Tetrahedron Letters No. 8, pp 529 - 532, 1975. Pergamon Press. Printed in Great Britain.

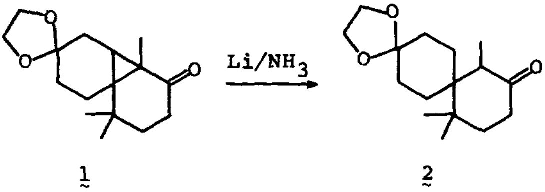
SYNTHESIS OF SPIRO LACTONES AND KETONES VIA CONJUGATE ADDITION TO CYCLOPROPYL MALONATES AND β-KETO ESTERS

Robin D. Clark and Clayton H. Heathcock*

Department of Chemistry, University of California
Berkeley, California 94720

(Received in USA 8 November 1974; received in UK for publication 14 January 1975)

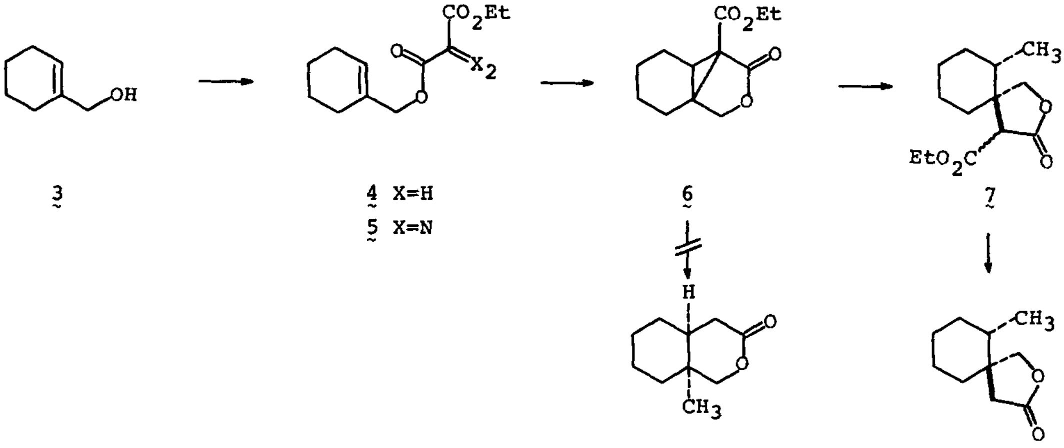
The reductive opening of cyclopropyl ketones with lithium in ammonia has been studied in detail and shown to be controlled primarily by stereoelectronic factors.[1] For example, White recently reported the opening of the cyclopropyl ketone 1 to the spiro[5.5]2-undecanone 2.[2] While exploring routes to angularly substituted δ-lactones (e.g., 9[3]), we studied the reaction of cyclopropyl lactone 6 with lithium dimethylcopper and observed a similar opening of the cyclopropyl ring to give the spiro lactone 7.[4]



Cyclopropyl lactone 6 was prepared as described in Scheme I.[5] Hydroxymethylcyclohexene 3 was converted to malonate ester 4 (ethyl malonyl chloride, ether-pyridine, 90%), which gave the diazomalonate 5 with tosyl azide in acetonitrile[6] (room temp, 12 hr, 100%). Thermolysis of 5 in refluxing toluene with cuprous iodide-trimethyl phosphite complex (20 mol per cent) for 3 hr afforded in 72% yield cyclopropyl malonate 6: bp 135°, 0.8 mm; ir (neat) 1780, 1735 cm^{-1} Reaction of 6 with 1.5 equivalents of lithium dimethylcopper at -30° with warming to 0° gave the isomeric spiro lactones 7 (90%). Hydrolysis and decarboxylation of 7 gave lactone 8 as the only product: bp 115°, 1 mm; ir 1782 cm^{-1};

pmr (CCl_4) δ 0.86 (3H, doublet, J=7 cps), 2.23 (2H, singlet), 4.00 (2H, AB quartet, J=10).[7] None of the other possible lactone **9**[3] could be detected by pmr or glc analysis.

Scheme I



3

4 X=H

5 X=N

6

7

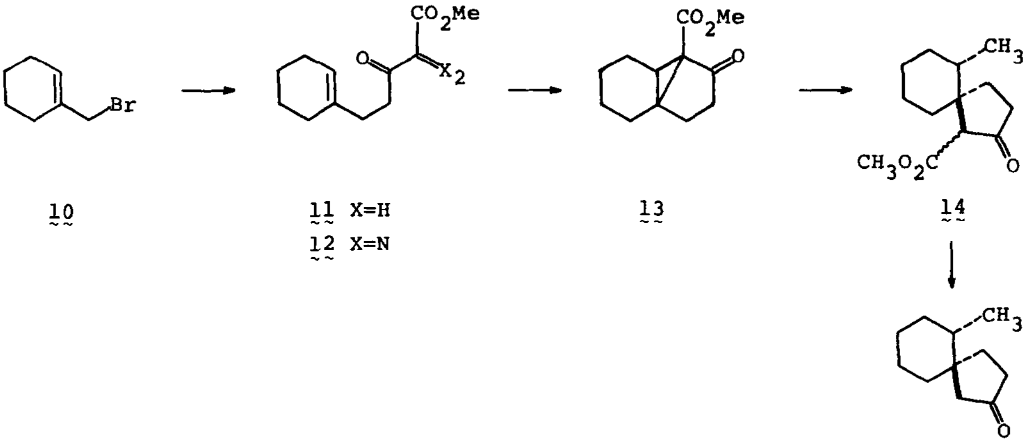
9

8

We have also prepared the spiro ketone **15** by a similar route (Scheme II). Alkylation of the dianion of methyl acetoacetate[8] with bromide **10** gave the β-keto ester **11** in 70% yield (bp 110-115°, 0.8 mm). Conversion to the diazo ester and thermolysis as before gave the cyclopropyl keto ester **13**: 70%, bp 120°, 0.8 mm; ir 1740, 1720 cm^{-1}. Reaction with $LiMe_2Cu$ followed by hydrolysis and decarboxylation gave the spiro ketone **15**: bp 100°, 1.5 mm; ir 1745 cm^{-1}; pmr δ 0.86 (3H, doublet, J=7 cps), 2.06 (2H, singlet).[9]

As in the opening of cyclopropyl ketone **1**,[2] an examination of models of **6** and **13** clearly shows that the observed bond scission involves the bond which overlaps well with the carbonyl π system. The other mode involves a bond which is orthogonal to the π system and is therefore not observed.

Scheme II



10

11 X=H
12 X=N

13

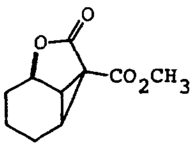
14

15

Acknowledgement: This work was supported by a grant from the National Institutes of Health, CA 12617.

References

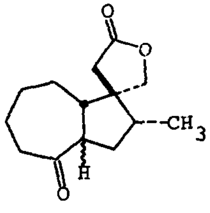
1. W.G. Dauben and E.J. Deviny, J. Org. Chem., 31, 3794 (1966); W.G. Dauben and and R.E. Wolf, ibid., 35, 374, 2361 (1970).
2. J.D. White, S. Torii and J. Nogami, Tetrahedron Lett., 2879 (1974).
3. R.D. Clark and C.H. Heathcock, ibid., 1713 (1974).
4. For another example of conjugate addition to a cyclopropyl malonate see E.J. Corey and D.L. Fuchs, J. Amer. Chem. Soc., 94, 4014 (1972). For addition to a cyclopropyl vinyl malonate see P.A. Grieco and R. Finkelhor, J. Org. Chem., 38, 2100 (1973).
5. The ester 16 has been prepared under conditions analogous to those reported here (reference 4 and F.E. Ziegler, A.F. Marino, O.A.C. Petroff, and W.L. Studt, Tetrahedron Lett., 2035 (1974)).



16

6. M. Regitz, Angew. Chem. Int. Ed. Eng., **6**, 733 (1967); B.W. Peace and D.S. Wulfman, Synthesis, 137 (1973).

7. This type of spiro lactone has recently been employed in several intermediates (e.g., **17**) in a synthetic approach to portulal by T. Tokoroyama, K. Matsuo, R. Kanazawa, H. Kotsuki, and T. Kubota, Tetrahedron Lett., 3093 (1974).

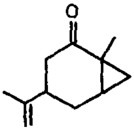


17

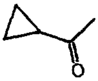
8. L. Weiler, J. Amer. Chem. Soc., **92**, 6702 (1970).

9. Conjugate addition to cyclopropyl enones has been reported, J.A. Marshall and R.A. Ruden, Tetrahedron Lett., 2875 (1971). As reported Marshall and Ruden, cyclopropyl ketones do not undergo the reaction. For example, ketones **18**[10] and **19** are recovered unchanged upon treatment with LiMe$_2$Cu at room temp for 16 hr.

9. Conjugate addition to cyclopropyl enones has been reported, see G.H. Posner Organic Reactions, **19** and references therein. Cyclopropyl ketones apparently do not undergo this reaction. We have found that ketones **18**[10] and **19** are recovered unchanged upon treatment with LiMe$_2$Cu at room temp for 16 hr.



18



19

10. E.J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., **87**, 1353 (1965).