The Chemistry of γ-Oxo Sulfones. 1. A Novel Rearrangement and a Method for the β-Alkylation of α,β-Unsaturated Ketones

José Fayos and Jon Clardy[1]

Ames Laboratory—USAEC and Department of Chemistry, Iowa State University, Ames, Iowa 50010

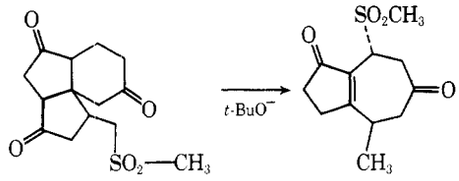
Lloyd J. Dolby* and Thomas Farnham

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

Received June 13, 1975

The base-induced rearrangement of the tricyclic diketo sulfone 1 into the hydroazulene derivative 2 is described. The structure of 2 is secured by x-ray crystallography. A reaction sequence for this novel transformation is proposed which involves addition of methanesulfinic acid to an α,β-unsaturated ketone. This reaction was examined in model compounds and a method for the β-alkylation of α,β-unsaturated ketones is reported.

During a study of the synthesis of gibberellic acid, the diketo sulfone 1 was found to undergo an extensive rearrangement upon treatment with potassium *tert*-butoxide.[2] The synthesis of 1 along with some of its transformations was presented previously along with the description of the rearrangement reaction.[2] We now wish to report the structure of the rearranged compound obtained previously and present a new method for the β-alkylation of α,β-unsaturated ketones which was suggested by the remarkable transformation of 1 in the presence of potassium *tert*-butoxide. The major product of the reaction, obtained in 30% yield after chromatography and recrystallization, has now been identified as the hydroazulene derivative 2.



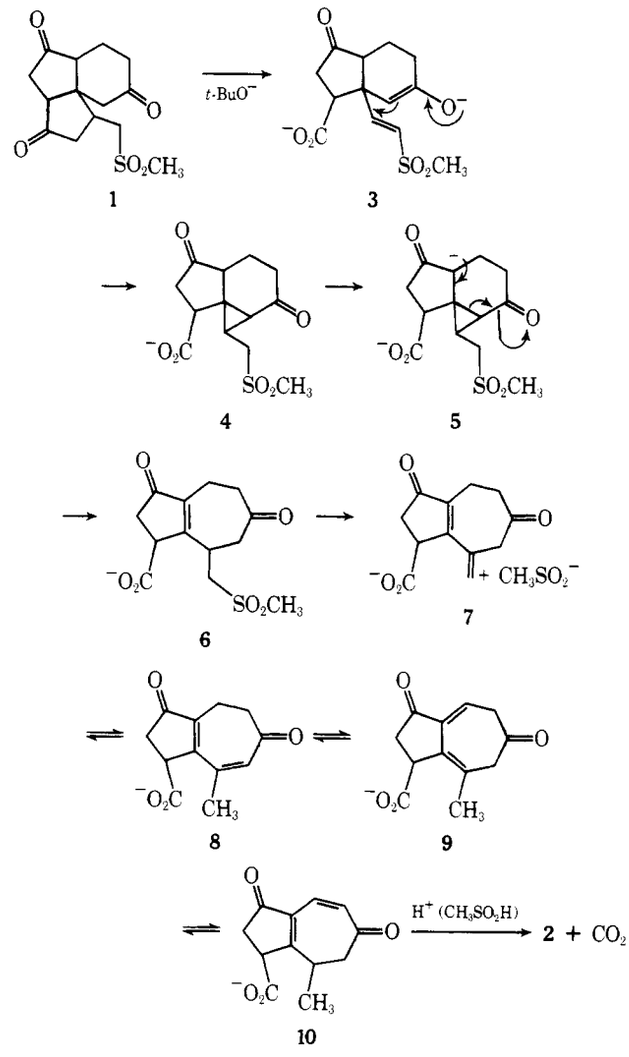
1 2

Crystals of **2**, $C_{12}H_{16}SO_4$, belong to the monoclinic crystal class with $a = 8.374$ (3), $b = 9.427$ (6), $c = 16.578$ (5) Å, and $\beta = 114.17$ (2)°. A calculated density of 1.42 g/cm^3 for $Z = 4$ indicated that the asymmetric unit of the uniquely determined space group $P2_1/c$ consisted of one molecule. A total of 1888 independent reflections were measured on a fully automated Hilger-Watts four-circle diffractometer using Ni-filtered Cu Kα (1.5418 Å) radiation. Following Lorentz, polarization, and background corrections a total of 1649 reflections with $F_o > 3\sigma(F_o)$ were considered observed. The structure was solved by a multisolution tangent formula approach using the program MULTAN[3] and the 134 normalized structure factors greater than 1.70. All nonhydrogen atoms were clearly revealed in the three-dimensional *E*-synthesis of the best set. Full-matrix least-squares refinement converged to the present minimum of 0.097 for the unweighted discrepancy index.

Figure 1 shows a computer generated drawing of the x-ray model. There is a double bond between atoms C(6) and C(10) with a bond length of 1.35 (1) Å. Atoms C(1), C(10), C(9), O(1), C(8), C(7), C(6), and C(5) are planar with an average deviation from the least-squares plane of 0.043 Å and no deviations greater than 0.10 Å. The methyl group, C(11), and the methanesulfonyl groups are on opposite sides of the seven-membered ring. All bond distances and angles agree well with generally accepted values and there are no abnormally short intermolecular contacts.

Scheme I is proposed as a working hypothesis to account for the base-induced conversion of 1 into 2. Elimination of carboxylate ion to give vinyl sulfone 3 is entirely expected since the corresponding ketal of 1 yields the ketal of 3 under identical reaction conditions. The formation of the seven-membered ring may be accounted for by cyclopropane formation and subsequent cleavage to give 6. The cyclopropane intermediate 4 could also be formed by a direct internal nu-

Scheme I



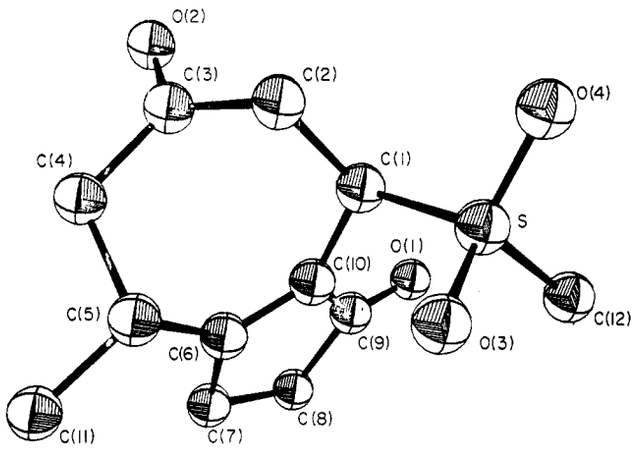
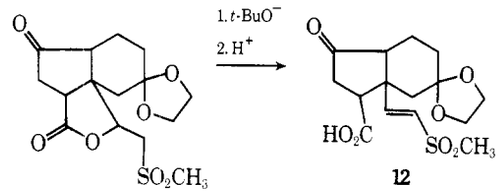
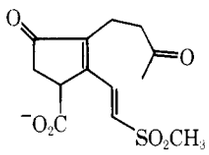


Figure 1.

cleophilic displacement. An alternative route would involve a retro-Michael reaction of **3** to give the dienedione **13** which



11 **12**

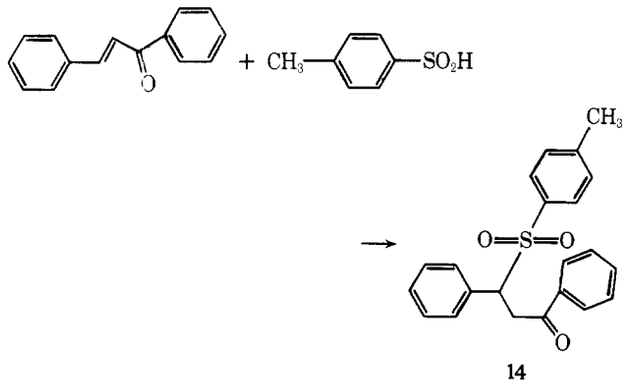


13

could give rise to intermediate **6** by a Michael condensation.

In any case, elimination of methanesulfonate from **6** would afford the diketodiene **7.** We find, in related systems, that such eliminations are rapid. The chance arrangement of carbonyl groups and double bonds in **7** ensures that the double bonds will be very mobile. Hence, isomers **8, 9,** and **10** are expected under the strongly alkaline reaction conditions. Finally, acidification of the reaction mixture would be expected to cause decarboxylation of the vinylogous β-keto acid and result in addition of methanesulfinic acid to the α,β-unsaturated ketone moiety.

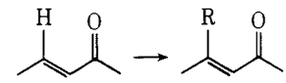
The remarkable migration of the methanesulfonyl group has occupied our attention and has suggested some very useful new synthetic sequences. Examination of the literature revealed that *p*-toluenesulfinic acid readily adds to the double bond of chalcone to give the keto sulfone **14.** In our initial



14

experiments we found that sodium *p*-toluenesulfinate does not react with α,β-unsaturated ketones but the reaction readily proceeds upon addition of 1 equiv of a proton source; acetic acid serves nicely. Methyl vinyl ketone and cyclohexenone are converted to the corresponding γ-oxo sulfones in better than 90% yields upon warming in ethanol solution with a slight excess of sodium *p*-toluenesulfinate and acetic acid. The ^{1}H NMR spectra of these materials rule out the isomeric sulfinate ester structures. The chemical shifts of the proton or protons attached to the sulfonyl-bearing carbon are consistent only with the sulfone structure.

The easily obtained γ-oxo sulfones suggested a new method for the β-alkylation of α,β-unsaturated ketones. While this manuscript was in preparation Kondo and Tunemoto[5] presented their results on this same synthetic scheme. In our



study of this process, the γ-keto sulfones were prepared by the addition of *p*-toluenesulfonic acid to the α,β-unsaturated ketones. This reaction proceeds in excellent yields. Kondo and Tunemoto used this reaction in one instance and also employed a sequence involving addition of benzenethiol to the unsaturated ketone or aldehyde and oxidation to the corresponding sulfone at a later stage, a method which requires an additional step.

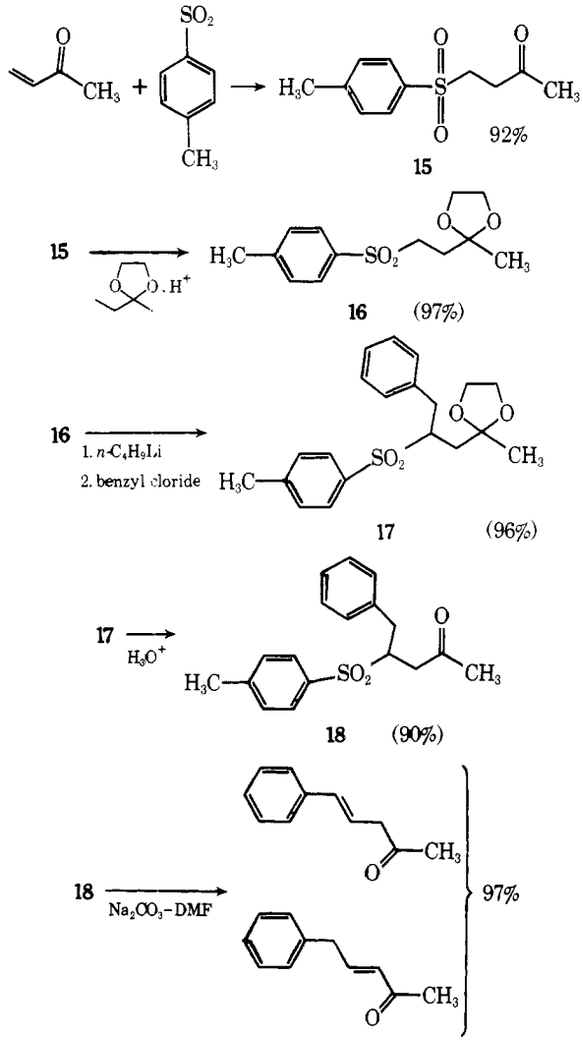
We reasoned that if the carbonyl group of a γ-oxo sulfone were blocked as a ketal or acetal, the sulfonyl group could be used to introduce alkyl groups. Subsequent hydrolysis of the protecting group and elimination of *p*-toluenesulfinic acid would complete the transformation indicated above. This proved to be the case. In the only sequence shown in Scheme II each of the individual steps proceeds in better than 90% yields. Moreover, all of the sulfone intermediates are nicely crystalline and easy to handle.

In the sequence shown in Scheme II, each of the intermediates was isolated, purified, and characterized. However, in routine synthetic applications, it would not be necessary to purify after the alkylation step. We observed no indication of dialkylation and the reaction product was remarkably clean. Hydrolysis of the ketal function and elimination of *p*-toluenesulfinic acid could undoubtedly be carried out without purification of the alkylated γ-oxo sulfone.

In the example shown in Scheme II elimination of *p*-toluenesulfinate from **21** under mild conditions produces nearly pure 5-phenylpent-3-en-2-one as judged from its spectral properties. This material has not been previously reported and earlier work indicated that the β,γ-unsaturated isomer, 5-phenylpent-4-en-2-one, was the only isomer obtainable in this tautomeric system.[6] We find that attempted purification causes equilibration to a mixture of the double bond isomers and more drastic elimination conditions produce a mixture containing 5-phenylpent-4-en-2-one and 5-phenylpent-3-en-2-one in a ratio of about 3:1. This mixture gives an easily purified semicarbazone of the β,γ-unsaturated isomer.[6,7]

The second example of this synthetic method demonstrates the application to cyclic α,β-unsaturated ketones and the preparation of β,β-dialkyl α,β-unsaturated ketones. Cyclohexenone was converted to 3-(*p*-toluenesulfonyl)cyclohexanone, which was in turn converted to the ketal and alkylated with methyl iodide. Hydrolysis of the ketal and elimination of the elements of *p*-toluenesulfinic acid afforded 3-methylcyclohex-2-en-1-one. Each of the steps proceeded in reasonable yield and this approach to the β-alkylation of α,β-unsaturated ketones appears to be a useful synthetic method.

Scheme II



Experimental Section[8]

4-(*p*-Toluenesulfonyl)butan-2-one (15). To 14.54 g (0.204 mol) of methyl vinyl ketone in a 300-mL flask equipped with magnetic stirrer was added a solution of 64.03 g (0.30 mol) of sodium *p*-toluenesulfinate dihydrate in 200 mL of 95% ethanol and 19.0 g of glacial acetic acid. The solution was stirred for 12 h at room temperature, then extracted with two 150-mL portions of $CHCl_3$. The $CHCl_3$ was washed with 150 mL of saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated under reduced pressure to give a viscous yellow residue which afforded 42.62 g (92%) of crystalline sulfone after triturating with hexane. Two recrystallizations from EtOH–Et_2O gave translucent needles: mp 74.5–75 °C; ^1H NMR ($CDCl_3$) δ 7.79, 7.37 (AB q, 4 H, J = 8 Hz), 3.37, 2.91 (t, 4 H, J = 7 Hz), 2.46 (s, 3 H), 2.18 (s, 3H).

Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24. Found: C, 58.23; H, 6.20.

4-(*p*-Toluenesulfonyl)-2,2-ethylenedioxybutane (16). A mixture of **15** (22.055 g, 97 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg) in 100 mL of 2-ethyl-2-methyl-1,3-dioxolane was distilled through a short Vigreux column such that 30 mL of butanone-enriched distillate was obtained over 7 h. The residual dioxolane reagent was removed under reduced pressure to yield a golden, crystalline aggregate which afforded 25.56 g (97%) of **16** after recrystallization from ethyl acetate–hexane. After a second recrystallization: mp 121–122 °C; ^1H NMR ($CDCl_3$) δ 7.80, 7.37 (AB q, 4 H, J = 8 Hz), 3.89 (d, 4 H, J = 4 Hz), 3.18, 2.04 (2 p, 2 H each, J = 4 Hz), 2.46 (s, 3 H), 1.28 (s, 3 H).

Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71. Found: C, 57.54; H, 6.78.

4-(*p*-Toluenesulfonyl)-5-phenyl-2,2-ethylenedioxypentane (17). To 21.729 g (80 mmol) of **16** in a 250-mL three-neck flask fitted with magnetic stirrer and reflux condenser were added 150 mL of freshly distilled THF and 50 mg (indicator amount) of triphenylmethane. Butyllithium (55 mL, 1.5 M in hexane) was added to give a persistent orange color and the resulting solution allowed to stir for 10 min. Cautious addition of 10.10 g (80 mmol) of freshly distilled benzyl chloride produced a yellow slurry which was refluxed for 3 h, then extracted with two 150-mL portions of ether. Evaporation under reduced pressure yielded 28.40 g (98%) of **16** as beige crystals from petroleum ether (bp 30–60 °C). Recrystallization from ethyl acetate–hexane gave fine, white needles: mp 73–73.5 °C; ^1H NMR ($CDCl_3$) δ 7.68, 7.27 (AB q, 4 H, J = 8 Hz), 7.16 (bs, 5 H), 4.0–2.8, 2.6–2.3 (m, 7 H), 2.41 (s, 3 H), 1.90 (p, 2 H), 1.10 (s, 3 H).

Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71. Found: C, 66.22; H, 6.65.

5-Phenyl-4-(*p*-toluenesulfonyl)pentan-2-one (18). To 1.200 g (3.3 mmol) of alkylated ketal sulfone dissolved in 30 mL of methanol was added 1 g of $HClO_4$ (70%). After 30 min, the mixture was extracted with 50 mL of ether, neutralized with 50-mL saturated $NaHCO_3$ wash, dried over Na_2SO_4, concentrated to 1.015 g (94%) of a yellow syrup under reduced pressure, and crystallized twice from hexane–ethyl acetate to yield white crystals: mp 85.5–86.5 °C; IR ($CHCl_3$) 1716 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.79, 7.35 (AB q, 4 H, J = 8 Hz), 7.3–7.0 (m, 5 H), 4.14 (m, 1 H), 3.4–2.3 (m, 4 H), 2.45 (s, 3 H), 1.96 (s, 3 H).

Anal. Calcd for $C_{18}H_{20}O_3S$: C, 68.33; H, 6.37. Found: C, 68.14; H, 6.57.

5-Phenyl-3-penten-2-one. A sample of **18** (0.2025 g, 0.64 mmol) in a 25-mL flask was dissolved in 10 mL of *N,N*-dimethylformamide and sodium carbonate (100 mg) added with continuous magnetic stirring. After 2.5 h, the cloudy mixture was extracted with 25 mL of hexanes, dried over Na_2SO_4, and evaporated to give a sample of the α,β-unsaturated phenyl pentenone isomer (0.0995 g, 97%): IR (CCl_4) 1673 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.16 (bd, 5 H, J = 6 Hz), 6.93 (m, 1 H, C-4 vinyl), 6.09 (d, 1 H, J = 16 Hz, C-3 vinyl), 3.55 (d, 2 H, J = 6 Hz), 2.22 (s, 3 H). A satisfactory combustion analysis was not obtained.

5-Phenyl-4-penten-2-one. A second sample of alkylated keto sulfone (13.3 g, 42 mmol) treated in similar fashion but heated to 60 °C for 9 h yielded 5.09 g (75%) of an isomeric mixture in 78:22 ratio favoring the β,γ-unsaturated component (thermodynamic equilibrium). A fraction of the styryl isomer was difficultly isolated by VPC, 20% Carbowax on Chromosorb W 20–10 mesh, 5 ft × 0.375 in. column, 150 °C: IR (CCl_4) 1713 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.5–7.1 (m, 5 H), 6.51 (d, 1 H, J = 16 Hz), 6.45–6.15 (m, 1 H), 3.33 (d, 2 H, J = 6 Hz), 2.20 (s, 3 H); semicarbazone mp 155–157 °C (EtOH–H_2O) (lit.[6] mp 160 °C).

3-*p*-Toluenesulfonylcyclohexanone. Sodium *p*-toluenesulfinate dihydrate (78.21 g, 0.37 mol) was dissolved in 250 mL of ethanol with 1 equiv (22 g) of glacial acetic acid, and added to 28.44 g (0.296 mol) of 2-cyclohexen-1-one in a 500-mL flask eqipped with a magnetic stirrer. The reaction mixture was maintained at 40–45 °C for 24 h, then extracted with two 250-mL portions of ether, washed with two 125-mL portions of saturated $NaHCO_3$, filtered, and evaporated to a bronze sludge (58.0 g, 78%). Two recrystallizations from hexane–ethyl acetate yielded white needles: mp 83–84 °C; ^1H NMR ($CDCl_3$) δ 7.76, 7.39 (q, 4 H, J = 8 Hz), 3.5–3.0 (m, 1), 2.47 (s, 3), 2.7–1.5 (m, 8 H).

Anal. Calcd. for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 61.80; H, 6.32.

3-(*p*-Toluenesulfonyl)-1,1-ethylenedioxycyclohexane. A mixture of 58.0 g (0.23 mol) of crude keto sulfone and 50 mg of *p*-toluenesulfonic acid monohydrate was dissolved in 250 mL of boiling 2-ethyl-2-methyl-1,3-dioxolane in a 500-mL flask equipped with a short Vigreux column. The rate of reflux was adjusted so that 100 mL of butanone-enriched dioxolane reagent was obtained over 7 h. The resulting product was initially isolated as off-color prisms from the residual dioxolane. Recrystallization from ethyl acetate–hexane afforded 65.47 g (96%) of beige prisms: mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 7.75, 7.36 (q, 4 H, J = 8 Hz), 3.92 (s, 4 H), 3.4–3.0 (m, 1 H), 2.46 (s, 3 H), 2.3–1.2 (m, 8 H).

Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.41; H, 6.93.

3-(*p*-Toluenesulfonyl)-3-methyl-1,1-ethylenedioxycyclohexane. A mixture of ketal sulfone obtained above (22.45 g, 0.0758 mol) and triphenylmethane (50 mg) in a 250-mL flask fitted with magnetic stirrer and reflux column was dissolved in 100 mL of THF. Approximately 50 mL of *n*-butyllithium (1.5 M in hexane) was added to a well-defined red end point, and, after 5 min, was followed by cautious addition of 5.0 g (0.08 mol) of methyl iodide with constant stirring. Refluxing for 1 h and in succession, ether extractions (300 mL), drying (Na_2SO_4), and evaporation yielded a brown gum which crystallized. The product was isolated as 23.29 g (99%) of discolored prisms after titrating with petroleum ether (bp 30–60 °C). Two recrystallizations

from hexane–ethyl acetate yielded beige prisms: mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 7.74, 7.25 (q, 4, J = 8 Hz), 3.90 (s, 4), 2.46 (s, 3), 2.0–1.5 (m, 8), 1.44 (s, 3).

Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14. Found: C, 61.79; H, 7.26.

3-Methyl-2-cyclohexen-1-one. A sample (0.5180 g, 1.67 mmol) of methylated ketal sulfone was dissolved in 11 mL of acidic aqueous 1,4-dioxane (3.5 mL of 50% $HClO_4$ in 7.5 mL of dioxane) and warmed (50 °C) for 12 h. The resulting auburn solution was made strongly alkaline with excess solid K_2CO_3, and after 30 min, extracted with three 50-mL portions of ether, dried over Na_2SO_4, and evaporated to a clear orange liquid. The residual dioxane was eliminated by preparative TLC (20 × 20 cm, 1000-μm silica gel GF in chloroform) to afford the crude ketone (0.156 g) which was isolated as the 2,4-DNP derivative. Recrystallization from ethyl acetate gave 0.242 g (50%) of dark red flakes, mp 176–178 °C corrected (lit.[9] mp 177–178 °C).

Registry No.—1, 28269-19-4; 2, 61476-93-5; 15, 61476-94-6; 16, 61476-95-7; 17, 61476-96-8; 18, 61476-97-9; methyl vinyl ketone, 78-94-4; sodium p-toluenesulfinate, 824-79-3; 2-ethyl-2-methyl-1,3-dioxolane, 126-39-6; benzyl chloride, 100-44-7; 5-phenyl-3-penten-2-one, 10521-97-8; 5-phenyl-4-penten-2-one, 877-94-1; 3-p-toluenesulfonylcyclohexanone, 14444-30-5; 2-cyclohexen-1-one, 930-68-7; 3-(p-toluenesulfonyl)-1,1-ethylenedioxycyclohexane, 61476-98-0; 3-(p-toluenesulfonyl)-3-methyl-1,1-ethylenedioxycyclohexane, 61476-99-1; 3-methyl-2-cyclohexen-1-one, 1193-18-6; methyl iodide, 74-88-4.

References and Notes

(1) Camille and Henry Dreyfus Foundation Awardee, 1972–1977.
(2) L. Dolby, S. Esfandiari, C. A. Elliger, and K. S. Marshall, *J. Org. Chem.*, **36**, 1277 (1971).
(3) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(4) H. Gilman and L. F. Cason, *J. Am. Chem. Soc.*, **72**, 3469 (1950).
(5) K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1007 (1975).
(6) R. P. Linstead and L. Williams, *J. Chem. Soc.*, 2735 (1926).
(7) D. R. Coulson, *Tetrahedron Lett.*, 3323 (1964).
(8) Infrared spectra were measured with either Beckman IR-5A or IR-7 infrared spectrophotometers. Proton magnetic resonance spectra were determined at 100 MHz with a Varian Model XL-100 spectrometer. The chemical shift values are expressed in δ values (ppm) relative to tetramethylsilane internal standard. In the presentation of the ^{1}H NMR spectra the following notations are used: b, broad; u, unsymmetrical; s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; and m, multiplet. All reactions, except ketalization, were diluted with three volumes of water before extraction with ether.
(9) G. F. Woods, P. H. Griswold, Jr., B. H. Armbrecht, D. I. Blumenthal, and R. Plapinger, *J. Am. Chem. Soc.*, **71**, 2028 (1949).

Decomposition of Conjugated p-Tosylhydrazones in Base. Partition between Solvolysis and Cycloaddition Products

Romano Grandi, Walter Messerotti, Ugo M. Pagnoni,* and Roberto Trave

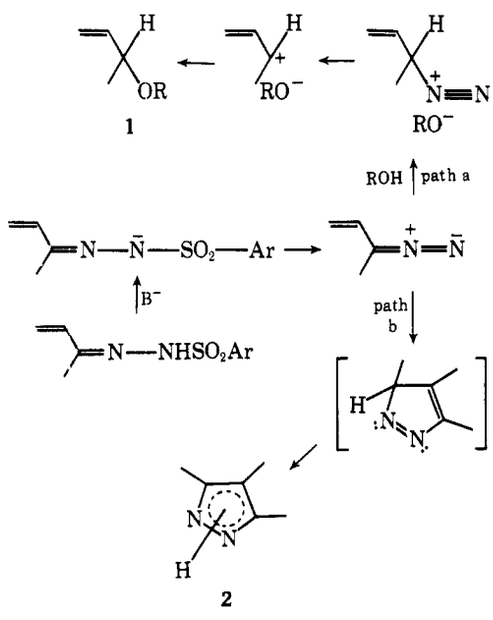
Istituto di Chimica Organica, Università di Modena, Via Campi 183, 41100 Modena, Italy

Received August 11, 1976

The p-tosylhydrazones of conjugated carbonyl compounds are not deoxygenated by $NaBH_4$ in methanol, but undergo an alkaline decomposition to diazoalkenes. The partition of the diazo compound between the solvolysis and intramolecular 1,3-dipolar cycloaddition processes depends on the degree and type of substitution at the β position. The use of base ($NaBH_4$, NaOR, or K_2CO_3) in alcoholic solvents provides a mild, convenient, and high-yield procedure for the preparation of a variety of (a) allylic ethers, in the case of cyclohexenones and β,β-dialkyl substituted carbonyl compounds; and (b) pyrazoles, in the case of acyclic α,β-unsaturated substrates having a β hydrogen.

Recently, we have found[1] that p-tosylhydrazones of some conjugated carbonyl compounds on treatment with $NaBH_4$ in alcoholic solvents undergo an elimination–substitution reaction in preference to the expected deoxygenation.[2,3] Allylic ethers are obtained in high yields by this method. A similar behavior was observed when RONa or K_2CO_3 was used instead of $NaBH_4$. The sequence p-tosylhydrazone → diazoalkene (aryldiazomethane) → diazonium–alkoxide ion pair[4] → ether (1) was suggested as the most suitable mechanistic description (path a). Hart and Brewbaker have shown[5,6] that 3-diazoalkenes, generated from the corresponding alkyl allylnitrosocarbamates, rapidly undergo intramolecular cycloaddition[7] to form pyrazoles (path b).[8] Although for the cyclohexenone and aromatic substrates previously examined by us[1] this cycloaddition was clearly impossible, the formation of only products of solvolysis (e.g., methyl ethers) for the case of the acyclic substrate, neral, was surprising since some intramolecular cycloaddition product may reasonably have been expected.

Scheme I



In a continuation of our studies on the anomalous behavior of p-tosylhydrazones of conjugated carbonyls toward $NaBH_4$ we wished to investigate how structural factors may determine the course of decomposition of these compounds. We therefore chose substrates (entries 1, 2, 5–8, Table I) which would yield diazoalkenes structurally analogous to those studied by Hart and Brewbaker. In these cases it could be expected that intramolecular cycloaddition should compete favorably with the elimination–substitution reaction process. In fact, treatment of these substrates with each of the three basic reagents employed previously[1] ($NaBH_4$, MeONa, and K_2CO_3 in methanol) leads to pyrazoles (**2a,b,c–f**) in high yields. No methyl ethers could be detected in the reaction mixtures. In Table I are reported the data for the reagent that is more generally useful (K_2CO_3 in methanol). With $NaBH_4$ or