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A FACILE METHOD FOR THE BISHOMOLOGATION OF KETONES TO FUNCTIONALIZED TRISUBSTITUTED OLEFINS

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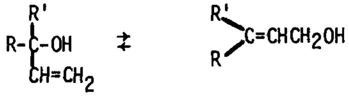
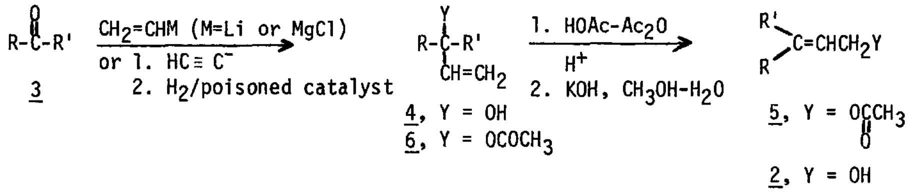
The acid-catalyzed isomerization of 3° vinyl carbinols (1) to the corresponding 1° allylic alcohols (2) is a reaction that has been reported in the chemical literature on many occasions in the past century.



1 2

For example, the rapid rearrangement of linalool [1, R = $(CH_3)_2C{=}CHCH_2CH_2$, R' = CH_3] to a mixture of products that included geraniol [2, R = $(CH_3)_2C{=}CHCH_2CH_2$, R' = CH_3] was recognized as early as the 1890's by Barbier while he was investigating the action of acetic anhydride on the former alcohol.[1] In 1946 I. N. Nazarov and coworkers reported[2] a study of this isomerization (1 ⇄ 2) conducted in 1-5% aqueous H_2SO_4 solution, and in general mixtures of both 1° and 3° alcohols and/or low yields of the 1° alcohol were obtained.[3]

In view of the recent interest in developing methods for the stereoselective synthesis of trisubstituted olefins[4] and the synthetic utility of 1° allylic alcohols of general structure 2 and their derivatives, we decided to investigate the usefulness of this allylic rearrangement in synthetic organic chemistry. Initial attempts to isomerize 3-propyl-1-hexen-3-ol to the corresponding 1° alcohol (2, R = R' = $CH_3CH_2CH_2$) using p-toluenesulfonic acid as a catalyst in a 60:40 tetrahydrofuran-water mixture proved fruitless.[5] An isolated report[6] of the preparation of $\Delta^{1,\beta}$-cyclohexylideneethyl acetate by allylic isomerization of 1-vinylcyclohexanol led us to examine the route outlined below for the preparation of functionalized trisubstituted olefins of general structure 2.



Once the optimum experimental conditions had been determined, the results of this isomerization study were even better than anticipated. As shown by the data in Table I, the allylic rearrangement proceeds[7] in high yield (65-90%) to give 1° acetates (5) uncontaminated by any of the corresponding 3° acetate (6), as shown by IR, NMR, and VPC analysis. As such, this method offers an alternate pathway to the modified Wittig reaction developed by Wadsworth and Emmons.[8]

The best conditions for effecting this allylic rearrangement involved rapid addition of a solution of 10.0 mmol of 3° alcohol in 25 ml of glacial acetic acid to a mixture of 25 ml of acetic acid and 10 ml of acetic anhydride[9] containing 600 mg of p-toluenesulfonic acid monohydrate. The reaction was quenched after 4-10 minutes at room temperature by pouring the mixture into 10 volumes of water, and the rearranged 1° acetate was then isolated by extraction with pentane.

In order to determine the scope of this allylic rearrangement, we examined the behavior of the vinyllithium adduct of hexanal under the standard reaction conditions. Spectral analysis of the product indicated that it consisted solely of the unrearranged 2° acetate, 3-acetoxy-1-octene.

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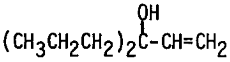
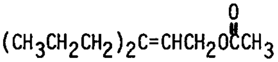
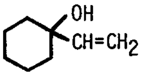
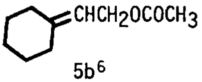
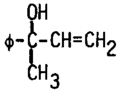
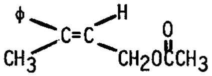
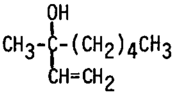
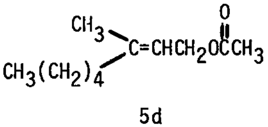
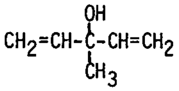
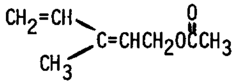
TABLE I

Isomerization of 3° Vinyl Carbinols (4)

	Rearranged 1° Acetate (5)				
Starting Material[10]	Structure	Distilled Yield (%)[11]	Reac. Time (min)	Reac. Temp. (°C)	^1H-NMR (CCl_4 vs TMS, δ in ppm)
 $(CH_3CH_2CH_2)_2\overset{OH}{C}-CH=CH_2$ 4a	 $(CH_3CH_2CH_2)_2C=CHCH_2O\overset{O}{\overset{\|}{C}}CH_3$ 5a[12]	65	30	20°	1.97(s, $O\overset{O}{\overset{\|}{C}}CH_3$); 4.52(d, J=7 Hz, $-CH_2O-$); 5.32(t, J=7 Hz, C=CH)
 4b	 5b[6]	55	10	20°	1.97(s, $O\overset{O}{\overset{\|}{C}}CH_3$); 4.51(d, J=7 Hz, CH_2O); 5.25(t, J=7 Hz, C=CH)
 $\phi-\underset{CH_3}{\overset{OH}{C}}-CH=CH_2$ 4c	 5c[13]	91	4	20°	2.01(s, $O\overset{O}{\overset{\|}{C}}CH_3$); 2.12(s, $C=CCH_3$); 4.71(d, J=7 Hz, CH_2O); 5.86(t, J=7 Hz, C=CH)
 $CH_3-\underset{CH=CH_2}{\overset{OH}{C}}-(CH_2)_4CH_3$ 4d	 5d E:Z ratio[14] was 70:30	70	25	0°	1.97(s, $O\overset{O}{\overset{\|}{C}}CH_3$); 1.70(s, W/2 = 4 Hz, $C=CCH_3$); 4.50 (d, J=7 Hz, CH_2O) 5.31(t, J=7 Hz, C=CH)
 $CH_2=CH-\underset{CH_3}{\overset{OH}{C}}-CH=CH_2$ 4e	 5e E:Z ratio[15] was 75:25	75	20	0°[16]	1.98(s, $O\overset{O}{\overset{\|}{C}}CH_3$); 1.83 (broad singlet, $C=CCH_3$); 4.64(d, J=7 Hz, CH_2O)

REFERENCES

1. The Terpenes, Volume I, edited by J. L. Simonsen (Cambridge University Press: 1947), pp 58-63 and references therein.

2. I. N. Nazarov, I. N. Azerbaev, and V. N. Rakcheeva, Bull. acad. sci. U.S.S.R., Classe sci. chim., 419 (1946).

3. For a review of this and related allylic rearrangements see: E. A. Braude, *Quart. Rev.*, *4*, 404 (1950).

4. For two recent reviews, see: D. J. Faulkner, *Synthesis*, 175 (1971) and J. Reucroft and P. J. Sammes, *Quart. Rev.*, *Chem. Soc.*, *25*, 135 (1971).

5. Use of 3 equiv of acid per mmol of substrate led to little, if any, isomerization (even after 15 hrs at room temperature), whereas larger amounts of acid and longer reaction times led to low yields of a horrendous mixture, the NMR analysis of which indicated the presence of little, if any, of the rearranged 1° allylic alcohol.

6. I. N. Nazarov and A. A. Akhrem, *Zhur. Obschchei Khim.*, *26*, 1186 (1956).

7. The only system examined that failed to react cleanly under our experimental conditions was the 3° vinyl carbinol obtained by the addition of vinyllithium to β-ionone. An intense green color was generated upon mixing the reactants, but neither the 3° acetate nor the rearranged 1° acetate could be isolated from the reaction mixture. As expected, linalool under the standard rearrangement conditions afforded α-terpineol acetate as the major product, in addition to the acetates of geraniol and nerol.

8. W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, *83*, 1733 (1961).

9. Further investigation of this allylic rearrangement, using alcohol *4a* as the substrate, demonstrated that either glacial acetic acid or acetic anhydride or a mixture of the two is suitable as a solvent for this reaction. The use of a strong acid catalyst is essential, however, for the rearrangement.

10. We prepared these 3° alcohols by dropwise addition of a 1 *M* ether solution of the corresponding ketone to a 10% excess of a 2 *M* solution of vinyllithium in THF at 0°. For the preparation of alcohol *4e*, better yields were obtained by using ethyl acetate instead of methyl vinyl ketone.

11. VPC analysis (using a 6' x 1/8" SE-30 column) indicated the rearrangement products to be of high purity, contaminated only by minor (10%) amounts of low-boiling impurities, presumably elimination products. In no case could any isomeric 3° acetate (*6*) be detected.

12. Satisfactory elemental analysis was obtained for this previously unreported compound.

13. NMR and VPC analysis of both the rearranged acetate (*5c*) and the corresponding alcohol obtained via saponification indicated the presence of only one stereoisomer.

14. This ratio was determined by VPC analysis of the acetate mixture and the corresponding mixture of alcohol stereoisomers obtained by saponification. This ratio was also consistent with the NMR integration of the vinyl methyl signals for these previously fully characterized alcohols. See: K. Ogura, T. Nishino, T. Koyama, and S. Seto, *J. Amer. Chem. Soc.*, *92*, 6036 (1970).

15. This ratio was determined via NMR and VPC analysis of the corresponding alcohol stereoisomers obtained via saponification of the crude product. $\delta^{CCl_4}_{TMS}$: 1.73 (s, W/2 = 3 Hz, "E" vinyl CH_3); 1.83 (s, W/2 = 4 Hz, "Z" vinyl CH_3).

    Treatment of the acetate mixture with maleic anhydride at room temperature led to rapid formation of a Diels-Alder adduct in high yield, thereby confirming the E-configuration of the major component. See: W. Oroshnik, *J. Amer. Chem. Soc.*, *78*, 2651 (1956).

16. If the reaction was run for 5 min at room temperature, the ratio of E:Z stereoisomers was 70:30.