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METHODOLOGIES FOR 2-ALKYLIDENE-1,3-CYCLOPENTANEDIONES

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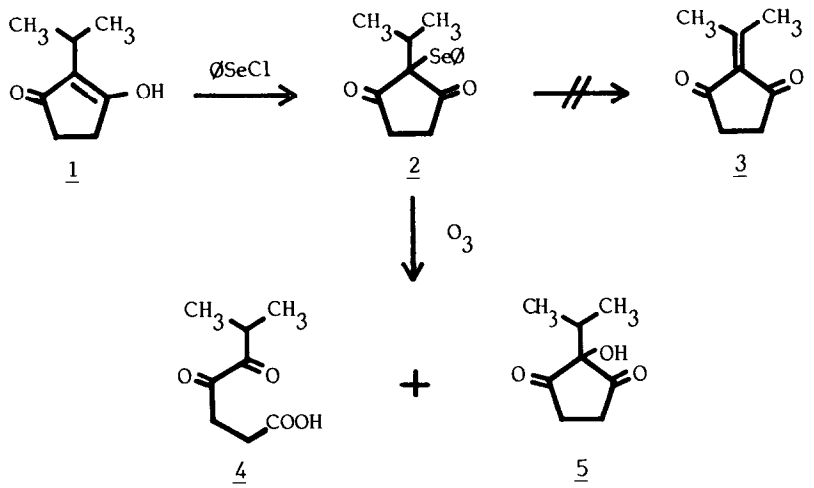
Abstract: Methods for the synthesis of 2-alkylidene-1,3-cyclopentanediones are given along with some preliminary information on the reactivity of these ene-diones.

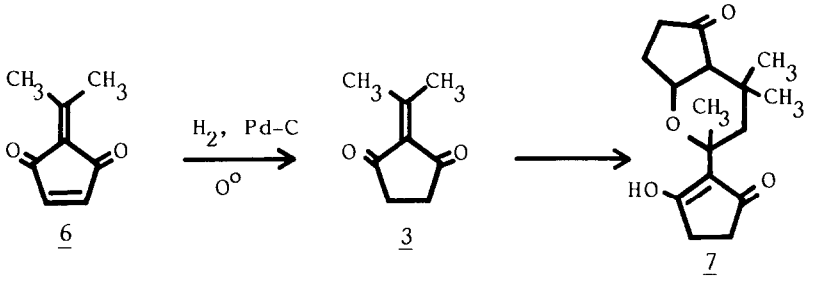
Simple 2-alkylidene-1,3-cyclopentanediones are little known. Singular examples in which the exocyclic double bond is stabilized by heteroatom substitution or by conjugation with aromatic or extended systems have been mentioned;[1] simpler "stripped down" derivatives of this ene-dione system are exceedingly rare.[2] We describe here an easy and probably general procedure for the preparation of these elusive compounds from readily available 2-alkyl-1,3-cyclopentanediones.

We first examined the utility of selenenylation/oxidation chemistry[3] as applied to 2-isopropyl-1,3-cyclopentanedione (1).[4] Treatment of a pyridine solution of 1 with phenylselenenylchloride gave an excellent yield of 2. That selenenylation had occurred on carbon, and not on oxygen, was confirmed by the nine-line CMR spectrum of the product, consistent in number, position, and multiplicity with the assigned structure, but not with its O-selenenylated isomer.[5] Oxidation of 2 with ozone at -70°C, followed by warming to room temperature, gave none of the expected elimination product 3. Instead, a mixture of deselenenylated material 1, ring-cleaved acid 4, and diketo alcohol 5 was obtained in a 3:6:2 ratio.



1 2 3 4 5

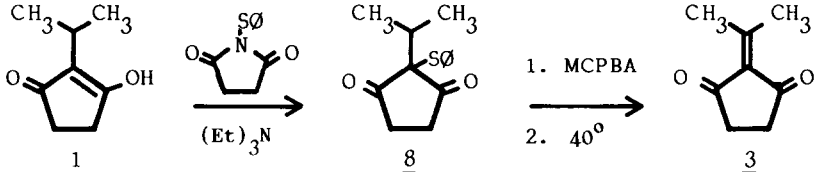
Worried by this result and the not unlikely possibility that compounds such as 3 might be exceptionally labile, we looked at their preparation by way of partial hydrogenation of the related diene-diones, sometimes available by oxidation of the corresponding fulvenes.[6] Indeed, catalytic hydrogenation of 6 over 10% palladium-on-carbon was quite rapid, but could be controlled (methylene chloride/0°C) to give selective reduction of the disubstituted double bond. The PMR spectrum of the crude product consisted of singlets at 2.64 and 2.54 ppm with an intensity ratio of 4:6, completely consistent with structure 3. This material was unstable, and within a few hours in the solid state converted entirely to a dimer, mp 200-202°C (dec), formulated as 7 in accord with its spectroscopic properties. Formally, 7 is the Diels-Alder adduct of the heterodiene system of one molecule of 3 with the terminal olefin of the dienol form of a second.



6 3 7

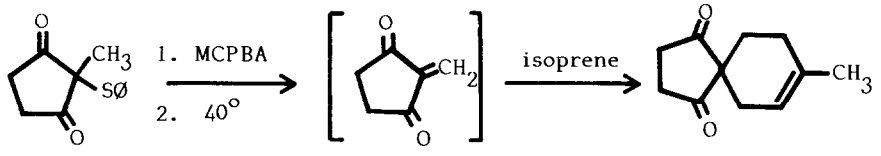
With the knowledge that 2-alkylidene-1,3-cyclopentanediones can be handled and characterized (albeit requiring some speed), we returned to the problem of their preparation from more available precursors. The anomalous chemistry of selenide 2 appeared due to homolytic lability of the carbon-selenium bond. As carbon-sulfur bonds are stronger than those to selenium, it seemed the analogous sulfur compounds could be exploited with more success; thus, substitution of sulfoxide for selenoxide might allow the normal pericyclic elimination[7] to compete successfully with homolytic bond cleavage.

The required phenyl sulfide 8 was prepared (97% yield) by treatment of 1 with N-phenylthiosuccinimide (NPTS) in triethylamine and benzene.[8,9] Oxidation of 8 with m-chloroperoxybenzoic acid, followed by warming to 40°C, effected elimination of phenyl sulfenic acid and provided cleanly ene-dione 3 (which then dimerized as before). Thus, for the first time, the conversion of a 2-alkyl-1,3-cyclopentanedione to its 2-alkylidene relative was accomplished.



1 8 3

Peracid oxidation of 9, prepared in good yield similarly from 2-methyl-1,3-cyclopentanedione, presumably led after elimination to 2-methylene-1,3-cyclopentanedione (10), but this simplest member of the series could not be isolated. It is apparently very reactive and in this case was trapped by Michael addition of the cognate phenyl sulfenic acid. Proof that 10 was formed free was obtained by carrying out the oxidation at 40°C in the presence of isoprene. The ene-dione 10 was then trapped as the spirocyclic Diels-Alder adduct 11 in 70% yield. The very mild conditions of this Diels-Alder reaction are notable, as is the fact that such additions allow easy entry into the spiro[4.5]decane sesquiterpene ring systems of a number of natural products.[10]



9 10 11

Application of this methodology to the preparation of peristylane derivatives, the impetus for this work, followed these model studies. Phenylsulfenylation of 12 with NPTS gave 13, which on oxidative elimination provided the ene-tetraone 14 [$\lambda_{max}^{CH_2Cl_2}$ 286(ε=12,200), 319 (8,700), 415 nm(225)]. This material, protected by the bulk of the peristylane system, is completely stable to dimerization. Still, the reactivity of the alkylidene-cyclopentanedione moiety is high enough to be exploited usefully. Thus, Diels-Alder addition of 2,3-dimethylbutadiene at 130°C provided 15, an attractive dodecahedrane precursor of stereochemically correct specification.[12]

A higher degree of synthetic convergence was sought. To this end, 2-(phenylthio)-1,3-cyclopentanedione 16 (mp 191-192°C) was prepared in 90% yield by phenylsulfenylation of 1,3-cyclopentanedione with one equivalent of NPTS. Reaction of 16 with 4-acetoxyperistylane-2,6-dione 17 and $(Et)_3N$ gave sulfide 13 in 81% yield in a single step. By this route, after oxidative elimination, ene-tetraone 14 was obtained from peristylane 17 in just two synthetic steps in 68% overall yield.

The sulfenylation/oxidation strategy outlined appears to provide a general route to 2-alkylidene-1,3-cyclopentanediones. The chemistry of this heretofore rare system is promising. As alkylation of 16 allows introduction of the group's synthon into complex molecules easily, its potential can now be fully explored.

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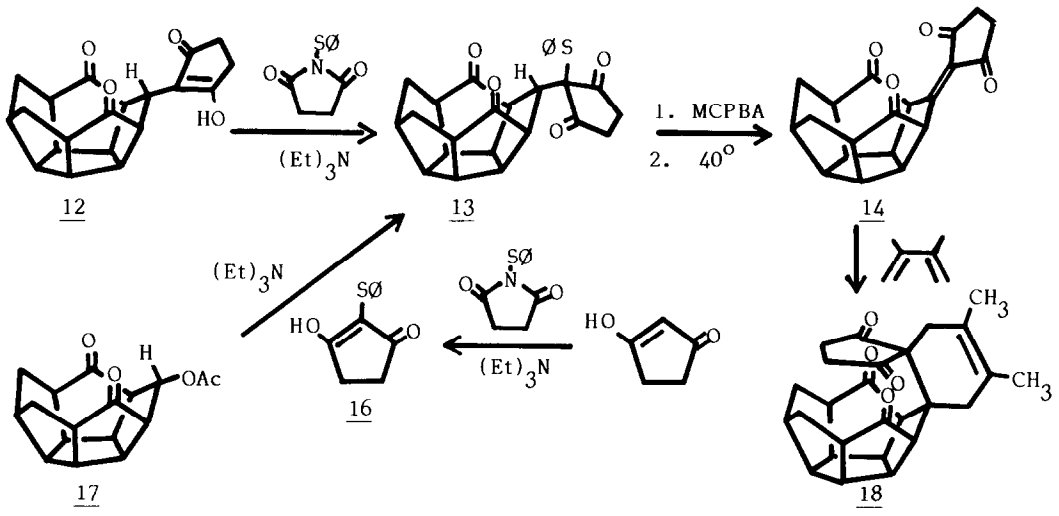

REFERENCES

1. a) N. Acton, A. Brossi, D.L. Newton, and M.J. Sporn, J. Med. Chem., 23, 805 (1980); b) T. Tsujikawa, Y. Nakagawa, K. Tsukamura, and K. Masuda, Chem. Pharm. Bull., 25, 2775 (1977).

2. We are aware of only one reported example: M.L. Bolte, W.D. Crow, and S. Yoshida, Aust. J. Chem., 35, 1411 (1982).

3. H.J. Reich, J.M. Renga, and I.L. Reich, J. Am. Chem. Soc., 97, 5434 (1975).

4. K. Hiroga, Chem. Pharm. Bull., 13, 1359 (1967).

5. A similar procedure for the selenenylation of 1,3-dicarbonyl compounds has been independently developed by Liotta and coworkers: D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer, and H.S. Kezar, III, J. Org. Chem., 46, 2920 (1981).

6. W. Skorianetz, K.H. Schulte-Elte, and G. Ohloff, Helv. Chim. Acta, 54, 1913 (1971).

7. B.M. Trost, T.N. Salzmann, and K. Hiroi, J. Am. Chem. Soc., 98, 4887 (1976).

8. M. Beforouz and J.E. Kerwood, J. Org. Chem., 34, 51 (1969).

9. T. Kumamoto, S. Kobayashi, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 45, 866 (1972).

10. For a review, see: J.A. Marshall, S.F. Brady, and N.H. Anderson, Fortschr. Chem. Org. Naturs., 31, 283 (1974).

11. P.E. Eaton, R.H. Mueller, G.R. Carson, D.A. Cullison, G.F. Cooper, T-C. Chou, and E-P. Krebs, J. Am. Chem. Soc., 99, 2751 (1977). P.E. Eaton, G.D. Andrews, E-P. Krebs, and A. Kunai, J. Org. Chem., 44, 2824 (1979).

12. P.E. Eaton, Tetrahedron, 35, 2189 (1979).

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