Preparation of a Substituted α-Methyleneoxetane by an Intramolecular Alkylation Reaction

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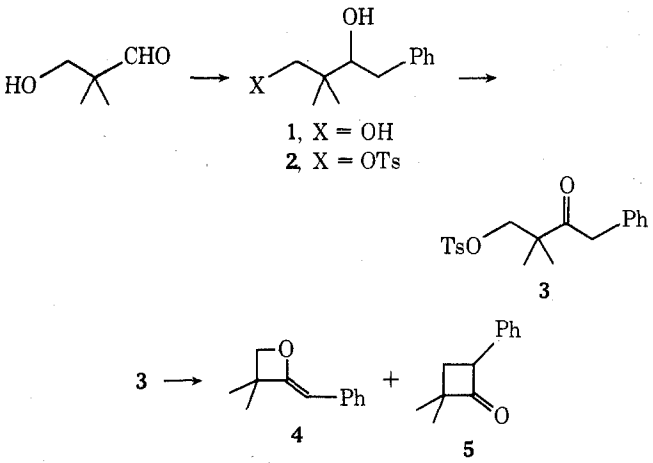
We have recently prepared α-methyleneoxetane by a retro-Diels–Alder reaction;[1] several substituted α-methyleneoxetanes have been prepared, primarily by cycloaddition reactions.[2] In connection with our interest in the use of α-methyleneoxetanes in organic synthesis,[1a,b] we have explored the possibility of generating these compounds by intramolecular O-alkylation reactions of ketone enolates.[3] This route would be potentially useful for the synthesis of a variety of substituted α-methyleneoxetanes which are not easily obtainable by existing methods. We report here an intramolecular alkylation reaction which yields a substituted α-methyleneoxetane (4) as the predominant product.



2,2-Dimethyl-4-phenyl-1,3-butanediol (1) was converted to the monotosylate 2 and oxidized to the keto tosylate 3. When 3 was treated with potassium hydride[5] in THF, products of both O- and C-alkylation were isolated. 2-Benzylidene-3,3-dimethyloxetane (4) and 2-phenyl-4,4-dimethylcyclobutanone (5) were formed in estimated yields of 36 and 25%, respectively. The double bond of 4 most likely has the *Z* configuration, based on steric considerations and on the chemical shift (δ 5.07) of the olefinic hydrogen. From the reported chemical shifts of α-methyleneoxetane[1a,b] and a shielding increment of 1.38 ppm for phenyl,[6] the predicted chemical shifts for the *E* and *Z* isomers are δ 5.41 and 5.01, respectively.

Surprisingly, the ratio of 4 to 5 was rather insensitive to variations in cation (Na, K) or solvent (THF, THF–HMPA, or THF with dicyclohexyl-18-crown-6), varying only from about 2:1 to 1:2. The ratio of C- to O-alkylation of enolates is normally influenced strongly by changes in cation or solvent.[7] A model study of the intermolecular alkylation reactions of benzyl *tert*-butyl ketone with ethyl tosylate under comparable conditions showed large cation and solvent effects. We found that the proportion of O-alkylation varied from less than 5% (with NaH in THF) to more than 90% (with KH in THF–HMPA).

Compared to intermolecular alkylations of simple ketones in THF, the reaction 3 → 4 + 5 gives a high proportion of O-alkylation. This may be a consequence of the requirements for orbital overlap in the transition states leading to 4 and 5.[8] If the transition state leading to the cyclobutanone 5 requires bond formation in a direction perpendicular to the plane of the enolate, it would be appreciably more strained than that leading to the oxetane 4.[9] The product ratio may also be influenced by the stereochemistry (*E*, *Z*) of the starting enolate; for example, the *Z* enolate may cyclize predominantly to the oxetane 4.

Intramolecular alkylation reactions are known in which cyclobutanones are formed from α,α-disubstituted ketones having a leaving group β to carbonyl.[10] These reactions, sometimes called homo-Favorskii reactions, normally produce a mixture of two isomeric cyclobutanones. Usually aqueous or alcoholic base has been employed, in contrast to the aprotic conditions used here. Although an α-methyleneoxetane was postulated as an intermediate in one case,[10e] such compounds have never before been isolated from these reactions.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium and benzophenone, pyridine was distilled from barium oxide, and hexamethylphosphoric triamide (HMPA) was distilled under reduced pressure from calcium hydride. Potassium hydride was obtained from Research Organic/Inorganic Chemical Corp., Belleville, N.J.; sodium hydride was obtained from Alfa Inorganics, Beverly, Mass. Elemental analyses were determined by Robertson Laboratory, Florham Park, N.J.

2,2-Dimethyl-4-phenyl-1,3-butanediol (1). Benzylmagnesium chloride was prepared by adding a solution of 12.6 g (0.10 mol) of benzyl chloride in 50 ml of ether to 2.4 g (0.10 mol) of magnesium in 60 ml of ether. To this was added a solution of 4.0 g (0.02 mol) of 3-hydroxy-2,2-dimethylpropanal[11] in 80 ml of ether with continuous stirring. After addition was complete, the reaction mixture was heated at reflux for 30 min, cooled to room temperature, and added to 40 ml of saturated NH_4Cl solution. The resulting mixture was extracted with three 30-ml portions of ether, and the combined ether extracts were washed with 10 ml of water and were dried (Na_2SO_4) and concentrated, yielding 8.5 g of a solid residue. This material was recrystallized once from hexane and three times from ether, yielding 7.1 g (93%) of 1 as white crystals: mp 95–96°; ir ($CHCl_3$) 2.85 (broad), 3.39, 6.25, 6.72, 6.82, 6.91, 9.55 μm; NMR ($CDCl_3$) δ 1.00 (s, 6 H), 2.5 (broad, OH) overlapping with 2.55 (doublet of doublets, J = 14, 10 Hz) (total 3 H), 2.96 (doublet of doublets, J = 14, 3 Hz, 1 H), 3.56 (broad s, CH_2OH) overlapping with 3.75 (doublet of doublets, J = 10, 3 Hz, CHOH) (total 3 H), 7.35 (broad s, 5 H); mass spectrum *m/e* 194 (M^+), 176, 103, 92, 91, 85, 65, 57, 56, 43.

Further recrystallization from ether provided the analytical sample, mp 96–96.5°. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.14; H, 9.60.

1-Phenyl-4-tosyloxy-3,3-dimethylbutan-2-ol (2). To a stirred, ice-cooled solution of 23 g (0.120 mol) of *p*-toluenesulfonyl chloride in 125 ml of pyridine was added 23 g (0.118 mol) of diol 1 in 125 ml of pyridine. After addition was complete, stirring was continued for 6 hr at room temperature. The reaction mixture was acidified with cold 2 *N* HCl and extracted with three portions of ether. The combined ether extracts were washed successively with dilute HCl, water, saturated $NaHCO_3$, and water, and were dried ($MgSO_4$) and concentrated. After volatile material was pumped off with a vacuum pump, 33 g of 2 remained as a pale yellow oil which solidified on cooling. This material was used without further purification in the next step.

Attempted recrystallization of this material was difficult. From a separate but similar experiment, 2 was obtained as a solid, mp 72–74°, ir ($CHCl_3$) 2.8 (broad), 3.37, 6.26, 7.40, 8.44, 8.53, 10.4 μm. The NMR spectrum ($CDCl_3$) showed three methyl singlets at δ 0.95, 1.04, and 2.45, and overlapping aromatic hydrogen absorptions at 7.2–8.0.

1-Phenyl-4-tosyloxy-3,3-dimethylbutan-2-one (3). To a solution of 30 g of the monotosylate 2 (from the above experiment) in 600 ml of acetone was added 79 ml of Jones reagent[12] with continuous stirring. The reaction mixture was allowed to stand overnight, 300 ml of saturated $NaHCO_3$ was added, the mixture was filtered, and the precipitate was washed with acetone. The combined filtrate was concentrated and extracted with five portions of ether. The ether extracts were washed successively with water, saturated $NaHCO_3$, and water, and were dried (Na_2SO_4) and concentrated, yielding 27.7 g of crude keto tosylate 3. A portion (21.3 g) of this crude material was crystallized from CH_2Cl_2–hexane and recrystallized from ether, yielding 17.2 g of 3 as white crystals: mp

88–89°; ir ($CHCl_3$) 3.35, 5.84, 6.26, 7.37, 8.41, 8.50, 10.3 μm; NMR ($CDCl_3$) δ 1.20 (s, 6 H), 2.48 (s, 3 H), 3.80 (s, 2 H), 4.08 (s, 2 H), 7.2–8.0 (m, 9 H); mass spectrum *m/e* 346 (M^+), 291, 255, 227, 155, 91.

Further recrystallization from ether provided the analytical sample, mp 89–89.5°. Anal. Calcd for $C_{19}H_{22}O_4S$: C, 65.87; H, 6.40. Found: C, 66.10; H, 6.62.

Treatment of Keto Tosylate 3 with Potassium Hydride. Potassium hydride (400 mg of a ~50% slurry in oil, ~5 mmol) was stirred with several portions of pentane; the liquid from each portion was removed by pipet. THF (25 ml) was added to the residue, the mixture was cooled in an ice bath, and a solution of 640 mg (1.85 mmol) of keto tosylate **3** in 25 ml of THF was added. The resulting mixture was stirred for 1 hr, the ice bath was removed, and stirring was continued for 1 hr at room temperature. The mixture was then cooled in a Dry Ice–acetone bath and 10 ml of saturated NaCl was added. After warming to room temperature, the mixture was extracted with five 20-ml portions of ether, and the combined extracts were washed with saturated $NaHCO_3$ (two portions) and water and were dried (Na_2SO_4) and concentrated, giving 282 mg of residue, which was chromatographed on Florisil. Elution with 5–10% CH_2Cl_2 in hexane yielded 103 mg of oxetane **4** as an oil; VPC analysis (SE-30, 150°)[13a] showed one peak at a retention time of 3.5 min. Further elution with 20–50% CH_2Cl_2 in hexane yielded 94 mg of oil; VPC analysis (SE-30, 150°)[13a] showed two peaks at 2.5 (**5**) and 3.5 min (**4**), in a 6:1 ratio. The total yields of **4** and **5** are estimated to be 36 and 25%, respectively.

2-Benzylidene-3,3-dimethyloxetane (**4**) had the following spectra: ir (film) 3.39, 5.92, 7.44, 9.23, 9.45, 10.56, 14.42 μm; NMR ($CDCl_3$) δ 1.40 (s, 6 H), 4.60 (s, 2 H, CH_2O), 5.07 (s, 1 H, PhCH=C), 7.0–7.5 (m, 5 H). From a separate but similar experiment, a portion was purified by preparative VPC, followed by evaporative distillation: mass spectrum *m/e* 174 (M^+), 159, 144, 143, 129, 128, 118, 90, 89, 63, 51, 41, 39. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.71; H, 8.12.

A pure sample of 2-phenyl-4,4-dimethylcyclobutanone (**5**), obtained by preparative VPC, had the following spectra: ir ($CHCl_3$) 3.45, 5.63, 6.91, 8.71, 9.42, 9.66, 9.80, 11.56 μm; NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.34 (s, 3 H), 2.04 (doublet of doublets, J = 11, 9 Hz) overlapping with 2.40 (t, $J \approx 11$ Hz) (total 2 H), 4.61 (doublet of doublets, J = 10.5, 9 Hz, 1 H, PhCH), 7.30 (s, 5 H); mass spectrum *m/e* 174 (M^+), 173, 159, 146, 131, 118, 104, 103, 91, 90, 70. Purified samples of **5** decomposed and solidified after standing a few days in the refrigerator.

From **5** was prepared a 2,4-DNP derivative, mp 124–124.5° (from (EtOH). Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12. Found: C, 60.87; H, 5.27.

A series of similar reactions was carried out in the presence of hexadecane as an internal standard for VPC analysis (SF-96, 140°).[13b] Typical retention times were as follows: cyclobutanone **5**, 7.5 min; oxetane **4**, 11.0 min; hexadecane, 26.4 min. The yield of oxetane **4** was determined directly using the measured relative detector response; because of the lability of **5**, its yield was estimated indirectly by using a detector response calculated by comparing the NMR and VPC of a mixture of **4** and **5**. With NaH in THF–HMPA (4:1), or with KH in THF, in THF–HMPA (4:1), or in THF containing 0.005 equiv of dicyclohexyl-18-crown-6, **4** was formed in yields of 35–46% and **5** was formed in yields of 22–45%. Using NaH in THF, **4** and **5** were formed in yields of 24 and 50%, respectively.

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Registry No.—**1**, 55853-34-4; **2**, 55853-35-5; **3**, 55853-36-6; **4**, 55853-37-7; **5**, 55853-38-8; **5** 2,4-DNP, 55853-39-9; 3-hydroxy-2,2-dimethylpropanal, 597-31-9; benzyl chloride, 100-44-7; *p*-toluenesulfonyl chloride, 98-59-9; potassium hydride, 7693-26-7.

References and Notes

(1) (a) P. F. Hudrlik and A. M. Hudrlik, *Tetrahedron Lett.*, 1361 (1971); (b) P. F. Hudrlik, A. M. Hudrlik, and C.-N. Wan, *J. Org. Chem.*, **40**, 1116 (1975). See also (c) J. Hasloulin and F. Rouessac, *C. R. Acad. Sci., Ser. C*, **276**, 1691 (1973).
(2) See references cited in ref 1a,b.
(3) We have recently devised a synthetic route to 3-acetoxy-3-buten-1-ol tosylate,[4] a possible precursor to an enolate which might give α-methyleneoxetane in an intramolecular O-alkylation. In experiments by A. M. Hudrlik in these laboratories, treatment of this acetoxy tosylate with nucleophiles expected to generate the enolate gave no α-methyleneoxetane (and no cyclobutanone). The presence of the *gem*-dimethyl group in ketone **3** prevents the possibility of a competing β-elimination reaction.
(4) P. F. Hudrlik and A. M. Hudrlik, *J. Org. Chem.*, **38**, 4254 (1973).
(5) For the use of potassium hydride to prepare ketone enolates, see C. A. Brown, *J. Org. Chem.*, **39**, 3913 (1974).
(6) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969); see also S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).
(7) W. J. Le Noble, *Synthesis*, 1 (1970), and references cited therein. For a recent study of the influence of crown ethers on C- vs. O-alkylation of enolates, see A. L. Kurts, P. I. Dem'yanov, I. P. Beletskaya, and O. A. Reutov, *J. Org. Chem. USSR*, **9**, 1341 (1973).
(8) For a discussion of the stereoelectronic factors which influence reactions of enols and enolates, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965, pp 307–314, and references cited therein.
(9) A similar argument has been used to rationalize the rates of certain solvolytic cyclizations onto aromatic rings, in which six-membered rings are formed faster than five: R. Heck and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3114 (1957). See also B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45 (1964).
(10) (a) R. M. Dodson, J. R. Lewis, W. P. Webb, E. Wenkert, and R. D. Youssefyeh, *J. Am. Chem. Soc.*, **83**, 938 (1961); (b) K. B. Wiberg and G. W. Klein, *Tetrahedron Lett.*, 1043 (1963); (c) P. C. Mukharji, P. K. Sen Gupta, and G. S. Sambamurti, *Tetrahedron*, **25**, 5287 (1969); (d) F. Nerdel, D. Frank, W. Metasch, K. Gerner, and H. Marschall, *ibid.*, **26**, 1589 (1970); (e) E. Wenkert, P. Bakuzis, R. J. Baumgarten, D. Doddrell, P. W. Jeffs, C. L. Leicht, R. A. Mueller, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **92**, 1617 (1970); (f) E. Wenkert, P. Bakuzis, R. J. Baumgarten, C. L. Leicht, and H. P. Schenk, *ibid.*, **93**, 3208 (1971); (g) S. Wolff and W. C. Agosta, *J. Chem. Soc., Chem. Commun.*, 771 (1973); (h) H. Marschall and F. Vogel, *Chem. Ber.*, **107**, 2176 (1974); and references cited therein.
(11) E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, and K. Folkers, *J. Am. Chem. Soc.*, **62**, 1787 (1940). This compound dimerizes on standing and was used in the form of its dimer. See H. J. Arpe, *Chem.-Ztg.*, **97**, 53 (1973).
(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(13) Vapor phase chromatographic analyses were carried out on a Varian Aerograph Model 90-P instrument, using the following columns: (a) 5% SE-30 on Chromosorb W, 5 ft × 0.25 in.; (b) 15% SF-96 on Chromosorb W, 5 ft × 0.25 in.