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REGIOSELECTIVE DEHYDRATION IN CYCLIC SYSTEM WITH TRIPHENYLPHOSPHINE-AZODICARBOXYLATE

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Summary: The regioselective dehydration of cyclohexanol derivatives was achieved by using the Mitsunobu reagent system. The reaction undergoes under mild and neutral conditions. The observed regioselectivity was explained by considering the importance of the orientation of the leaving group at the elimination stage.

Various effective methods for dehydration of alcohols to olefins have been developed and widely used in synthetic organic chemistry.[1] However, there still exist several problems associated with the regioselectivity (the proportions of Saytzeff and Hoffmann products[2]). Namely, it is difficult to estimate the regioselectivity especially in cyclic systems. The main reasons for these uncertainty are in complexity of the reaction mechanism: E1 or E2 (anti or syn) elimination and a combination of competing S_N2 displacement and successive anti elimination.[3] Herein, we wish to report the dehydration which proceeds under anti E2 elimination with high regioselectivity in neutral conditions. The mechanism rationalizing these selectivity will also be presented.

Previously we reported novel regioselective dehydration of tetrahydropyran derivatives using the Mitsunobu reaction conditions (Ph_3P - $EtO_2CN{=}NCO_2Et$), which were summarized in TABLE 1.[4]

TABLE 1

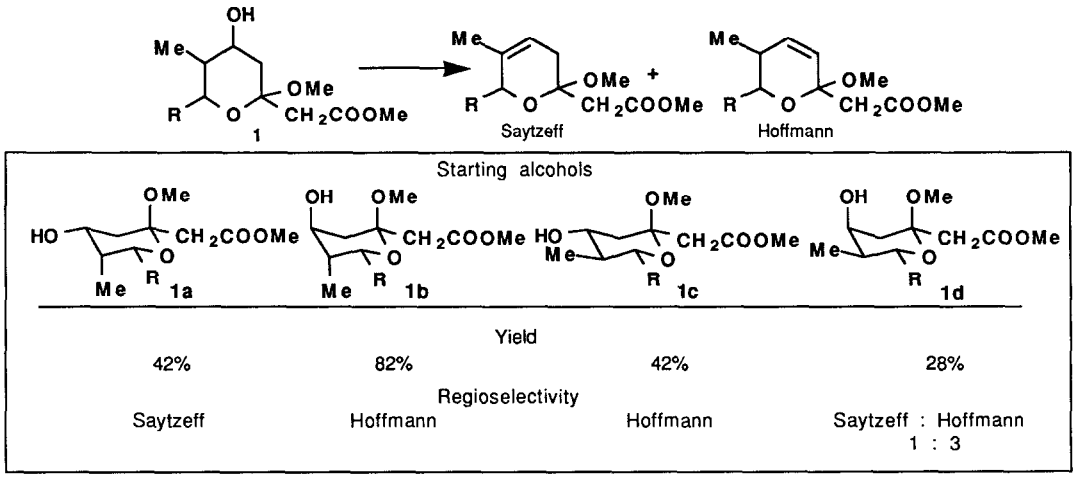
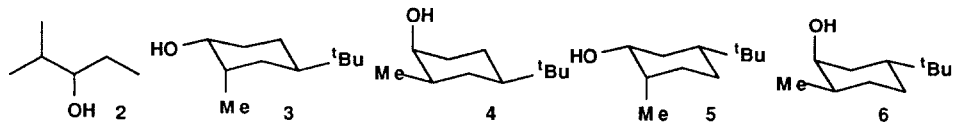


TABLE 2



	Yield[a]			
	68%	77%	74%	57%
	Selectivity (Saytzeff : Hoffmann)[b]			
3 : 1	20 : 1	30 : 1	18 : 1	50 : 1

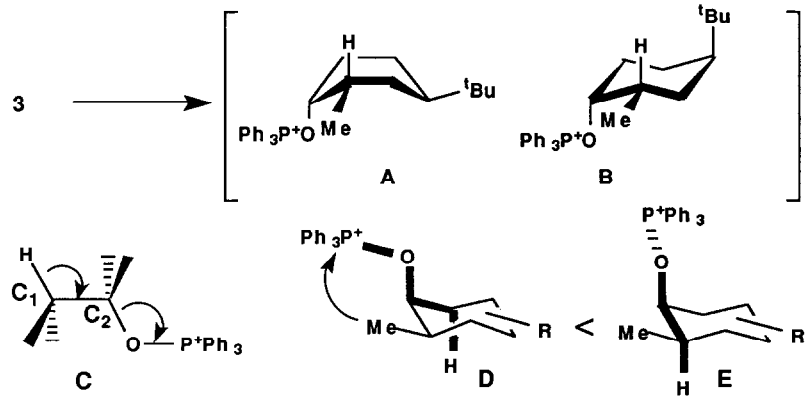
[a]Isolated yields varies due to their high volatility.
[b]Ratios were determined by ^{1}H NMR.[5]

These reactions are presumed to proceed by E2 mechanism, since the so-called Mitsunobu reaction usually undergoes with complete inversion of configurations.[6] The Hoffmann selectivity[2] observed in the elimination of **1b** and **1c** can be explained by the standard anti-elimination mechanism.[7] However, the Saytzeff selectivity[2] observed in **1a** is an interesting case where the result is hardly explained by this simple consideration. Bunnett has proposed *nearly E1* mechanism[8] to explain the Saytzeff selectivity obtained in sterically hindered cyclic systems.[9] However, this mechanisms may not be applied for **1a**, since if this mechanism is operative, the high Saytzeff selectivity should be obtained in **1b** to **1d** as well as **1a**.

For the purpose of examining whether this Saytzeff selectivity is observed generally in the related compounds, dehydration of several much simpler alcohols having the methyl group on the α-position were undertaken. Initially 2-methyl-3-pentanol (**2**) was chosen as an acyclic reference compound. In this case, a slight Saytzeff selectivity (3 : 1) was observed by ^{1}H NMR analysis.[5] Then, dehydration of several cyclohexanol derivatives[10] from which both Saytzeff and Hoffmann products can be produced were investigated (TABLE 2). High Saytzeff selectivity was observed for all the compounds examined. In **4** and **6** with axial hydroxyl groups, the dehydration apparently proceeds by anti-elimination. In **3** and **5** with equatorial hydroxyl groups, the elimination is presumed to proceed via a skew boat conformation (represented as **A**, which is drawn as boat form because of simplicity), whose hydroxyl group is now quasi-axial and thus anti-periplanar arrangement of two eliminating group is possible.[11] It is also possible to consider a completely flipped chair conformer **B** which was calculated to be less stable by 0.4 kcal/mol than **A** by the MM2 calculation[12] of its methyl ether (similarly by 1.2 kcal/mol in the case of **5**).

In order to explain the above high Saytzeff selectivity we now propose an orientation effect of the leaving group at the elimination stage. Considering a stereoelectronic effect[13], the ability of the oxo-phosphonium group (-O-P$^+$Ph$_3$) as a leaving group will be most powerful when the phosphonium group in it lies in the same plane as that involving two eliminating groups (H and O) and the central carbon-carbon bond (C_1-C_2). Thus, conformation **C** in which C_1 and the

phosphonium group are oriented anti to each other across the C_2-O bond should be the most plausible conformer for effecting elimination smoothly. When the above consideration is simply applied to **4** and **6** having axial hydroxyl group, two conformers **D** and **E** expecting to produce the Hoffmann and Saytzeff products, respectively, are envisioned. Furthermore, even in **3** and **5** with equatorial hydroxy groups, since the transient skew boat (**A**) or chair (**B**) conformer discussed above involves the same partial structure as **4** and **6** do, contributed of conformer corresponding to **D** or **E** is again evident for a facile elimination. Comparison of the stereostructure of conformers **D** and **E** show that the former is apparently less stable than the latter because of the severe 1,3-syn interaction (arrow) between the α–methyl and the phosphonium groups. Thus the dehydration is highly expected to proceed via conformer **E** affording the Saytzeff product predominantly.



Most of the result obtained thus far can be explained by the above mechanistic consideration except in **1d**, in which the presence of an axial methoxy group may be playing an important role for the destabilization of the conformer **E**, but the detail remains unknown.

It is note worthy that the present Mitsunobu reagents-promoted new dehydration reaction of α-substituted alcohols not only produces olefins regioselectively but also proceeds under a very mild and neutral condition. Thus, a wide variety of applications for the syntheses of the trisubstituted olefins in the complex molecules are expected.

Typical procedure of dehydration: To a solution of alcohol (1mmol) and triphenylphosphine (2mmol) in 5ml of THF was added diethyl azodicarboxylate (2mmol) in an ice bath. The reaction mixture was stirred at room temperature for 1 day. After evaporation of THF (ca. 40mmHg), the gummy residue was chromatographed over silica gel (hexane : ether 1 : 1) to remove polar materials. Purification by flash chromatography affords the product.

REFERENCES and NOTES

(1) (a) Buehler, C. A.; Peason, D. E. *Survey of Organic Synthesis;* Wiley: New York, 1970, Vol 1, pp. 71-75; Vol 2, pp. 78-83. (b) Wolkoff, P. *J. Org. Chem.* **1982**, *47,* 1944.

(2) The term "Saytzeff" expresses more substituted olefin and "Hoffmann", less substituted one in this paper.

(3) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry;* Plenum: New York, 1984, pp. 345-361. (b) D'Onard, F.; Scettri, A. *Synthesis* **1985**, 1159. (c) Hutchins, R. O.; Hutchins, M. G.; Milewski, C. A. *J. Org. Chem.* **1972**, *37,* 4190.

(4) Akita, H.; Yamada, H.; Matsukura, H; Nakata, T.; Oishi, T. *Chem. Pharm. Bull.* **1990**, *38,* 2377. See also, Ohtsuka, Y; Oishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 4722.

(5) ^{1}H NMR integration **2:** 5.09 (1H), 5.4 (0.60/2H). **3:** 5.38 (1H), 5.6 (0.10/2H). **4:** 5.38 (1H), 5.43 and 5.65 (0.06/2H). **5:** 5.37 (1H), 5.8 (0.11/2H). **6:** 5.37 (1H), 5.53 and 5.64 (0.04/2H).

(6) (a) Mitsunobu, O. *Synthesis* **1981**, 1. Although dialkoxyphosphorane $Ph_3P(OR)_2$ is presumed to be formed at the initial stage, oxo-phosphonium salt should be a reactive intermediate in the present elimination reaction: (b) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045 and references therein.

(7) In **1c**, when a ring-flipped conformation is taken into consideration in the transition state (cf. conformer **A** or **B**), the two eliminating groups should be in the same trans diaxial relationship as that in **1b**.

(8) Bunnett, J. F. *Angew. Chem. Int. Ed.* **1962**, *1*, 225.

(9) Saytzeff selectivity of the elimination of trimethylethylneomenthylammonium ion was explained by *steric pressure*: Hughes, E. D.; Wilby, J. *J. Chem. Soc.* **1960**, 4094.

(10) As we were interested in differences of selectivity between equatorial and axial alcohols, we used *tert*-butylcyclohexanols as substrates. Alcohol **3** was prepared according to the literature: (a) Huff, B. J. L.; Tuller, F. N.; Caine, D. *J. Org. Chem.* **1969**, *34*, 3070. (b) Cherest, M. *Tetrahedron* **1980**, *36*, 1593. ^{1}H NMR ($CDCl_3$) **3:** 0.95 (d, J=7Hz, 3H, Me), 3.68 (dt J =11, 5Hz, 1H, C*H*OH). Alcohol **4** was prepared by inversion of the corresponding alcohol[10b] (1. $EtO_2CN{=}NCO_2Et$, Ph_3P, PhCOOH. 2. KOH.). ^{1}H NMR ($CDCl_3$) **4:** 0.96 (d, J=7Hz, 3H, Me), 3.75 (br d, J =2Hz, 1H, C*H*OH). Alcohols **5** and **6** were prepared by inversion of epimeric mixture of the alcohols[10c] and separated by flash chromatography. (c) House, H. O.; Lusch, M. J. *J. Org. Chem.* **1977**, *42*, 183. ^{1}H NMR ($CDCl_3$) **5:** 0.90 (d, J=7Hz, 3H, Me), 3.72 (dt , J =11, 5Hz, 1H, C*H*OH). **6:** 0.95 (d, J = 6Hz, 3H, Me), 3.87 (br s, 1H, C*H*OH).

(11) A cyclic syn-elimination may also be considered. However, this possibility can be eliminated since the present reactions take place quite smoothly at room temperature although pyrolytic conditions are usually required for this type of reaction. Moreover, opposite regioselectivity obtained by the elimination of **1a** and **1c** can not be explained by the syn-elimination mechanism.

(12) The program MacroModel was employed for this calculation: Still, W. C.; Mohamadi, F.; Richard, N. G. L.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; Degunst, F.; Hasel, W. MacroModel V 2.5, Department of Chemistry, Columbia University, New York, NY 10027.

(13) A similar W shape conformation is adopted for 1,4-elimination reactions: Deslongchamps, P. *Stereoelectronic Effect in Organic Chemistry;* Pergamon: Oxford, 1983, pp. 252-266.

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