

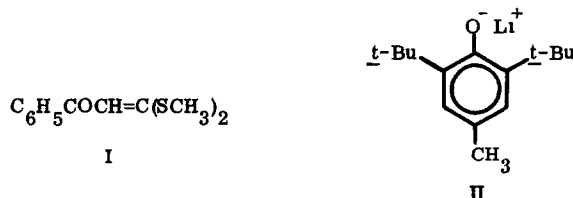
α -DITHIOMETHYLENE KETONES GENERATION AND APPLICATION TO SYNTHESIS

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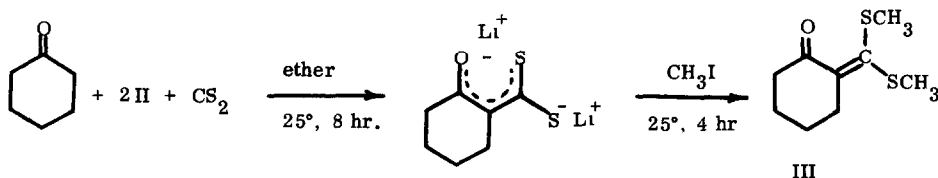
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In 1910 the α -dithiomethylene derivative I was reported to result in low yield upon treatment of acetophenone with powdered potassium hydroxide and carbon disulfide followed by methylation with methyl iodide.¹ Ketonic derivatives such as I have not found use in synthesis in the intervening period despite their



not inconsiderable potential. In connection with other projects currently under investigation in this Laboratory, we embarked upon the study of the formation and use of these α -dithiomethylene ketones.

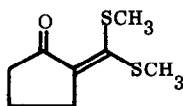
The lithium salt of 4-methyl-2,6-di-*t*-butylphenol (II), which is readily obtained in ethereal solution by treatment of the phenol with 1 equiv. of *n*-butyllithium, reacts only very slowly with carbon disulfide relative to the rate of proton abstraction from typical ketones. Thus it is not surprising that treatment of cyclohexanone with 2 equiv. of II and 5 equiv. of carbon disulfide results in dithiocarboxylation.² Reaction of the intermediate so formed with methyl iodide (2.3 equiv.) produces the dithiomethylene ketone III in 86% yield. This experiment clearly shows that α -dithiomethylene derivatives of a variety of ketones are



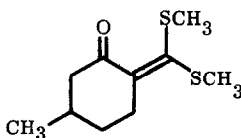
potentially available by a simple one-step process. In addition, the conversion of cyclohexanone to III also illustrates a useful principle—activation of a neutral substrate for anionic reaction with an electrophile by a sterically shielded base which cannot attack the electrophile, but which can deprotonate the substrate.²

The following experiment provides details of a typical preparation of III. Slow addition of 4 ml. of 2 *M* *n*-butyllithium in hexane to 1.8 g. (8.1 mmol.) of 4-methyl-2,6-di-*t*-butylphenol in 50 ml. of ether (<0°) produced a colorless precipitate of II which dissolved upon warming to 25°. To this reagent 1.4 g. (20 mmol.) of carbon disulfide and 0.38 g. (3.8 mmol.) of cyclohexanone were added. The mixture was stirred for 12 hr. at 25°, and then 1.42 g. (10 mmol.) of methyl iodide was added. After 4.5 hr. the mixture was diluted with water, and the phases were separated. The mixture of III and 4-methyl-2,6-di-*t*-butylphenol obtained after drying and concentration of the organic layer were separated chromatographically on silica gel (40 g.). The phenol was eluted by petroleum ether, and III (0.61 g., 86%)³ was eluted by petroleum ether--ether (1:1) and obtained as a yellow liquid.

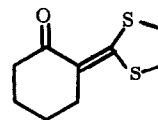
By procedures analogous to that above for the preparation of III, cyclopentanone and acetophenone were converted smoothly to the yellow α -dithiomethylene derivatives IV and I, respectively. 3-Methylcyclohexanone yielded V as the major product.⁴ Further, cyclohexanone was transformed into the



IV



V



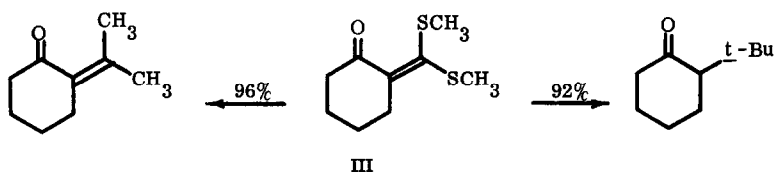
VI

crystalline yellow bicyclic derivative VI, m. p. 101-103°, when 1,2-dibromoethane rather than methyl iodide was used in the above described experiment.

A number of practical uses of α -dithiomethylene ketones can be envisaged. Perhaps the most obvious applications are (1) the protection of ketonic α -methylene or methyl groups in a fashion analogous to α -monothiomethylene derivatives⁵ and (2) their function as protected precursors of an α -placed carboxyl function. A matter of more immediate interest to us, however, was the possibility that the α -dithiomethylene group could provide access to units such as A and B which occur in a number of important natural products.^{6,7} Studies to date have led to the realization of this possibility.

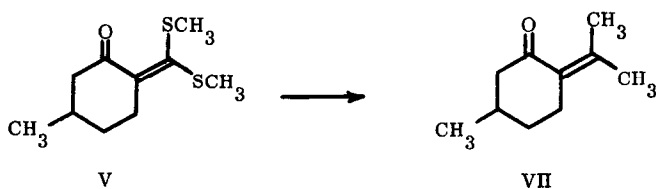


Reaction of III in ether at -78° with either 2 or 3 equiv. of dimethylcopperlithium for 20 min. followed by quenching with methanol and extractive isolation gave 2-isopropylidene cyclohexanone in 96% yield.⁸



When III was treated with 3 equiv. of dimethylcopperlithium at 0° for 1 hr., 2-t-butylcyclohexanone could be isolated in 92% yield. Similarly, IV was converted into 2-t-butylcyclopentanone in 90% yield.

Reaction of V with 2 equiv. of dimethylcopperlithium at -78° produced pulegone (VII) in 95% yield.



In our view, the two-step process from ketones via α -dithiomethylene derivatives represents the method of choice for the introduction of sec-alkylidene or t-alkyl groups alpha to a keto function.⁹ The development of a number of other highly useful processes involving α -dithiomethylene ketones can be expected.¹⁰

References

1. C. Kelber, Chem. Ber , 43, 1252 (1910). See also, W O Foye, J Chem. Ed ,46, 841 (1969)
2. The base II also reacts only slowly with carbon dioxide, a fact which makes possible efficient carboxylation of substrates such as cycloalkanones, methyl or α -methylene ketones, sulfones, and terminal acetylenes [E. J. Corey and R. H. K. Chen, J. Org. Chem. , in press].
3. Satisfactory IR, NMR and mass spectral data were obtained for all new compounds.
4. The product of dithiomethylenation at the alternative methylene group was also formed as a minor product (ca. 15% yield), separation from V was easily effected chromatographically.
5. See R. E. Ireland and J A. Marshall, J Org. Chem. , 27, 1615 (1962)
6. Examples of well-known naturally occurring substances having the unit A include ar-tumerone, germacrone, β -elemenone, and fukunone.
7. The intriguing terpenoids from Ginkgo species, ginkgolide and bilobalide, are t-butyl-substituted cyclopentanes [See K Nakanishi et al. , J. Amer. Chem. Soc. , 93, 3544 (1971)]
8. For other examples of conjugate addition-elimination of β -substituted enones, see (a) R M. Coates and R. L. Sauerby, J. Amer Chem. Soc. , 93, 1027 (1971), and (b) C. P. Casey, D. F Marten, and R. A. Boggs, Tetrahedron Lett. , 2071 (1973)
9. In the past a general method for the introduction of t-alkyl groups onto a cycloalkane ring has been lacking. However, mention should be made of a recent finding that α, α' -dibromocyclohexanone reacts with t-butoxy-t-butylcopperlithium to afford 2-t-butylcyclohexanone (66% yield) [See G. H. Posner and J. J Sterling, J. Amer. Chem. Soc. , 95, 3076 (1973)]. This method is clearly limited to symmetrical ketones.
10. This work was assisted financially by the National Science Foundation.