducts formation indicates the high the efficiency of this methodology and representing the importance of the catalytic system.

The reaction has a broad substrate scope and we have only shown



This Work: Cheap Mo(VI) catalysed dehydrative construction of C-O and C-S bonds.



Scheme 2. Generalization of the metal catalyzed C-O and C-S bond formation.

## Table 1

Optimization of reaction condition.

OH	$(10 \text{ mol}\%)^{a}$ $MoO_{2}(acac)_{2}$ $DCE, 60 \text{ °C}, 24 \text{ h}$ $+$	$\sim$	
1a	2a (dr = 1:1) 2a'		
Entries	Catalyst	Solvent	Yields of <b>2a</b> (%) <sup>b</sup>
1 <sup>c</sup>	MoO <sub>2</sub> Cl <sub>2</sub>	DCM	28
$2^{c,d}$	MoO <sub>2</sub> (acac) <sub>2</sub>	DCM	42
3	$MoO_2Cl_2$	DCE	61
4	$MoO_2(acac)_2$	DCE	82
5	Mo(CO) <sub>6</sub>	DCE	10
6	MoO <sub>3</sub>	DCE	< 5
7	(NH <sub>4</sub> ) <sub>6</sub> Mo <sub>7</sub> O <sub>24</sub> .4H <sub>2</sub> O	DCE	0
8	$MoO_2(acac)_2$	Toluene	20
9	MoO <sub>2</sub> (acac) <sub>2</sub>	Benzene	29

[a] **1a** : 0.03 M, [b] yields are reported after isolation from silica coumn, [c] reaction was done at 30 °C, [d] MoO<sub>2</sub>(acac)<sub>2</sub>: Bis(acetylacetonato)dioxomolybdenum (VI), DCE : 1,2-dichloroethane.

### Table 2



[a] 1a: 0.03 M, [b] Yield of the reaction were reported after purification from silica column, [c] MoO<sub>2</sub>(acac)<sub>2</sub> :Bis(acetylacetonato)dioxomolybdenum(VI), DCE: 1,2-dichloroethane.

[a] **1a** : 0.03 M, [b] Yield of the reaction were reported after purification from silica column, [c] MoO2(acac)2 :Bis(acetylacetonato)dioxomolybdenum (VI), DCE : 1,2-dichloroethane.

the variation on the alcohols. Various 1-aryl ethanol 1 and thiophenol 3a was subjected to standard reaction condition delivering the desired aryl thioethers 4a-4g in excellent yield (entries 1–7). 1-phenyl ethanol 1a and 1-phenyl propanol 1b reacts with thiophenol in the presence of  $MoO_2(acac)_2$  afforded desired thioether products 4a and 4b in 89% and 91% yield respectively with a small amount of 2a and 3a' (entry1–2).

To explore the influence of electronic effects on the dehydration reaction we used various electron-donating and electron-withdrawing substitution such as *p*-Me, OMe, Cl and Br at the para position of the phenyl group in alcohol **1c–1e** and **1g** delivering the corresponding thioethers **4c–4f** in 90–94% yield (entry 3–6). Diphenyl carbinol **1f** was also applicable substrate for this transformation and delivered the corresponding thioether **4g** in 95% yield (entry 7).

We have presented a plausible catalytic cycle for this transformation (Scheme 3). Both oxoether and thioether product formation is explained. In the catalytic cycle for the formation of oxoether molybdenum catalyst coordinates with the alcohol 1 to form the intermediate **A** which was simultaneously attacked with the second molecule of alcohol to afford intermediate **B**. In this process (A - > B) there is a cleavage of C–O bond and in situ formation of stable secondary carbocation takes place. Upon dehydration corresponding oxoether products **2** was produced with the liberation of Mo catalyst<sup>12h</sup>. The rationale of thioether formation mechanism for the formation is the oxidation of alcohol 1 to corresponding ketone [13] **C** by reducing the molybdenum and then it was attacked by thiols to give intermediate **D** which liberates the water molecule to deliver corresponding thioether products **4**.

### Conclusion

In conclusion, we have developed dehydrative C–O and C–S bond formation reaction by using cheap and commercially available molybdenum catalyst delivering oxoethers and thioethers in excellent yield. The use of cheap catalysts and liberating water as sole byproducts indicates the foliage and effectiveness of this methodology. Also, this method highlighted the activation of the hydroxyl functional group of alcohol selectively affording desired products in high yields. Further studies were going on in our laboratory for the use of molybdenum catalyst in various C-heteroatom bond formation reactions.



[a] **3a** : 0.03 M, [b] Yield of the reaction were reported after purification from silica column, [c]  $MoO_2(acac)_2$ :Bis(acetylacetonato)dioxomolybdenum(VI), DCE : 1,2-dichloroethane.





Scheme 3. Plausible catalytic cycle for the formation of Oxoether and Thioether.

### Credit author statement

The idea was designed and conceived by principal author Dr. Radhey S. Srivastava. Alex Whittington an undergraduate student has done the synthesis of 2 molecule in oxoether and 5 molecules in thioether substrate scope in the supervision of Dr. Rahul Kumar Rajmani Singh a post-doctoral research associate. Rest molecules were synthesized by Dr. Rahul Kumar Rajmani Singh.

### **Declaration of Competing Interest**

Author declare no conflict of interest.

### Acknowledgment

The authors are grateful to the University of Louisiana at Lafayette for financial support of this work.

### References

- [1] (a) S. Mandal, S. Mandal, S.K. Ghosh, P. Sar, A. Ghosh, R. Saha, B. Saha, RSC Adv. 6 (2016) 69605;
  - (b) M. Pagliaro, R. Ciriminna, H. Kimura, M. Rossi, C.D. Pina, Angew. Chem. Int. Ed. 46 (2007) 4434;
- (c) W.H. Miles, K.B. Connell, J. Chem. Educ. 83 (2006) 285.[2] A.I. Williamson, Ueber die Theorie Der Aetherbildung, Justus Liebigs Ann. Chem.
- 77 (1851) 37.
- [3] a) A. Suzuki, H.C. Brown, Organic Syntheses Via Boranes 3 Aldrich Chemical Company, Milwaukee, WI, 2003;
  b) X.-Y. Ke, V.W.L. Ng, S.-J. Gao, Y.W. Tong, J.L. Hedrick, Y.-Y. Yang, Biomaterials
  - 35 (2014) 1096.
- [4] (a) H. Liu, X. Jiang, Chem. Asian J. 8 (2013) 2546;
  - (b) Z. Qiao, X. Jiang, Org. Biomol. Chem. 15 (2017) 1942;
    (c) G.-P. Lu, C. Cai, Adv. Synth. Catal. 355 (2013) 1271;
  - (d) E. Calce, M. Leone, F.A. Mercurio, L. Monfregola, S. DeLuca, Org. Lett. 17
  - (2015) 5646;
  - (e) J.E. Baer, R.G. Lockwood, J. Am. Chem. Soc. 76 (1954) 1162;
  - (f) O. Kundrat, V. Eigner, H. Dvorakova, P. Lhotak, Org. Lett. 13 (2011) 4032;
  - (g) S. Murru, B.K. Patel, J. LeBras, J. Muzart, J. Org. Chem. 74 (2009) 2217;
  - (h) Y. Yang, Z. Ye, X. Zhang, Y. Zhou, X. Ma, H. Cao, H. Li, L. Yu, Q. Xu, Org.

Biomol. Chem. 15 (2017) 9638.

- [5] S.-S. Meng, Q. Wang, G.-B. Huang, L.-R. Lin, J.-L. Zhao, A.S.C. Chan, RSC Adv. 8 (2018) 30946.
- [6] (a) S. Podder, J. Choudhury, S. Roy, J. Org. Chem. 72 (2007) 3129;
- (b) L. Zhang, A. Gonzalez-de-Castro, C. Chen, F. Li, S. Xi, L. Xu, J. Xiao, Mol. Catal. 433 (2017) 62;
- (c) S. Shirakawa, S. Kobayashi, Org. Lett. 9 (2007) 311;
- (d) Y.-L. Liu, L. Liu, Y.-L. Wang, Y.-C. Han, D. Wang, Y.-J. Chen, Green Chem. 10 (2008) 635;
- (e) A. Zhu, L. Li, J. Wang, K. Zhuo, Green Chem. 13 (2011) 1244;
- (f) K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, Angew. Chem. Int. Ed. 45 (2006) 2605;
- (g) J. Li, X. Zhang, H. Shen, Q. Liu, J. Pan, W. Hu, Y. Xiong, C. Chen, Adv. Synth. Catal. 357 (2015) 3115;
- (h) Q. Xu, H. Xie, P. Chen, L. Yu, J. Chen, X. Hu, Green Chem. 17 (2015) 2774.
- [7] (a) P.E. Maligres, J. Li, S.W. Krska, J.D. Schreier, I.T. Raheem, Angew. Chem. Int. Ed. 51 (2012) 9071;
  - (b) S.V. Ley, A.W. Thomas, Angew. Chem. Int. Ed. 42 (2003) 5400;
  - (c) J.F. Hartwig, Angew. Chem. Int. Ed. 37 (1998) 2046.
- [8] (a) K.C.K. Swamy, N.N.B. Kumar, E. Balaraman, K.V.P.P. Kumar, Chem. Rev. 109 (2009) 2551;
  - (b) D. Ma, Q. Cai, Acc. Chem. Res. 41 (2008) 1450;
  - (c) T.Y.S. But, P.H. Toy, Chem. Asian J. 2 (2007) 1340;
  - (d) K. Kunz, U. Scholz, D. Ganzer, Synlett (2003) 2428.
- [9] (a) M.C. Haibach, C. Guan, D.Y. Wang, B. Li, N. Lease, A.M. Steffens, K. Krogh-Jespersen, A.S. Goldman, J. Am. Chem. Soc. 135 (2013) 15062;

(b) N. Sakai, T. Moriya, T. Konakahara, J. Org. Chem. 72 (2007) 5920;
(c) M.B. Sassaman, K.D. Kotian, G.K.S. Prakash, G.A. Olah, J. Org. Chem. 52 (1987) 4314.

- [10] (a) J. Roane, O. Daugulis, Org. Lett. 15 (2013) 5842;
  (b) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang, B.-F. Shi, Chem. Sci. 4 (2013) 4187; (2012) 7313;
  (c) S.-Y. Zhang, G. He, Y. Zhao, K. Wright, W.A. Nack, G. Chen, J. Am. Chem. Soc. 134 (2012) 7313;
  (d) W. J. P. Grag, L. G. Chem. 57 (2012) 2020.
  - (d) W. Li, P. Sun, J. Org. Chem. 77 (2012) 8362.
- [11] (a) K. Manabe, S. limura, X.-M. Sun, S. Kobayashi, J. Am. Chem. Soc. 124 (2002) 11971;
- (b) K. Tanabe, W.F. Hölderich, Appl. Catal. A Gen. 181 (1999) 399;
- (c) I. Nowak, M. Ziolek, Chem. Rev. 99 (1999) 3603;
- (d) K. Klier, A. Beretta, Q. Sun, O.C. Feeley, R.G. Herman, Catal. Today 36 (1997) 3.
- [12] (a) R.M.P. Veenboer, S.P. Nolan, Green Chem. 17 (2015) 3819;
   (b) A.B. Cuenca, G. Mancha, G. Asensio, M. Medio-Simón, Chem. Eur. J. 14 (2008) 1518;
  - (c) J. Kim, D.-H. Lee, N. aluntharage, C.S. Yi, ACS Catal. 4 (2014) 3881;
  - (d) K.J. Miller, M.M. Abu-Omar, Eur. J. Org. Chem. (2003) 1294;
  - (e) G.V.M. Sharma, A.K. Mahalingam, J. Org. Chem. 64 (1999) 8943;
  - (f) Z. Zhu, J.H. Espenson, J. Org. Chem. 61 (1996) 324;
  - (g) K. Kucinski, G. Hreczycho, Eur. J. Org. Chem. (2017) 5572;
- (h) P.K. Sahoo, S.S. Gawali, C. Gunanathan, ACS Omega 3 (2018) 124.
- [13] I. Sorribes, A. Corma, Chem. Sci. 10 (2019) 3130.