Tetrahedron Letters,Vol.24,No.45,pp 4923-4926,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A CONVENIENT ROUTE TO FUNCTIONALIZED MIXED ACETALS VIA OXYMERCURATION-DEMERCURATION

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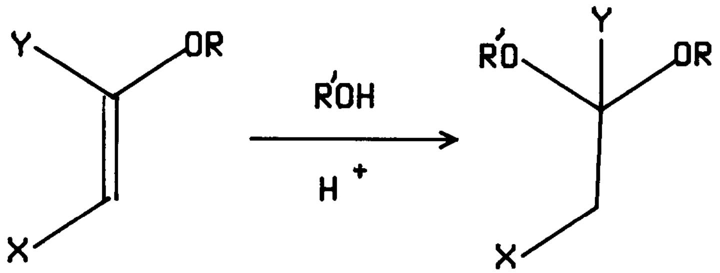
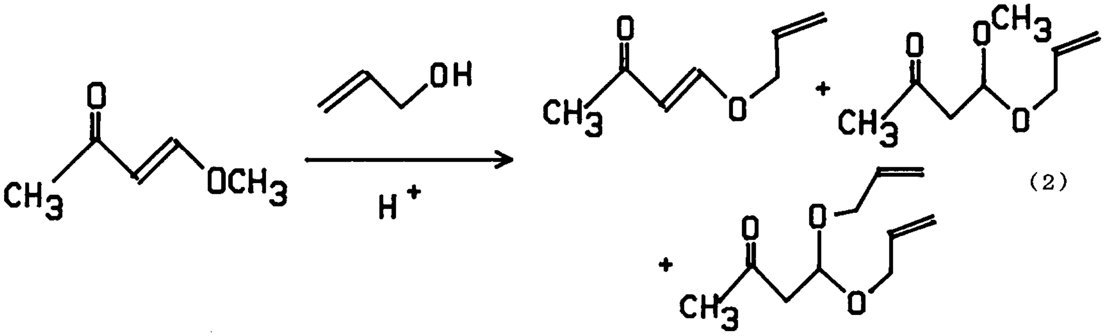
Abstract: Mixed acetals of olefinic and acetylenic alcohols and β-carbonyl and other substituted aldehydes are readily obtained by acetoxymercuration followed by demercuration utilizing $NaBH_4$ or Na_2CS_3.

In conjunction with studies of intramolecular 4 + 2 cycloaddition as protocol for the preparation of complex lactones, an alternative linking group was required due to difficulties associated with the cycloaddition of esters.[1] The acetal group was chosen as an ideal solution since requirements for orbital alignment in the transition state are largely absent.[2] However, a convenient procedure for the preparation of the required functionalized mixed acetals of unsaturated alcohols was not available. In the case of readily available vinyl ethers (Eqn. 1 X=Y=alkyl or H) or alcohols (ROH), acidic conditions can be utilized provided neither the vinyl ether nor the alcohols are inordinately sensitive to proton acids. However, the procedure is particularly limited when both components are valuable and/or sensitive,



(1)

and when electron poor groups (Eqn. 1 X=CN, COOR, $\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{=CH_3}$) are present since facile addition-elimination occurs, usually resulting in a complex mixture of products in these cases (Eqn. 2).



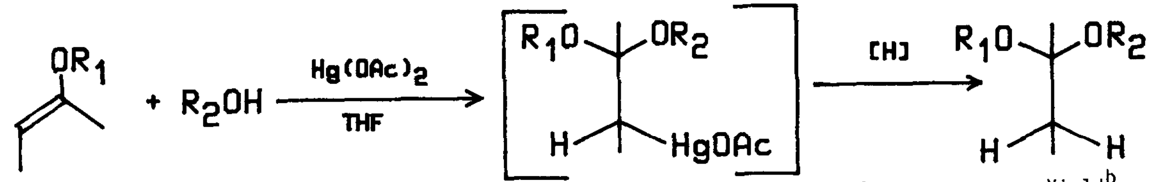
(2)

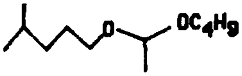
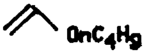
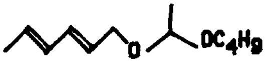
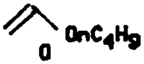
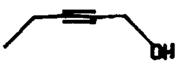
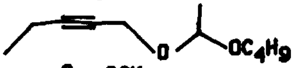
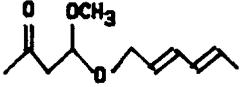
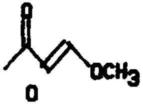
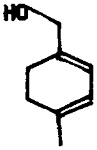
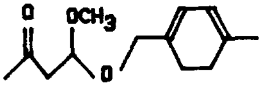
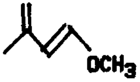
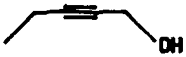
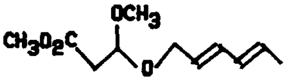
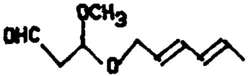
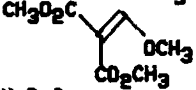
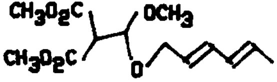
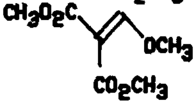
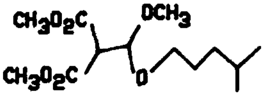
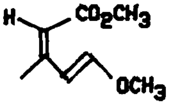
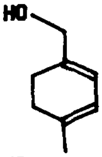
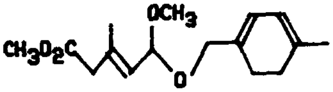
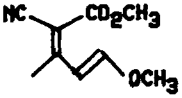
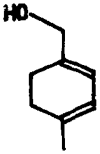
One solution to this difficulty lay in rendering the initial addition irreversible. Metal electrophiles (eq. Hg^{+2}) are well known to catalyze exchange of alcohols in vinyl ethers[3], however, except in rare instances, the intermediate organomercurials have not been isolated or further transformed[4,5]. In this note, we wish to report the ready preparation and demercuration of these intermediate organomercurials formed under kinetic control, providing a facile and mild method to obtain a variety of functionalized mixed acetals while maintaining close to ideal stoichiometry with respect to the alcohol and vinyl ether components.

Treatment of a mixture of vinyl ether (1 eq.) and $Hg(OAc)_2$ (1 eq.) in THF with the alcohol (1.3-1.5 eq.) at 0°C (<5 min. for alkyl substituted vinyl ethers and 12h-48h at room temperature for vinyl ethers bearing electron withdrawing groups),provided upon concentration the crude organomercurial in essentially quantitative yield. Demercuration in unfunctionalized cases could be accomplished by reduction with $NaBH_4$ in 1:1 THF/H_2O containing NaOH which afforded the mixed acetals in excellent (65-90%) yields.[6] However, use of these reduction conditions resulted in substantial amounts of reductive elimination in the case of systems bearing conjugating electron withdrawing groups. In these cases, use of sodium trithiocarbonate[7] at -23°C in NaOH/MeOH/H_2O afforded good to excellent (40-80%) yields of the required functionalized mixed acetals.

We have examined a selection of typical substrates as shown in Table 1. The reaction conditions generally tolerate use of acetylenic and olefinic alcohols as reaction components with no evidence of oxymercuration of most alcohols under these conditions. The vinyl ether can be a dienol ether as

TABLE 1[a]

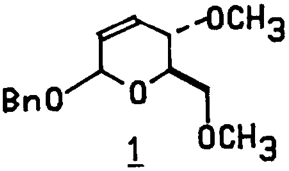


Case	Vinyl Ether	Alcohol	Reducing Agent	Acetal	Yield[b]
1			$NaBH_4$		60%
2			$NaBH_4$		85%
3			$NaBH_4$		80%
4			Na_2CS_3		80%
5			Na_2CS_3		78%
6		$\equiv\!-(CH_2)_8CH_2OH$	Na_2CS_3	$HOCH_2(CH_2)_8COCH_3$	51%
7	"		—	—	0%[c]
8			Na_2CS_3		70%
9			Na_2CS_3		45%
10			$NaBH_4$		61%
11			$NaBH_4$		60%
12			Na_2CS_3		40%
13			**NO REACTION**		

a) All new substances possess consistent spectral and exact mass analytical data
b) Overall yields of chromatographically pure acetals based upon vinyl ether component
c) Acetoxymercuration of the acetylene occurs exclusively in this case

can be seen from case 12. However, in these instances, reductive demercuration occurs with olefin transposition. The only limitations upon the reaction encountered thusfar occur when a cyano group is present in the vinyl ether and when acetylenic alcohols are used with deactivated vinyl ethers.[8] In these instances, no reactivity with the vinyl ether is observed using mercuric acetate at room temperature; instead oxymercuration of the acetylene occurs.

Although the use of Na_2CS_3 for reductive demercuration is quite effective in the acyclic cases cited above, there are limitations encountered in some instances. For example, in the oxymercuration of glucal trimethyl ether with benzyl alcohol using the method previously described[9], reduction with Na_2CS_3 proceeds cleanly to afford the pseudo glucal 1 (75%) whereas $NaBH_4$ affords the 2-deoxyglycoside 2 (70%). This result is consistent with the outcome observed previously with thiourea[9], and suggests the sulfur-based reducing agents function by a distinctly different mechanism.[10]



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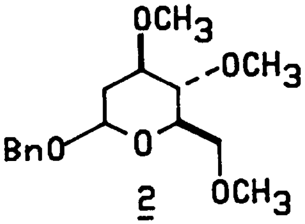

2

With a facile preparation of functionalized mixed acetals now available, we are currently exploring the use of mixed acetals as linking groups in intramolecular cycloaddition reactions.

Acknowledgement. This investigation was generously supported by research grants from the National Science Foundation (CHE-81-19823) and the National Cancer Institute (CA-29108) of the National Institutes of Health to whom we are extremely grateful.

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8. Cyano groups effectively complex Hg^{+2} rendering it unreactive as an electrophile: Birks, A. M.; Wright, G. F. J. Am. Chem. Soc., **1940**, 42, 1991.
9. Takiura, K.; Honda, S. Carbohyd. Res., **1972**, 21, 379.
10. Reduction of organomercurials by $NaBH_4$ is known to proceed by a radical mechanism, whereas sulfur-based reagents probably proceed by an ionic mechanism where reductive elimination can compete with protonation if a leaving group (OCH_3,OAc) is situated rigidly in a trans-anti relationship to the C-Hg bond (cf ref 7).

(Received in USA 15 August 1983)