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# Electrophilic Assistance for Cross-Coupling Reactions: a Simple Synthesis of Mixed Allylic Ethers

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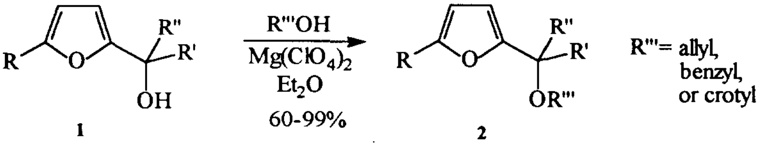
***Abstract:*** *Magnesium perchlorate, acting as a mild Lewis acid, is an efficient reagent for the synthesis of unsymmetrical ethers from allylic alcohols.*

During our studies on (2-furyl)-1-alcohols **1** as intermediates in the synthesis of cyclopentenones[1] and pyranones[2], we needed an easy procedure to ether derivatives **2**. In this report we wish to describe a mild and efficient method for a direct synthesis of ether derivatives **2** by cross-coupling of alcohols in presence of magnesium perchlorate .

Electrophilic assistance at the appropriate C-X bond is a common phenomenon in nucleophilic substitution reactions and represents one of the most widely used methods for the preparation of ethers.[3] Accordingly, alkyl halides are employed as precursors of carbocation species, which can be captured by suitable nucleophiles, such as alcohols. Silver salts are frequently used for halides so that reaction rates are enhanced and ethers are obtained in good yields.[4,5] A few synthetic methods for the direct synthesis of ethers from alcohols are available. Particularly, two procedures are reported describing a cross-coupling of different alcohols for the formation of mixed ethers. Both methods require the use of alcohols able to generate stable carbocations by action of a Lewis acid, such as iodine[6] and zinc chloride.[7]

We have found that magnesium perchlorate acts as a mild Lewis acid able to convert acid sensitive compounds **1** into the corresponding unsymmetrical ethers **2**, through a cross-coupling reaction (Scheme 1). Primary, secondary and even tertiary (2-furyl)-1-alcohols undergo alkylation with primary allylic alcohols in good to quantitative yields (Table 1).



**Scheme 1**

The method is also effective with benzyl alcohol (Table 1), whereas it fails with saturated alcohols, such as methanol and ethanol, probably because of the low stability of the ion pair described below. However, an easy access to ethoxy ethers can be achieved by reaction of **1** with ethanol and HCl.[8]

**Table 1.** Ethers formation.

| R | R' | R" | R"' | time | Yield(%)[1] |
|---|---|---|---|---|---|
| H | H | H | Allyl | 2h | 60 |
| H | Me | H | Crotyl | 2h | 60 |
| H | Ph | Ph | Allyl | 5min | 99 |
| H | Ph | Ph | Crotyl | 5min | 99 |
| Me | Et | H | Crotyl | 2h | 60 |
| Me | *n*Bu | H | Crotyl | 1h | 99 |
| Me | *n*Bu | H | Bn | 1h | 99 |
| H | Cyclohexyl | | Crotyl | 5min | 99 |

1) The reported yields refer to isolated, chromatographically pure compounds.
All the structures have been confirmed by IR, $^1$H-NMR and $^{13}$C-NMR. GC-MS analysis were in agreement with previously described data.
Homoethers R'''OR''' can be seen as by-products

[(5-methyl)-2-furyl]-1-cyclohexanol underwent quantitative dehydration to the corresponding unsaturated furan derivative, whereas (2-furyl)-1-cyclohexanol gave the expected ether.

We suppose that the role of magnesium perchlorate can be interpreted as an electrostatic catalysis which favours the formation of an ion pair $R^+|\,|^-\ ClO_4$,[9] that gives the product by reaction with the nucleophile present in the medium.

Our method was also shown to be effective for one step preparation of 6-alkoxy-pyran-3(6H)-ones, which are widely utilised both in cyclopentenone and oligosaccharide chemistry.[10] The corresponding benzylic and crotylic ethers were obtained in quantitative yields and short reaction time.

**General Procedure.** 3 mmol of $Mg(ClO_4)_2$ were added to a stirring ether solution (10 ml) of **1** (1 mmol) and alcohol (allylic or benzyl alcohol, 3 mmol) at room temperature. After the reaction was over (TLC), the mixture was washed with water (NaCl sat) and extracted with ether. The organic layer was separated, dried ($Na_2SO_4$), and evaporated under reduced pressure. The product was isolated by column chromatography on silica gel. An analogous procedure was used for pyranone derivatives.

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