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From Intermolecular Alcohol Additions on a Double Bond to Electrocyclizations of Non-Activated γ, δ-Unsaturated Alcohols : An Easy Synthesis of Tetrahydrofurans

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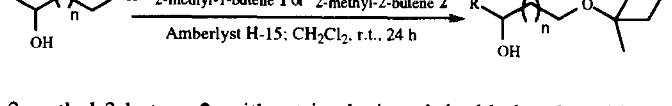
Abstract: Tetrahydrofurans have been synthesized in high yields through an electrocyclization reaction, by simple treatment of non activated γ, δ- or β, γ-unsaturated alcohols with an acidic resin (Amberlyst H-15) in CH_2Cl_2 at room temperature. © 1997 Elsevier Science Ltd. All rights reserved.

Tetrahydrofurans are found in many natural products of biological interest[1]. The preparation of such important subunits is still a challenge for the synthetic chemists[2], in order to find more chemo- and diastereoselective processes, safer and milder conditions as well as more "friendly" reagents. Electrocyclization of non-activated γ, δ-unsaturated alcohols has been an attractive approach to the preparation of substituted THF. Thus, the use of electrophiles such as : e.g. iodine, phenylselenium chloride, mercuric and palladium salts, has been reported in the literature[2,3]. Nevertheless, a second step for removal of the electrophile was always necessary for the synthesis of the corresponding unfunctionalized substituted THF. In this letter, we wish to report an extremely mild and efficient electrocyclization of non-activated γ, δ-unsaturated alcohols using as electrophile H^+. Indeed, addition of an alcohol on a double bond in an acidic medium is a well known reaction[4] which follows the Markovnikov's rule, and the order of reactivity : primary- > secondary- >> tertiary alcohols. Recently, we took advantage of this and shown that primary hydroxyls, in the presence of a secondary hydroxyl, added on the most substituted site of the α,α'-disubstituted double bond of 2-methyl-1-butene **1**, in the presence of either a catalytic amount of $BF_3.OEt_2$ or Amberlyst H-15, leading directly to the corresponding *tert*-amyl ethers[5] without any workup (Fig. 1). This method is now used for the chemoselective protection of primary alcohols in multistep syntheses of natural products[6], since the procedure is general, and the *tert*-amyl ethers so obtained stable in acidic and alkalin media and easily cleaved by TMSOTf into either the corresponding free alcohols or the trimethylsilyl ethers[7].

Figure 1



We then found that 2-methyl-2-butene **2**, with a tri-substituted double bond could advantageously replace alkene **1**, and when alcohols were submitted to the same reaction conditions than those used precedently the corresponding *tert*-amyl ethers were again obtained, following the Markovnikov's rule (Fig. 1). We then decided to examine the reaction of non-activated γ, δ-unsaturated primary and secondary alcohols with Amberlyst H-15 in CH_2Cl_2 at room temperature (Fig. 2 and Table 1). In the case of a γ,δ-unsaturated primary alcohol possessing a trisubstituted double bond, we observed a clean cyclization, in 4 hours at room temperature, leading to the corresponding tetrahydrofuran in high yields (entry 1). With secondary alcohols it is worthnoting that the cyclization does not occur (entry 3), which is in accord with the results observed in the acyclic cases (corresponding to the intermolecular reaction). However, in the cases of 4-alkenyl primary alcohols possessing a α, β-disubstituted double bond, no reaction occured (entry 2). This is probably due to the low acid-catalyzed activation of the double bond by the resin. For the compounds possessing a α,α'-disubstituted double bond, we observed the cyclization of the γ,δ-unsaturated primary alcohol in excellent yields, but with a longer time of reaction (entry 4).

Figure 2

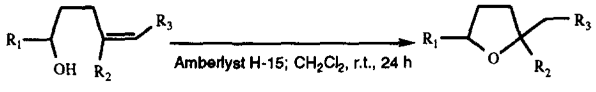
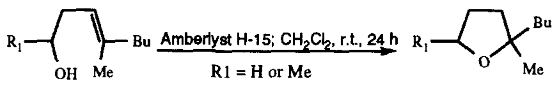


Table 1

entry	R^1	R^2	R^3	Time (h)	Yield (%)
1	H	Me	Et	4	98
2	H	H	Bu	24	no reaction
3	Me	H	Bu	24	no reaction
4	H	Ph	H	6.5	89

Interestingly, in all cyclizations we observed only the 5-*exo*-cyclization products[8], *versus* the 6-*endo*-cyclization. Then we tested the reaction of non-activated β, γ-unsaturated primary and secondary alcohols with Amberlyst H-15 in CH_2Cl_2 at room temperature (Fig. 3).

Figure 3



Again, we were satisfied to observe that primary alcohols cyclized in 24 h (in 95 % yield), slower that in the precedent case (4 h), probably because the 5-*endo*-cyclization is less favorable that the 5-*exo*-cyclization. Not surprisingly with secondary alcohol the reaction did not occur. In conclusion, the mild acid-catalyzed cyclizations with Amberlyst H-15 of either 4- or 3-alkenyl primary alcohols[9] bearing either a trisubstituted double bond or a α,α'-disubstituted double bond is an efficient method for the synthesis of tetrahydrofurans. This procedure does not require any workup, is clean since no side-products are formed. Indeed, it is noteworthy that no cationic rearrangements occured during the process. Furthermore, the procedure described herein shows high chemoselectivities : (i) primary- *versus* secondary alcohols, (ii) trisubstituted- *versus* α,β-disubstituted double bonds, and (iii) 5-*exo* *vs.* 6-*endo* cyclizations. Application of this new methodology to the preparation of natural products will be reported in due course.

References and notes :

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