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Screening of Lewis acids catalyzed cross etherification of benzylic and primary alcohols

Anvar Mirzaei*

Department of Chemistry, Sanandaj Branch, Islamic Azad University, Sanandaj, Iran

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Abstract: The recent application of transition metals to direct functionalization processes has opened an opportunistic new class of carbon-oxygen bond forming reactions. In this work, a screening of different transition metal complexes for their ability to catalyze different substitution reaction of benzylic alcohols was performed.

Keywords: Lewis acid, Benzylic alcohols, Williamson reaction, Ether formation.

Introduction

The search for low-waste technologies and multifunctional processes in organic synthesis is becoming more and more pressing for both economical and environmental concerns. In fact the use of traditional stoichiometric reagents for the preparation of organic molecules is still widely common, especially due to their high activity and specificity [1-8]. Ether formation is an important reaction in organic synthesis, for both bulk and fine chemicals preparation, and it is traditionally performed with the Williamson reaction starting from an alcohol and a halide by using a strong base for the alkoxide formation [9-10]. Actually, the reaction is particularly useful for the preparation of mixed ethers, as it involves the direct nucleophilic displacement of halogen in the alkyl halide by the alkoxide ion. Moreover, the use of the conditions requested strongly limits the industrial applications, but above all imposes serious environmental and economical concerns due to waste disposal processes. Thus, to avoid the use of bases and halide reagents could be a successful strategy in order to set up a cleaner and simple protocol. Brønsted acid catalysts are known to promote ether formation starting from the corresponding alcohols by means of a dehydration process [11-14]. In fact alcohols are attractive electrophiles as they are cheap and readily available However, the cleavage of oxygen-carbon bonds poses a great challenge in organic chemistry, demanding harsh conditions due to the fact that hydroxide ions are poor leaving groups. Carbon-Oxygen bond formation using alcohols as electrophiles has attracted much attention recently as the only by product in this methodology is water.

Results and discussion

The most common catalysed S_N1 benzylic alcohols reported in the literature is the cross etherification with an aliphatic alcohol. Butanol was chosen as the nucleophile as it is a small molecule and has relatively high boiling point. The general reaction is shown in scheme **1**. Benzyl alcohol proved to be unreactive in the presence of $FeCl_3$, $BiCl_3$, $BiBr_3$, and $NaAuCl_4$. Etherification using $BiBr_3$ was attempt according to the procedure described by Boyer et al. but the alcohol remained unreactive. The reaction was also attempted in DCE (Dichloro ethane) and with varying amount of the catalyst but with the same unsatisfactory result. The yield of the reaction was increased to 65% by using the 4-methoxybenzyl alcohol (**1a**). Reactions

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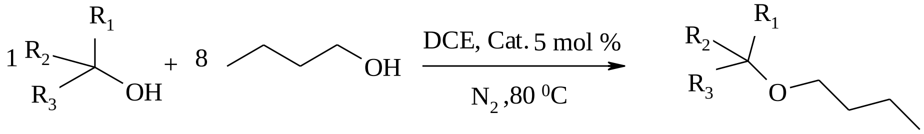
*Corresponding author. Tel: (+98) 871 3288661, Fax: (+98) 871 3288662, E-mail: mirzaei.anvar@iausdj.ac.ir

involving diphenylmethanol (**1b**) and n-butanol (**2**) worked well and yielded 89% of the desired product (**3b**). Etherification of triphenylmethanol (**1c**) afforded the desired product but only in poor yield (25%). In one instance triphenylmethane was obtained as the main product, which is formed through disproportionation of alcohol.

Screening of transition metals:

During the reactions, samples were taken out regularly for ^{1}H-NMR spectroscopic analysis. The samples were filtered through silica to remove the catalyst and the solvent was evaporated *in vacuo*. To the samples of different mixtures a solution of 1, 4-dioxane as internal standard was added and quantification of the products was performed by comparing of known signals off product and internal standard. The results of these experiments are shown in scheme **1.**



1 a-c **2** **3 a-c**

1	R1	R2	R3	Catalyst	time (hr)	Yilde%, **3a-c**
a	4-Meo-Ph	H	H	$FeCl_3$	20	10
				$PdCl_2$	20	25
				$ReBr(CO)_5$	20	65
				$NaAuCl_4$	20	24
				PTSA	20	15
b	Ph	Ph	H	$FeCl_3$	8	60
				$PdCl_2$	8	50
				$ReBr(CO)_5$	8	89
				$NaAuCl_4$	8	70
				PTSA	8	79
c	Ph	Ph	Ph	$FeCl_3$	6	25
				$PdCl_2$	6	20
				$ReBr(CO)_5$	6	16
				$NaAuCl_4$	6	8
				PTSA	6	18

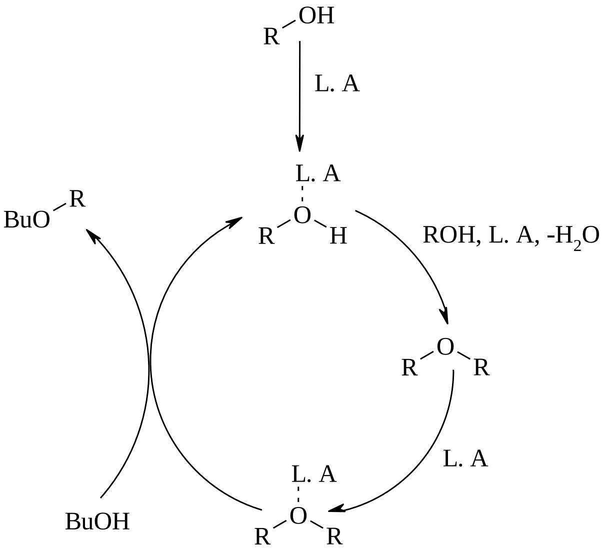
Scheme 1. Screening of different Lewis acids

Mechanistic consideration:

According to the information available in the literature [15-16], It was found that all these reactions proceed via the symmetrical ether and the follow mechanism can be proposed (Scheme **2**).

Lewis acids vs. Brønsted acids as catalyst:

To compare the Lewis acid catalysts used in this work with the efficiency of Brønsted acid, a reaction using 4-toluenesulfonic acid was preformed. Although Brønsted acids seem to function as efficient catalyst for this type of reactions, many desired substrates may be acid sensitive and metal based acids are preferred. This metal based catalyst may also have greater potential, because Brønsted acids are limited by the fact that they only protonate the substrate, while the specific interaction between metal based catalysts can be developed further [17-18].



Scheme 2. Proposed mechanism for the Lewis acid catalyzed substitution reaction of benzylic alcohols.

Conclusion

In summary, a screening of different transition metal complexes for their ability to catalyze different substitution reaction of benzylic alcohols was performed. The screening was designed for the comparison of the reactivities of $FeCl_3$, $NaAuCl_4$, $ReBr(Co)_5$, $ReMeO_3$, $PdCl_2$ and PTSA, for S_N1 reactions using oxygen central nucleophiles. We have shown effectiveness of different catalysts for the synthesis of unsymmetrical benzylic ethers. From the results of the screening experiments it can be concluded that the catalysts efficiencies are depended on both substrate and catalyst.

Experimental

Compounds **1-3** were obtained from *Sigma Aldrich* and used without further purification, uncorrected. ^{1}H-, ^{13}C-NMR Spectra: *Bruker DRX-500-Avance* instrument or Varian *500*- INOVA in $CDCl_3$ at 500 and 125 for hydrogen and carbon. ; *δ* in ppm, *J* in Hz. Elemental analyses (C, H, N): *Heraeus CHN-O-Rapid* analyzer.

General procedure for the synthesis of compounds **3**:

A well dried round flask was charged with the catalyst, the substrate (1 mmol) was added and the flask was purged with nitrogen for 1 minute, then the nucleophile (8 mmol), and solvent (5 ml) were added. Then heated at 80 °C for appropriate time. The solvent was removed under reduced pressure and the residue was separated by silica gel (Merck 230–400 mesh) column chromatography using *n*-hexane–EtOAc (7:1) mixture as eluent to get pure product **3**.

*Para methoxybenzyl buthyl ether (**3a**):*

Colorless oil, ^{1}H-NMR: 0.97 (3 H, t, ^3J= 7.4, CH_3), 1.41-1.49 (2 H, m, CH_2), 1.62- 1.67 (2 H, m, CH_2), 3.50 (2 H, t, ^3J= 6.6, O-CH_2), 3.85 (3 H, s, OMe), 4.49 (2 H, s, O-CH_2-Ph), 6.92 (2 H, d, ^3J = 7.5, 2 CH), 7.31 (2H, *d*, *J*= 7.5, 2 CH). ^{13}C-NMR: 14.0 (CH_3), 19.6 (CH_2), 32.1 (CH_2), 55.4 (OCH_3), 70.1 (OCH_2), 72.7 (OCH_2-Ph), 114 (2 CH), 129.2 (2 CH), 131.1 (C), 159.3 (C). Anal. Calc. For $C_{12}H_{18}O_2$ (194.28): C 74.19, H 9.34; found: C 74.25, H 9.20.

*Diphenylmethanol buthyl ether (**3b**):*

Colorless oil, ^{1}H-NMR: 1.0 (3 H, t, ^3J = 7.5, CH_3), 1.48-1.55 (2 H, m, CH_2), 1.70- 1.75 (2 H, m, CH_2), 3.54 (2 H, t, ^3J = 6.5, O-CH_2), 5.42 (1 H, s, O-$CHAr_2$), 7.29-7.45 (10 H, m, 10 CH). ^{13}C-NMR: 14.2 (CH_3), 19.8 (CH_2), 32.3 (CH_2), 69.2 (OCH_2), 83.9 (O-$CHAr_2$), 127.2 (4 CH), 127.6 (4 CH), 128.6 (2 CH), 143.0 (2 C). Anal. Calc. For $C_{17}H_{20}O$ (240.35): C 84.96, H 8.39; found: C 85.1, H 8.25.

*Triphenylmethanol buthyl ether (**3c**):*

White solid, mp: 115 °C, ^{1}H-NMR: 0.9 (3 H, t, ^3J = 7.4, CH_3), 1.43-1.50 (2 H, m, CH_2), 1.64- 1.70 (2 H, m, CH_2), 3.80 (2 H, t, ^3J = 6.6, O-CH_2), 7.27-7.49 (15 H, m, 15 CH). ^{13}C-NMR: 14.3 (CH_3), 19.7 (CH_2), 32.4 (CH_2), 63.5 (OCH_2), 86.4 (O-CAr_3), 126.9 (6 CH), 127.8 (6 CH), 128.9 (3 CH), 144.7 (3 C). Anal. Calc. For $C_{23}H_{24}O$ (316.45): C 87.30, H 7.64; found: C 87.20, H 7.75.

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