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RESPONSE OF 2-LITHIO-4,5-DIHYDROFURAN — KETONE ADDUCTS TO ACID CATALYSIS[†]

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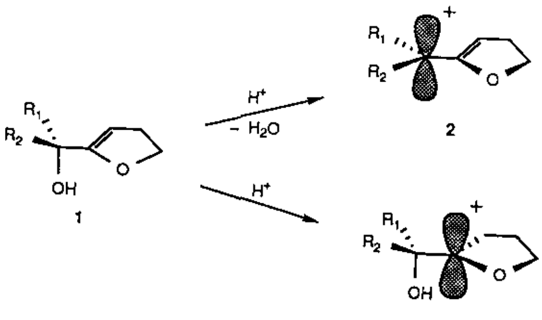
Abstract — Tertiary allylic alcohols derived from 1,2-addition of 2-lithio-4,5-dihydrofuran to ketones are shown to be capable of conversion to dimeric spiro-1,4-dioxanes or to monomeric ring-expanded spirocyclic ketones depending upon the conditions of acid catalysis employed.

Allylic cations are easily generated in solution. Indeed, they are known to be stable in concentrated sulfuric acid provided that the terminal carbon atoms are fully alkylated.[2] Although the resonance energy of $CH_2{=}CH{-}CH_2^+$ remains elusive,[3] its gas-phase heat of formation has been approximated to be 226 kcal/mol.[4] The ability of a hetero atom to stabilize positive charge on an adjacent carbon has also been studied. Clearly defined by these investigations is the key role played by the electron-donating power of X, its size, and its ability to support bond angle deformation. In general, the smaller the heteroatom, the better its capacity for cationic stabilization (e.g., O > S > Se).[5] Nonetheless, the gas-phase ΔH_f^o of $HOCH_2^+$ (172 kcal/mol)[3] indicates that the thermodynamic advantages derivable from a heteroatom do not outweigh those provided by a flanking double bond.

Curiously, no systematic investigation of these effects in combination under kinetically controlled conditions has appeared. We have therefore sought to assess the degree of regiocontrol that might be attainable in systems such as 1. The two pathways that can serve



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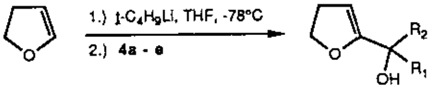
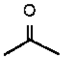
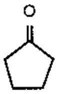
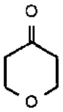
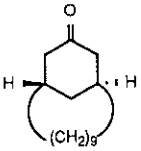
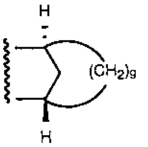
[†] This paper is dedicated to the memory of Professor Tetsuji Kametani, whose career as a leading pioneer of organic synthesis was exemplary.

as leading contenders to product formation are (a) protonation at the tertiary allylic hydroxyl group with subsequent loss of water to give allylic cation 2 and (b) protonation of the vinyl ether double bond to generate oxonium ion 3. *We now show that, contrary to expectation,* conversion to 3 operates very effectively, but that the ultimate fate of 3 is dependent upon its mode of generation.

Carbinols **1a-e** were prepared by metalation of 4,5-dihydrofuran with <u>tert</u>-butyllithium and subsequent condensation of the α-lithio species[6] with ketones **4a-e** as summarized in Table I. In certain cases such as 4d, the presence of anhydrous $CeCl_3$ was required to promote the desired 1,2-addition.[7] The highly reactive nature of the products caused losses to be incurred during their isolation as reflected in the yields. In fact, the exceptional sensitivity of **1e** precluded its direct characterization. When allowed to stand as a neat oil at room temperature, this alcohol gradually crystallized as a result of its rapid conversion to the ring-expanded spirocyclic ketone 5, mp 85.5-87 °C (80% from 4e).[8]

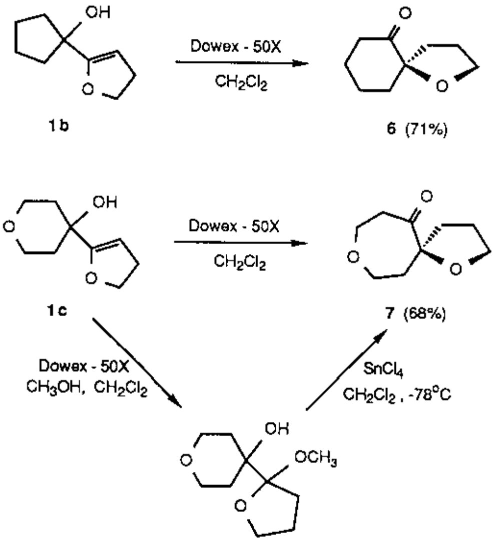


Ketone		Alcohol	Yield, %
	(4a)	$R_1 = R_2 = CH_3$ (1a)	57
	(4b)	$R_1, R_2 = (CH_2)_4$ (1b)	58
	(4c)	$R_1, R_2 = (CH_2)_2O(CH_2)_2$ (1c)	35
	(4d)	$R_1, R_2 =$  (1d)[a, b]	43
	(4e)	$R_1, R_2 =$  (1e)	c

[a]Required the presence of 1.3 equiv of anhydrous $CeCl_3$ to deter competing enolization. [b]Based on recovered starting material. [c]Too reactive for isolation (see text).

1a 5

Comparably efficient transformations of analogous type were most expediently carried out by stirring the carbinol with methanol-free Dowex 50X resin in dichloromethane at room temperature. The rearrangements that give rise to 6 and 7 are exemplary. The same chemical change can be effected stepwise if desired, as illustrated with 1c. Addition of methanol to the vinyl ether double bond can be performed in dichloromethane containing Dowex 50X that has been pre-moistened with methanol (59% of 8). Subsequent treatment of 8 with tin(IV) chloride at -78 °C promotes ionization exclusively as in 3 to furnish only 7.



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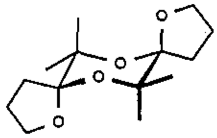
When the same alcohols are exposed instead to the action of *p*-toluenesulfonic acid in chloroform, dimerization to 1,4-dioxanes occurs cleanly instead. Thus, 1a was converted into 9 (87%), a crystalline solid identical in all respects to the acetal obtained by Favorskaya via a different route.[9] The 8-line ^{13}C nmr spectrum of 9 is considered confirmatory for the $\underline{S}_2$-symmetric nature of the molecule. Similar considerations apply to 10, which was produced in 90% yield from 1b under identical conditions. In both instances, the less symmetric dimer could also have been formed but was present in quantities too small to isolate. This was not the situation with 1c, which dimerized with somewhat lessened efficiency. Direct precipitation of the rather insoluble 11 (nine ^{13}C signals) permitted subsequent chromatographic purification of 12 (fourteen ^{13}C peaks). The response of 1d was entirely statistical, a 1:1 mixture of the diaxial and axial/equatorial dimers being produced (90% combined yield).



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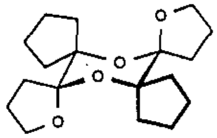

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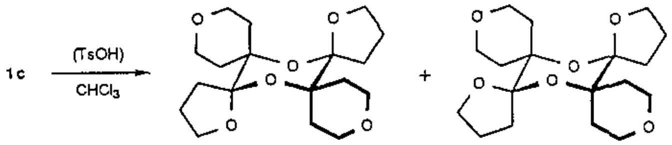

11 (53%)

12 (17%)

Since select examples of both classes of product gave evidence only for low-level (< 10%) mutual interconversion under the alternative reaction conditions, we conclude that both transformations proceed under kinetic control. Spiro ether formation, which should normally be favored because of its intramolecular nature, is noted to operate particularly well when the carbinol is weakly bound to an acidic resin or sterically congested. However, dimerization can compete effectively under the proper circumstances, presumably because cations such as 3 are often reasonably long-lived and have an appreciable tendency to capture alcohols (e.g., 1c → 8) more rapidly than experience 1,2-alkyl shift to complete the pinacol-like isomerization.

Additional studies in this area will be published elsewhere.[10]

REFERENCES AND NOTES

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10. This research was supported by the National Science Foundation (D.E.L.) and the National Institutes of Health (C.A.T.).

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