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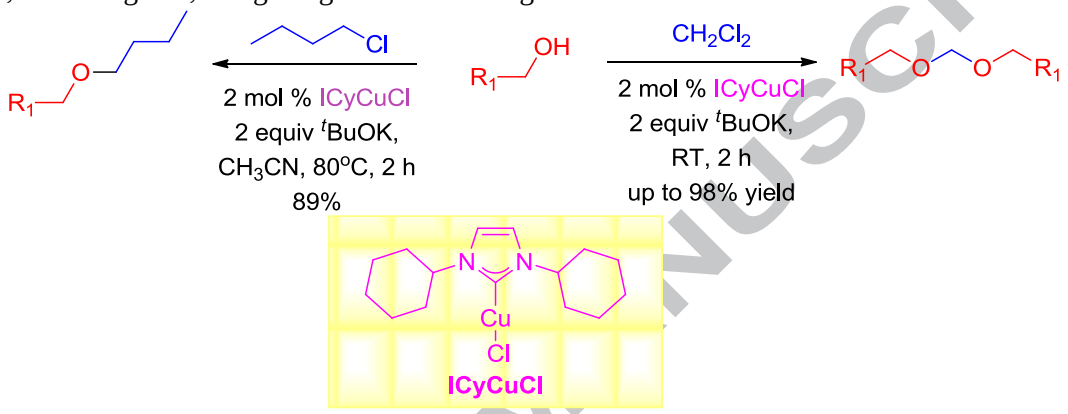

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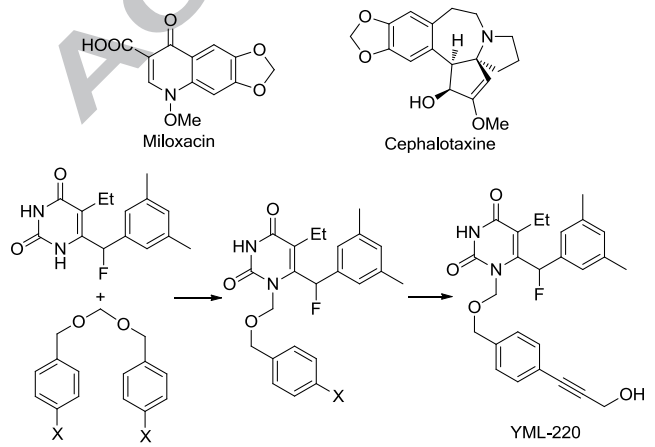
ABSTRACT

A facile, rapid and efficient method for the preparation of dialkoxymethanes from dichloromethane with alcohols catalyzed by a Cu-NHC complex is reported. A variety of symmetrical dialkoxymethanes can be prepared under mild condition in excellent yields (up to 98%). The unsymmetrical ether is also obtained in 89% yield from the etherification of *p*-tolylmethanol and *n*-butyl chloride catalyzed by ICyCuCl complex at 80 °C. The reaction provides a new method for the preparation of dialkoxymethanes under mild conditions in excellent yields.

The preparation of ethers is one of the most fundamental and frequently used important reactions in synthetic organic chemistry.[1] The first example of the formation of carbon-oxygen single bonds, the Williamson ether synthesis, has been widely used for the preparation of symmetrical and unsymmetrical ethers.[2] The preparation of dialkoxymethanes is a kind of reaction to synthesis ethers. The dialkoxymethanes are important structural motif in bioactive compounds such as Miloxacin[3] or Cephalotaxine[4], and they are also the key raw material for preparation of bioactive compound YML-220, which showed microbicidal activity in long-term assays with heavily infected MT-4 cells (Scheme 1)[5].



Scheme 1 Some bioactive compounds with dialkoxymethane motif.

The frequently used methods for the preparation of dialkoxymethanes mainly include the acetal reaction and the S_N2 reaction (Scheme 2). Generally, the dialkoxymethanes could be prepared by the condensation of formaldehyde with alcohols in the presence of Lewis acid catalysts, but it suffers from a major drawback that formaldehyde is highly toxic to all animals. Paraformaldehyde was employed as a synthetic building block in the preparation of dialkoxymethanes instead of formaldehyde, but this transformation required harsh conditions (ca. 120 °C for 8-12 h).[6] Barot and Pinnick reported a method for preparation of dialkoxymethane compounds based on an acetal interchange reaction with loss of a volatile symmetrical acetal in refluxing toluene for 36 h.[7] The utilization of dihalomethane as a synthetic building block has been used in the preparation of dialkoxymethanes. Colla used dibromomethane as synthetic building block for preparation of dialkoxymethane compounds in the presence of NaH at 0 °C.[8] However, the intake of dibromomethane has significant harm to human health. Surprisingly, dichloromethane, which is a relatively inert compound, was employed as a synthetic building block in the preparation of dialkoxymethanes. For example, Cornelius reported the synthesis of dialkoxymethane compounds from primary alcohols and dichloromethane catalyzed by montmorillonite at 100 °C for 3 days[9], the reaction was also completed at 100 °C for 12 h in presence of Cs_2CO_3 and N-methyl pyrrolidone[10]. And the dichloromethane was also used for preparation of methylene diesters with acids using microwave as activators.[11] Alcohols also reacted with the mixture of chlorotrimethylsilane and dimethyl sulfoxide in refluxing benzene for overnight to get the dialkoxymethanes.[12] To date, the

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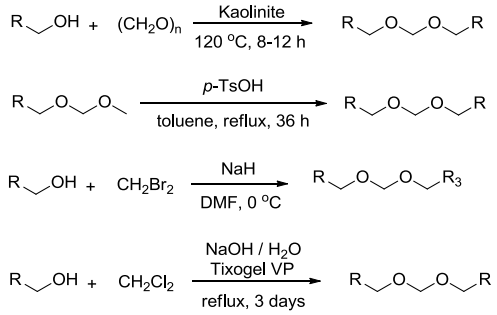
existing methods for the synthesis of dialkoxymethanes suffer from one or more of the following disadvantages: long reaction time, high temperature, use of harmful raw material, use of sensitive and costly reagent, etc.



Scheme 2 Synthesis of dialkoxymethanes

Transition metal catalysis is one of the most powerful tools available to chemists for the development of cleaner and more sustainable processes. [13] Recently N-heterocyclic carbenes (NHCs) have gained a prominent place in the chemist's toolbox due to their outstanding affinities to metal centers[14], which have naturally led to their application in a lot of organic transformations[15]. The strong electronic donating properties of NHCs in conjunction with copper, yields catalyst which are often very robust, demonstrating air, moisture and thermal stability. In the decade, the Cu-NHC catalysts have been shown to functionalize a large variety of substrates, including carbonyls, alkenes, alkynes or aromatics. Here, we report an effective, simple and mild reaction using Cu-NHC complexes[16, 17] as catalyst for preparing symmetrical dialkoxymethanes derived from primary alcohols in excellent yields. To the best of our knowledge, there is no example has been reported in the literature using of the Cu-NHC complexes to catalyze this reaction.

Initially, we explored the reaction of 4-chlorobenzyl alcohol **1a** with dichloromethane using potassium hydroxide as base under the catalyst of kinds of Cu-NHC complexes (Figure 1) for the preparation of dialkoxymethane **2a**. We mainly got 4-chlorobenzaldehyde when using the Cu-NHC as the catalyst under oxygen atmosphere (Table 1, entries 1 - 5), but the desired ether **2a** could be isolated in 32% yield when using the ICyCuCl as the catalyst (Table 1, entry 3). When the reaction was carried out under argon atmosphere and the base was changed into ^{t}BuOK, the reaction was finished within 2 hours at ambient temperature and the desired product was isolated in 95% yield (Table 1, entry 6). Without the ICyCuCl as catalyst, the desired ether **2a** was only isolated in 52% yield for 24 h (Table 1, entry 7). Decreasing the amount of base to 1.1 equivalents coursed the reducing the yield of product dramatically (Table 1, entry 8).

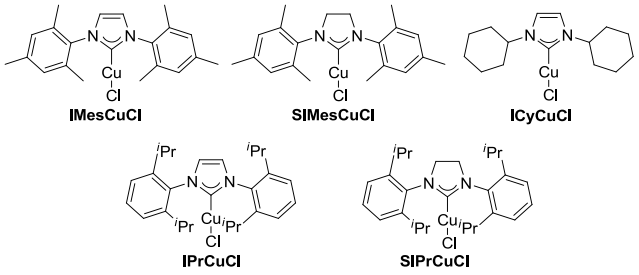
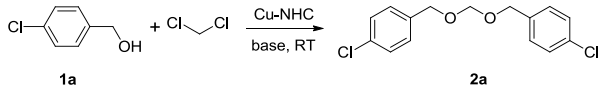


Figure 1 The structure of the Cu-NHCs

Table 1

Studies of the reaction conditons.



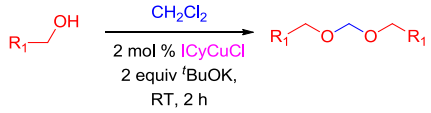
Entry	Catalyst (mol%)	Base (equiv)	Time (h)	Yield (%) [a]
1[b]	IMesCuCl (2)	KOH (2.0)	12	trace
2[b]	SIMesCuCl (2)	KOH (2.0)	12	trace
3[b]	ICyCuCl (2)	KOH (2.0)	12	32
4[b]	IPrCuCl (2)	KOH (2.0)	12	trace
5[b]	SIPrCuCl (2)	KOH (2.0)	12	trace
6[c]	ICyCuCl (2)	^{t}BuOK (2.0)	2	95
7[c]	--	^{t}BuOK (2.0)	24	52
8[c]	ICyCuCl (2)	^{t}BuOK (1.1)	12	76

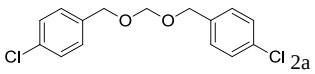
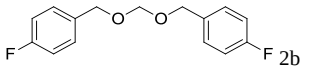
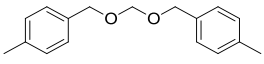
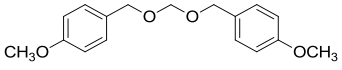
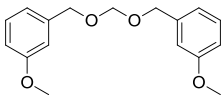
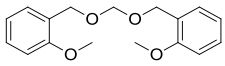
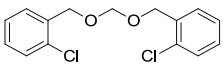
[a] Isolated yield. [b] The reaction was carried out under oxygen atmosphere. [c] The reaction was carried out under argon atmosphere.

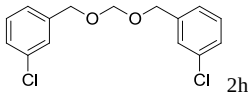
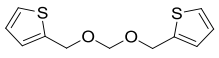
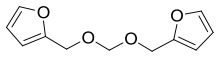
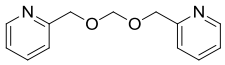
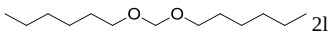
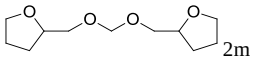
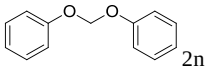
The scope of the substrates was investigated and the results were listed in Table 2. We found that under optimized reaction condition the transformation could be accomplished with various alcohol substrates. The benzyl alcohols all could react efficiently and universally to afford the corresponding dialkoxymethanes in excellent yield, no matter whether the substituents were electron-rich or electron-deficient (Table 2, entries 1 - 4). The position of the substituent showed no obvious steric hindrance effect on the dialkoxymethanes yields (Table 2, entries 1, 7, 8 and 4 - 6). Similar to benzyl alcohols, heterobenzylic counterparts reacted efficiently to afford the heterobenzylic formaldehyde dialkylacetals in good yields (Table 2, entries 9 - 11). This method was also suitable for aliphatic alcohols, we could get the bis(hexyloxy)methane **2l** in 77% yield (Table 2, entry 12). High yield of tetrahydrofurfuryl formaldehyde dialkylacetal was obtained from tetrahydrofurfuryl alcohol (Table 2, entry 13). For the phenol and catechol, we could also get the desired products in moderate yield at 80 °C (Table 2, entries 14-15).

Table 2

The preparation of dialkoxymethanes from dichloromethane with alcohols using ICyCuCl as catalyst.

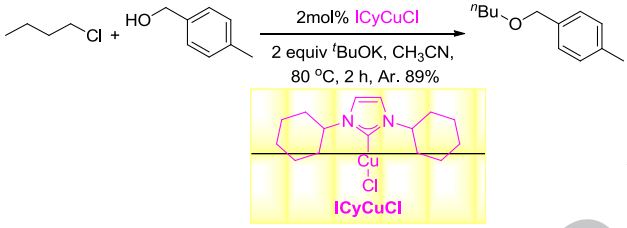


Entry	Product	Yield (%)[a]
1	 2a	95
2	 2b	85
3	 2c	98
4	 2d	94
5	 2e	92
6	 2f	91
7	 2g	98

8	 2h		92
9	 2i		91
10	 2j		95
11	 2k		89
12	 2l		77
13	 2m		91
14[b]	 2n		86
15[b]	 2o		84

[a] Isolated yield. [b] The reaction was carried out at 80 °C in DCM/CH_3CN (2:3) in sealed tube.

The unsymmetrical ether was also obtained from the etherification of *p*-tolylmethanol and *n*-butyl chloride in 89% yield (Scheme 2).



Scheme 3 The synthesis of unsymmetrical ether under the catalyst of ICyCuCl

In conclusion, a method for preparation of dialkoxymethane catalyzed by ICyCuCl complex was discovered and studied, which is effective for a variety of alcohols. We could get the symmetrical dialkoxymethane under mild condition in excellent yield. The unsymmetrical ether was also obtained from the etherification of *p*-tolylmethanol and *n*-butyl chloride catalyzed by ICyCuCl.

Acknowledgments

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Supplementary Material

Highlights:

1. First report to prepare $ROCH_2OR$ from DCM with alcohols using Cu(NHC) as catalyst.
2. The reaction conditions are mild and the yields are excellent.
3. The unsymmetrical ethers are also obtained using the similar method.

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