the epoxide. The specificity in the case of **2**[17] undoubtedly involves the alkoxide, rather than the free alcohol, and is operative in both the cis and trans series. A pertinent analogy is seen in the work of Fried, wherein a remote hydroxyl (presumably as the alkoxide) is efficacious in directing epoxide opening by an organoalane.[18,19] In the cases studied here (**7** and **8**), one can not clearly discern such an effect, though it may be operative as one of several competing forces.

There emerges from our data an empirically based approach for the construction of variations of system **4** with complete stereospecificity and acceptable regioselectivity by utilization of suitable organometallic equivalents of $^{-}CH_2CO_2H$. The feasibility of using this methodology in total synthesis contexts is receiving continuing attention.

Acknowledgements. This study was supported by PHS Grant CA-12107-12 and by an unrestricted Grant from the Merck Corp. We also thank Professor Clayton Heathcock of the University of California (Berkeley) for providing us with prepublication experimental conditions (ref 9) and Professor Frederick Ziegler of Yale University for making the comparison of our sample of **14** with his authentic sample.

References and Notes

(1) S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.*, **98**, 3028 (1976).

(2) S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).

(3) For the first total synthesis of *dl*-vernolepin and *dl*-vernomenin, see P. A. Grieco, M. Nishizawa, S. D. Burke, and M. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976).

(4) See E. Eliel, "The Stereochemistry of Carbon Compounds", McGraw Hill, New York, N.Y., London, 1962. That the ground-state conformation of **1** is the one in which the hydroxyl and vinyl are equatorial to the B ring was strongly suggested by high field NMR analysis of its derived acetate; see ref 1, footnote 18.

(5) (a) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); (b) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nazoe, "Natural Products Chemistry", Vol. 1, Academic Press, New York, N.Y., London, 1974.

(6) (a) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972). (b) For recent syntheses of α-methylenelactones, see N. Marinovic and M. Miyashita, *ibid.*, **40**, 1670 (1975); S. M. Ali and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, 584 (1976); J. P. Marino and J. S. Farina, *J. Org. Chem.*, **41**, 3213 (1976).

(7) (a) For a study of the reduction of epoxides bearing vicinal alkyl groups, see B. Rickborn and W. E. Lamke, *J. Org. Chem.*, **32**, 537 (1967). (b) For a similar study on vicinally oxygenated opoxides, see B. C. Hartman and B. Rickborn, *ibid.*, **37**, 4246 (1972). (c) For a study of cuprate additions to vicinally oxygenated epoxides, see B. C. Hartman, T. Livinghouse, and B. Rickborn, *ibid.*, **38**, 4346 (1973).

(8) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957). NMR spectral analysis indicated that starting materials **5** and **7** were uncontaminated with one another.

(9) C. G. Chavdarian and C. H. Heathcock, *Synth. Commun.*, **6**, 277 (1976). We thank Professor Heathcock for apprising us of his excellent method prior to its publication.

(10) In our experience, the yields of epoxide openings using the Creger method[6] do not exceed 70% even with very simple substrates. The virtue of the method is that the reagent is quite stable to temperatures up to 60–70 °C where this becomes necessary. However, for reasons not yet understood, substantial starting material is recovered even with copious excesses of reagent and long reaction times.

(11) NMR analysis of the parent alcohols gives the same conclusions. However, in the three compounds which have trans-fused γ-lactones, the carbinol methine proton signal overlaps with that arising from the oxygen-bound lactonic methine.

(12) This trend has been noted in a variety of cis- and trans-fused γ-lactones with and without α-hydroxyl groups. The oxygen-bound lactonic methine proton absorbs in the region δ 4.6–5.0 ppm while that of the trans series absorbs in the region 3.8–4.1 ppm. This is the case in seven sets of isomers which we have prepared.

(13) (a) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. L. Studt, *Tetrahedron Lett.*, 2035 (1974); (b) S. Danishefsky, T. Kitahara, and R. K. Singh, *J. Org. Chem.*, **41**, 1669 (1976).

(14) S. M. Kupchan and R. M. Schubert, *Science*, **185**, 791 (1974).

(15) Y. Houminer, *J. Chem. Soc., Perkin Trans. 1*, 1663 (1975).

(16) H. C. Dalzell, R. K. Razdan, and R. Sawdaye, *J. Org. Chem.*, 41, 1650 (1976).

(17) In the case of compound **1** the total regiospecificity must involve factors in addition to alkoxy participation. The shielding effect of the axial bond of the ortho ester would appear to be a reasonable explanation. This would account for the failure of **1** tetrahydropyranyl ether to react at all, since the expected mode, based on compound **6**, would occur at carbon **6**. For a possibly related case, in the synthesis of luciduline, see W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.*, **94**, 4780 (1972).

(18) J. Fried, J. C. Sih, C. H. Lin, and P. Dalven, *J. Am. Chem. Soc.*, **93**, 4343 (1972).

(19) J. Fried and J. C. Sihm, *Tetrahedron Lett.*, 3899 (1973).

Samuel Danishefsky,* Mei-Yuan Tsai
Takeshi Kitahara
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

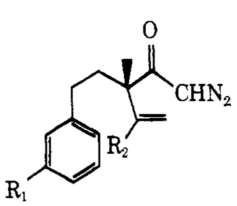
Received June 1, 1976

β,γ-Unsaturated Diazo Ketones. A New Initiator for Polyolefinic Cationic Cyclization

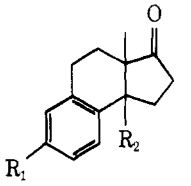
Summary: The synthetic utility of β,γ-unsaturated diazo ketones as initiators for polyolefinic cationic cyclization is described.

Sir: Recently, we have demonstrated that β,γ-unsaturated diazo ketones are synthetically useful precursors of both simple and annulated cyclopentenone derivatives when subjected to acid-catalyzed decomposition.[1] We now wish to report that such species hold considerable potential for the initiation of polyolefinic cyclizations.[2] To our knowledge unsaturated diazo ketones have not previously been employed in this manner.[3]

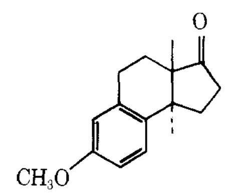
In order to investigate this question, we selected diazo ketones **1a–c** which would not be expected to become involved in complex structural rearrangements. In addition, diazo ketone **1a** appeared ideally suited for our initial study since two of the four possible tricyclic products (**2a** and **3**) have recently been prepared and their stereochemistry established rigorously by Jeger and co-workers.[4]



1



2

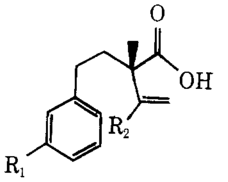


3

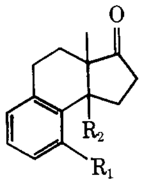
a, $R_1 = OCH_3$; $R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = H$; $R_2 = H$
d, $R_1 = OH$; $R_2 = CH_3$

The required diazo ketones **1a–c** were prepared in the usual manner (oxalyl chloride, CH_2N_2) from the corresponding β,γ-unsaturated acid derivatives **4a–c**[5] readily available via alkylation of the ethyl esters of either 2,3,3-trimethylacrylic acid or tiglic acid with the tosylate ester of phenethyl or *m*-methoxyphenethyl alcohol, employing as base the lithium diisopropylamide–hexamethylphosphoramide complex in THF described recently by Rathke[6] and Schlessinger.[7] Subsequent hydrolyses of the resultant esters (5% aqueous NaOH, 14 h) yielded **4a**[5] and **4b**[5] as crystalline solids (mp 73.5–74.5 °C and 67–68 °C, respectively), whereas **4c**[5] was obtained as a viscous oil. The overall yields based on the tosylate were 43–48%.

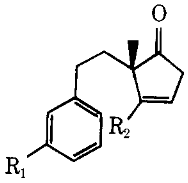
After examination of a variety of Lewis acid and complementary solvent systems, it was determined that 1.1 equivalent of $BF_3 \cdot Et_2O$ in freshly distilled nitromethane at room temperature for 0.5 h constituted the optimal conditions[8] to effect the desired cyclizations. In that event diazo ketone **1a** yielded two tricyclic products, **2a** and **5a**,[5] accompanied by a small amount of **6a**[5] (31, 12, and 10% yield, respectively).[9] Interestingly, when methylene chloride was employed as solvent, a small amount (2%) of **8**[5,10] was formed in addition to **2a**, **5a**, and **6a**. Similar cyclizations ($BF_3 \cdot Et_2O/CH_3NO_2$; 0.5 h) of **1b** yielded **2b**,[5] **6b**,[5] and **7**[5] (46, 10, and ∼2% yield, respectively) while **1c** gave only **9**[5] in 21% yield. Finally, treatment of **6b** under the above conditions led to its complete recovery. The above structures were deduced from the spectroscopic properties, after resolution of the product mixtures via a combination of separation techniques including VPC on 6% Carbowax 20M and HPLC on SIL-X-1 (CH_2Cl_2:hexane, 3:2). Confirmation of structure **2a** was obtained by comparison of the IR and NMR spectra with those obtained originally by Jeger.[11]



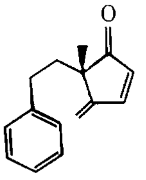
4



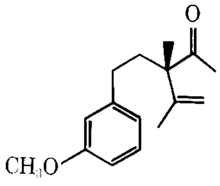
5



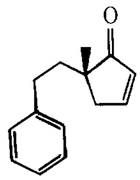
6



7



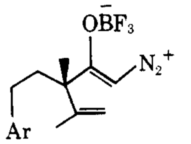
8



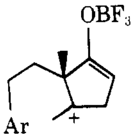
9

Drieding molecular model studies of diazo ketones **1a–c** indicated that the most favorable conformation for cyclization would lead to a cis C/D ring fusion. This result is due primarily to the tetrahedral geometry of the α-carbon center. That in fact the cyclization in each case proceded stereospecifically to yield the cis-fused tricyclic ketones **2a**, **2b**, and **5a** followed initially from a comparison of their 220-MHz NMR spectra. Second, ketone **5a** and the previously known **2a** were individually transformed to **2b** employing a demethylation–dehydroxylation reaction sequence. To this end, cleavage[12] of the phenolic methyl esters with BBr_3 led to phenols **2d**[5] and **5d**, which were transformed to the corresponding diethyl phosphate ester with diethyl chlorophosphate. Subsequent reduction with excess potassium in liquid ammonia, employing ether as a co-solvent according to the method of Rossi and Bunnett,[13] gave in both cases a single tricyclic ketone which was identical in all respects (e.g., IR, 220 MHz NMR, and retention properties) with **2b**.

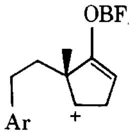
A reasonable reaction pathway for the above cyclizations involves initial complexation by BF_3 with the oxygen of the diazo ketone functionality to yield intermediate **10**; subsequent loss of nitrogen and cyclization then leads in the case of **1a** and **1b** to a tertiary carbocation (**11**).[14] The exact nature of this initial cyclization is currently unknown but at least two alternatives exist. The initial loss of nitrogen could preceed σ-bond formation, and/or the π system of the β,γ-olefinic bond could participate directly in nitrogen loss. The resultant tertiary carbocation is, in most instances, sufficiently long lived to suffer capture by the π system of the aromatic ring before the cation can be removed from the reaction coordinate by proton loss. Support for the stepwise nature of this sequence arises from the BF_3-catalyzed decomposition of **1c** which yields cyclopentenone **9** as the major product. In this case the initial cyclization leads to a less stable, short-lived secondary carbocation (**12**) which rapidly losses a proton before capture by the aromatic system can take place.



10



11



12

The synthetic utility of this approach to polycyclic ketones is readily apparent when one considers alternative approaches to such tricyclic systems. For example **2a** was prepared by Jeger in eighteen steps from dehydroabietic acid.[4] Studies are continuing in our laboratory to extend the synthetic use of acid-catalyzed decomposition of unsaturated diazo ketones.

Acknowledgment. We are glad to acknowledge the generous support of this investigation by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by Research Corporation.

References and Notes

(1) A. B. Smith, III, *J. Chem. Soc., Chem. Commun.*, 695 (1974), and A. B. Smith, III, S. J. Branca, and B. H. Toder, *Tetrahedron Lett.*, 4225 (1975).
(2) For reviews of this general area, see W. S. Johnson, *Bioorg. Chem.*, **5**, 51 (1976); W. S. Johnson, *Angew. Chem., Int. Ed. Engl.*, **15**, 9 (1976); E. E. Van Tamelen, *Acc. Chem. Res.*, *8*, 152 (1975); K. E. Harding, *Bioorg. Chem.*, **2**, 248 (1973); D. Goldsmith, *Fortschr. Chem. Organ. Naturst.*, **29**, 363 (1971); E. E. Van Tamelen, *Acc. Chem. Res.*, **1**, 111 (1968); W. S. Johnson, *ibid.*, **1**, 1 (1968); W. S. Johnson, *Trans. N.Y. Acad. Sci.*, **29**, 1001 (1967).
(3) The acid-catalyzed decomposition of several γ,δ-unsaturated diazo ketones leading to the closure of a single ring have been reported recently; see for example D. J. Beames and L. N. Mander, *Aust. J. Chem.*, **27**, 1257 (1974); D. J. Beames, T. R. Klose, and L. N. Mander, *ibid.*, 1269 (1974); D. W. Johnson and L. N. Mander, *ibid.*, 1277 (1974); R. Malherbe, N. T. T. Tam, and H. Dahn, *Helv. Chim. Acta*, **55**, 245 (1972); P. N. Chakrabortty, R. Dasgupta, S. K. Dasgupta, S. R. Ghosh, and U. R. Ghatak, *Tetrahedron*, **28**, 4653 (1972); W. F. Erman and L. C. Stone, *J. Am. Chem. Soc.*, **93**, 2821 (1971), and reference cited therein. For an example of a β,γ-unsaturated diazo ketone leading to a cyclobutanone, see U. R. Ghatak and B. Sanyal, *J. Chem. Soc., Chem. Commun.*, 876 (1974).
(4) v. T. Wirthlin, H. Wehrli, and O. Jeger, *Helv. Chim. Acta*, **57**, 351 (1974).
(5) This new compound gave satisfactory spectroscopic properties (IR and 220-MHz NMR) as well as elemental analysis and/or exact mass of the molecular ion by high resolution mass spectroscopy.
(6) M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 4249 (1972).
(7) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).
(8) Similar conditions were employed by L. N. Mander and co-workers; see ref 3.
(9) Yields were determined by calibrated VPC measurements and are based on converted starting material. Isolated yields were ∼5–7.5% lower.
(10) An authentic sample of ketone **8** was prepared from acid **4a** by treatment with 2 equiv of CH_3Li: M. J. Jorgenson, *Org. React.*, **18**, 1 (1970).
(11) We are grateful to Dr. W. Graf and Professor Oskar Jeger for providing the IR and NMR spectra of authentic **2a** and **3**.
(12) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).
(13) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 2314 (1973).
(14) Alternatively, BF_3 complexation could take place at the diazo carbon atom. Subsequent cyclization via nucleophilic displacement of N_2 by the π system would then lead to a tertiary carbonium ion from which the various products arise.

Amos B. Smith, III,* R. Karl Dieter
Department of Chemistry, The Laboratory for
Research on the Structure of Matter and
The Monell Chemical Senses Center
University of Pennsylvania
Philadelphia, Pennsylvania 19174

Received September 16, 1976