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THE SYNTHESIS OF OXYGENATED BICYCLIC SYSTEMS VIA THE 4+2 CYCLOADDITION REACTION OF TRIMETHYLSILYLOXY CYCLOHEXADIENES

G.M. Rubottom* and D.S. Krueger

Department of Chemistry, University of Idaho, Moscow, Idaho 83843

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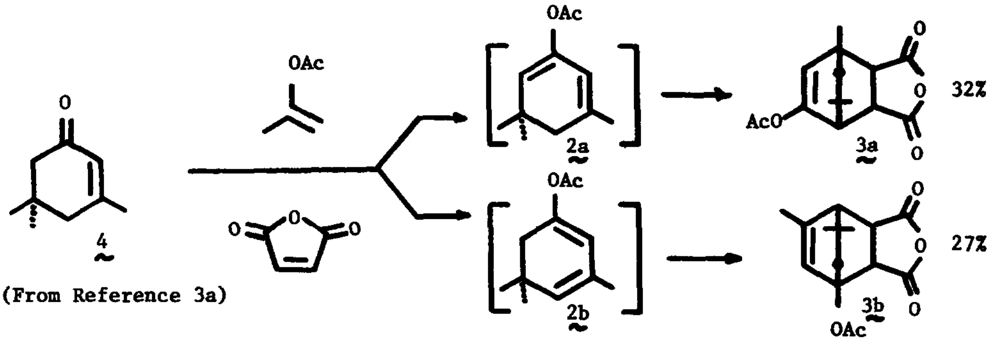
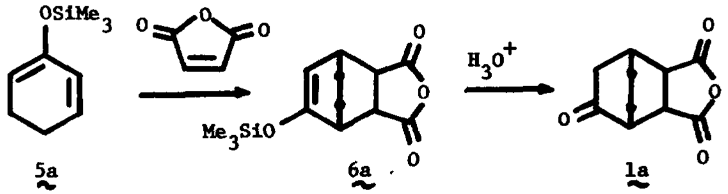
Synthetic approaches for the preparation of oxygenated bicyclo (2.2.2) octanes, 1, include among others,[1] the use of 4+2 cycloaddition reactions of both dienolates[2] and their acetoxy derivatives, 2.[3] The former method suffers from the fact that the reaction conditions are strongly basic, while the latter is limited by the consideration that generation of 2 under equilibrium conditions affords mixtures of isomeric diene acetates, and hence, mixtures of the corresponding 4+2 products, 3. This second point is illustrated in Scheme I for the reaction of isophorone, 4.

SCHEME I



(From Reference 3a)

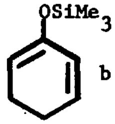
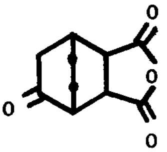
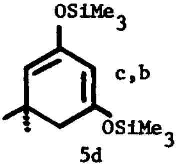
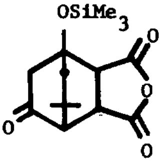
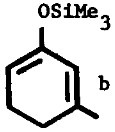
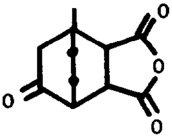
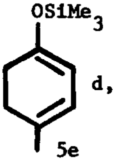
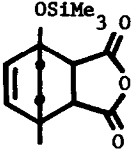
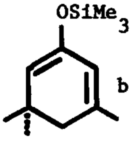
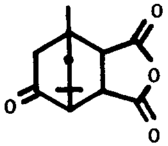
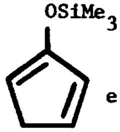
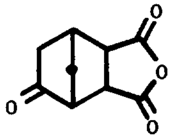
We should like to report that the use of alkyl substituted trimethylsilyloxy cyclohexadienes, 5, circumvents both of the difficulties noted above and offers an extremely high yield, general method for the production of 1.[4,5,6] The utility of the method is indicated below in Table I, wherein the 4+2 cycloaddition reaction of 5 with maleic anhydride (Equation 1) is summarized.



(Eq. 1)

TABLE I

The Reaction of Substituted Trimethylsilyloxy Cyclohexadienes, 5, with Maleic Anhydride

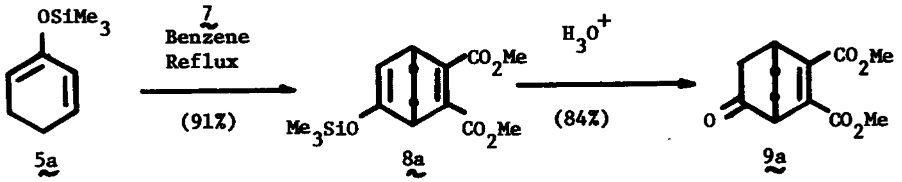
5[a]	1[a], Isolated % Yield 1, mp 1°C (Lit. mp).	5[a]	1[a], Isolated % Yield 1, mp 1°C (Lit. mp).
 b 5a	 1a, 94%,227-228	 c,b 5d	 1d, 90%,159-161
 b 5b	 1b, 93%,218-218.5	 d,b 5e	 1e, 86%,51-52
 b 5c	 1c, 93%,159-160 (160.5-161.5[f])	 e 5f	 1f, 79%,228-229 (228.5-230[f])

a) All compounds have ir, NMR, and ms properties consistent with the proposed structures; all new compounds show C and H analyses within ±0.3% of theoretical. b) Prepared by the method cited in reference 5. c) Prepared from 5,5-dimethyl-3-trimethylsilyloxy-2-cyclohexen-1-one. d) Prepared by the method cited in reference 6a. f) Value cited in reference 3a.

Several entries in Table I merit comment. Along with the advantage of high yield transformations, the isomer problem encountered with the use of 2 is not a factor in the present method. Control of the placement of the double bond system in 5 (e.g., 5b in contrast to 5e) gives corresponding control over the placement of substituents in the 4+2 product 1. Comparison of 1c and 1f with known compounds[3a] assures the general endo-stereochemistry of 1, and the flexibility of the method is exemplified by the production of 1f.[7] Although, as a matter of convenience, 1 was isolated, it is possible to isolate the potentially useful intermediate 6[8] by means of anhydrous workup conditions.

In a typical procedure, a solution of 2 mmol of 5a and 2 mmol of maleic anhydride in 10 ml of dry benzene was stirred 8 hr under an atmosphere of nitrogen. The benzene was then removed *in vacuo* and the residue placed in 5 ml of wet ether. The crude 1a, which gradually precipitated over a period of about 3 hr, was crystallized from benzene to afford 94% of pure 1a, mp 227-228°C.

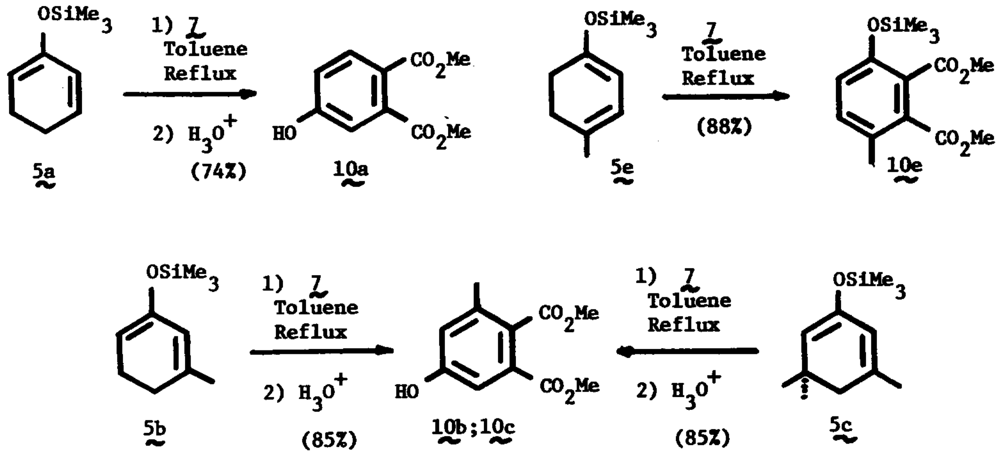
In a series of related experiments, it was found that 5 reacts smoothly with dimethyl acetylenedicarboxylate, 7, to produce 8 in high yield. Mild acid hydrolysis gives the corresponding ketone 9 (Equation 2). The reaction temperature becomes crucial in this transformation,



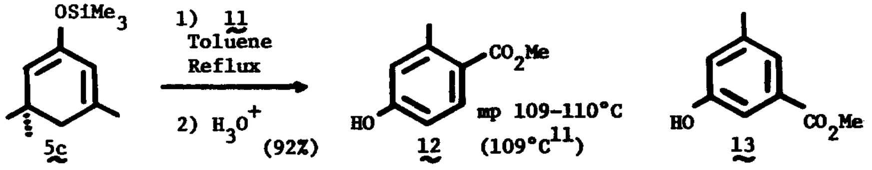
(Eq. 2)

since substitution of toluene for benzene cleanly effects debridging of 8 to give 10 as shown in Scheme II.[9,10] The regiospecificity of the addition process is indicated by the reaction of

SCHEME II



5c with methyl propynoate, 11, in refluxing toluene. The only phenolic product obtained from hydrolytic workup of the crude reaction mixture (92% yield) was the known compound 12.[11] NMR analysis of the crude reaction product prior to hydrolysis revealed that no compound corresponding to the regioisomer 13 was present (Equation 3).[12]



(Eq. 3)

Further extensions of the present method are being actively explored in these laboratories.

FOOTNOTES AND REFERENCES

1) a) For the reactions of cyclohexadienes as dienes, see: A.S. Onishchenko, "Diene Synthesis," Israel Program of Scientific Translations, D. Davey & Co., New York, N.Y., 1964, pp. 353-369; and references cited therein. b) For examples of *in situ* isomerization and subsequent 4+2 cycloaddition of 1,4-cyclohexadienes, see: A.J. Birch, P.L. Macdonald, and V.H. Powell, *Tetrahedron Lett.*, 351 (1969). c) For the reactions of dienamines, see: 1) J.W. Scott, W. Vetter, W.E. Oberhänsli, and A. Fürst, *ibid.*, 1719 (1972); 2) H. Nozaki, T. Yamaguti, S. Uedo, and K. Kondo, *Tetrahedron*, **24**, 1445 (1968). d) For the reactions of α,β-unsaturated ketones acting as both ene and diene, in the same transformation, see: references 9-12 cited in reference 2a below. e) For examples of intramolecular Friedel-Crafts reactions leading to bicyclic systems, see: S.A. Monti and G.L. White, *J. Org. Chem.*, **40**, 215 (1975). f) J.D. Roberts, W.T. Moreland, Jr., and W. Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953).

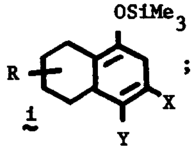
2) a) R.A. Lee, *Tetrahedron Lett.*, 3333 (1973). b) R.M. Cory and D.M.T. Chan, *ibid.*, 4441 (1975).

3) a) C.M. Cimarusti and J. Wolinsky, *J. Am. Chem. Soc.*, **90**, 113 (1968). b) J. Wolinsky and R.B. Login, *J. Org. Chem.*, **35**, 1986, 3205 (1970). c) S. Geribaldi, G. Torri, and M. Azzaro, *Comptes Rendus (C)*, **274**, 2121 (1972).

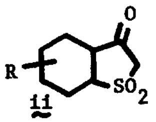
4) Presented, in part, at the 31st Meeting of the Northwest Region of the American Chemical Society, Reno, Nevada, June 14-15, 1976, Abstract G-93.

5) For an account of the preparation of compounds of type **5**, see: a) C. Girard and J.M. Conia, *Tetrahedron Lett.*, 3327 (1974); reference 6b.

6) For the use of substituted trimethylsilyloxy butadienes in 4+2 cycloaddition reactions, see: a) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974). b) M. Jung and C.M. McCombs, *Tetrahedron Lett.*, 2935 (1976). c) C. Symmes, Jr. and L.D. Quinn, *J. Org. Chem.*, **41**, 238 (1976). d) We have utilized the 4+2 reaction for the preparation of synthetic intermediates of type **i** and **ii**, ; Reference 4.



i ;



ii

7) The preparation of **5f** finds close analogy in the kinetic as well as thermodynamic preparation of **5a**; see: references 5 and 6b.

8) For a concise bibliography on the uses of trimethylsilyl enol ethers in synthesis, see: R.M. Coates, L.O. Sandefur, and R.D. Smillie, *J. Am. Chem. Soc.*, **97**, 1619 (1975).

9) See Table I, footnote a).

10) The temperature needed for debridging varies in the examples shown. For instance, the conversion of **5e** into **10e** will also occur in benzene. Toluene provides a solvent which is generally useful. The temperature required for the reaction seems to be somewhat lower than those normally used for the Alder-Rickert reaction (i.e., about 200°C); see: 1) Reference 3b. 2) K. Alder and H.F. Rickert, *Justus Liebigs Ann. Chem.*, **524**, 180 (1936). This point is now being studied in these laboratories.

11) D. Peltier, *Bull. Soc. Sci. Bretagne*, **31**, 7 (1956).

12) For examples of regioselectivity with substituted butadienes, see: a) Reference 1a, pp. 214-217; and the references cited therein. b) H.O. House, W.F. Gannon, R.S. Ro, and D.J. Wluka, *J. Am. Chem. Soc.*, **82**, 1463 (1960). c) Reference 6a. d) The high degree of regiospecificity noted in the **5c** into **12** transformation seems to be a general phenomenon in the cycloaddition reactions of **5**; see reference 6b.