One of the most interesting classes of compounds included in Table I are the hydroxy acids which proved extremely effective in accelerating the oxidation of isopropyl alcohol. Aldehydo acids, keto acids, and diglycolic acid (containing an ether function) show less impressive but still quite substantial rate accelerations.

Another very high rate acceleration was observed for picolinic acid. The change in the value in the last column indicates that the reaction probably follows a different rate law than observed previously for oxalic acid.[3] Glycine affects the rate of the oxidation of isopropyl alcohol only to a very small extent.

Detailed investigations of several of the reactions reported in this communication are in progress.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS AT
CHICAGO CIRCLE
CHICAGO, ILLINOIS 60680

FARIZA HASAN
JAN ROČEK*

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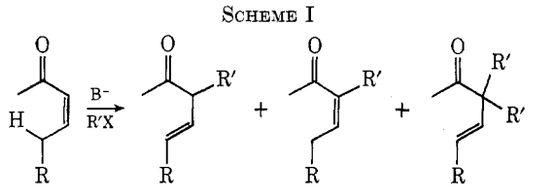
Regioselective Methylations of 2-Thioalkoxyenones

Summary: Methylation (methyl iodide) of the kinetic enolate generated from 2-thio-*n*-propyl-5,5-dimethyl-2-cyclohexen-1-one and lithium hexamethyldisilazide in tetrahydrofuran takes place at C_6, whereas methylation of the potassium enolate in *tert*-butyl alcohol occurs at C_2.

Sir: Alkylation of an α,β-unsaturated ketone having γ-hydrogen atoms under enolate equilibrating conditions usually results in formation of an α-alkyl-β,γ-unsaturated ketone (Scheme I). A major problem,

SCHEME I

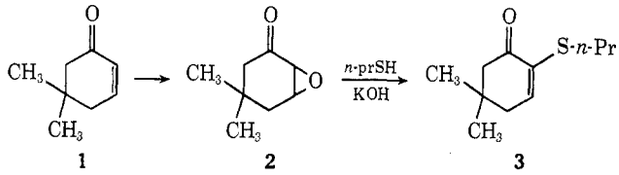


however, is that this initial product may be isomerized to an α-alkyl-α,β-unsaturated ketone or may undergo further alkylation.[1] This problem could not arise during alkylation of 2-thioalkoxyenones, in which the enone α-hydrogen atom is replaced by a potentially removable thioalkoxy group (*e.g.*, **3**).

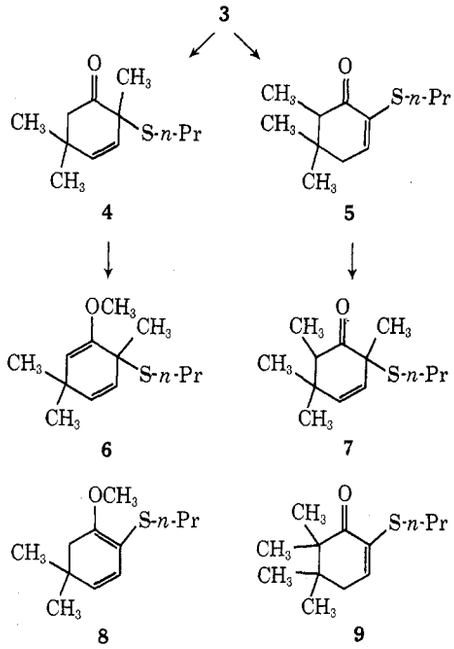
We wish to report some preliminary alkylation studies of thioalkoxyenones, here represented by 2-thio-*n*-propyl-5,5-dimethyl-2-cyclohexen-1-one (**3**). By simply varying the reaction conditions, we have been able to effect nearly quantitative carbon alkylation at either the 2 position in **3** to give enone **4** or at the 6 position to give enone **5** (Scheme III).

Cyclic 2-thioalkoxyenones may be efficiently prepared from the corresponding enone *via* an epoxy ketone.[2] In the present case (Scheme II), potassium

SCHEME II



SCHEME III



hydroxide catalyzed reaction of epoxide **2**[3] with *n*-propyl mercaptan in ethanol gave 2-thioalkoxycyclohexenone **3** in 94% isolated yield [bp 94–96° (~0.3 Torr), *m/e* 198].

Methylation of the potassium enolate of **3** generated by addition of **3** (10 g) to a solution of 1.1 equiv of potassium *tert*-butoxide in dry *tert*-butyl alcohol followed by addition of 2 equiv of methyl iodide gave predominately the 2-alkylated enone **4** (95%), some dialkylated enone **7** (4%), and a trace of enol ether **6** (Scheme III).[4] Enone **4** [80% isolated yield, bp 90° (~0.4 Torr), *m/e* 212] displayed olefinic proton resonance centered at δ 5.43 and 5.72 (J_{AB} = 10 Hz) and ir absorption at 5.87 μ (film).

It is noteworthy that oxygen alkylation of **3** to give **8** did not occur under these conditions. Indeed, even when the potassium enolate[5] of **3** was methylated in tetrahydrofuran (THF) solution (conditions known to facilitate oxygen alkylation), no oxygen alkylation of **3** could be detected. Under these conditions, **4** (75% yield), **5** (14%), **6** (6%), and recovered **3** (3%) were obtained. This result is to be contrasted with methylation of the potassium enolate of ketone **4** in THF–hexamethylphosphoramide (HMPA) solution to give predominately oxygen-alkylated **6** (90%), along with **7** (10%).

(1) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9.

(2) M. A. Tobias, J. G. Strong, and R. P. Napier, *J. Org. Chem.*, **35**, 1709 (1970).

(3) R. L. Wasson and H. O. House, *Org. Syn.*, **37**, 58 (1957).

(4) An F & M Model 700 gas chromatograph fitted with a thermal conductivity detector and a 6 ft × 1/8 in. stainless steel column filled with 10% UC-W98 on Chromosorb W, 80–100 mesh size, at 170° was used.

(5) Generated by addition of **3** to a suspension of potassium hydride in THF. This base–solvent combination has been used to generate ketone enolates in their equilibrium ratios: C. A. Brown, private communication; C. A. Brown, *J. Amer. Chem. Soc.*, **95**, 982 (1973).

Lithium secondary amide bases have been used to generate kinetic enolates from α,β-unsaturated ketones[6] and 3-alkoxycyclohexenones.[7] However, we have found that lithium hexamethyldisilazide (LHDS) is clearly superior to diisopropylamide or isopropylcyclohexylamide in methylation studies with 2-thioalkoxyenones.[8]

The following procedure is typical. A solution of **3** (10 g) in THF was added over 15 min at −78° to 1.1 equiv of LHDS (generated *in situ* from hexamethyldisilazane and *n*-butyllithium at ice bath temperature) in THF. HMPA (1.5 equiv), followed by methyl iodide (2 equiv), was added and the resulting solution was allowed to warm to room temperature and, after 1.2 hr, water was added. Analysis[4] revealed that 2-thio-*n*-propyl-5,5,6-trimethyl-2-cyclohexen-1-one (**5**, 92% yield) and enone **4** (0.3%), along with dialkylated compounds **9** (2.7%) and **7** (1.6%), as well as recovered **3** (4.1%), were present. Thioalkoxyenone **5** [88% isolated yield, bp 120° (~0.3 Torr), *m/e* 212] displayed olefinic proton resonance centered at δ 6.58 (J = 4.5 Hz) and ir absorption at 5.96 μ (film).

The ratio of α' to α alkylation using LHDS is vitally dependent upon the order in which HMPA and **3** are added to the base. Using conditions identical with those already described (in which **5** and **4** formed in a ratio of 300:1); except that HMPA was added to LHDS before **3**, resulted in a ratio **5**:**4** of 6:1. These results suggest that the basic properties of LHDS are modified in the presence of HMPA. Recently, a lithium diisopropylamide–HMPA complex has been reported to exhibit markedly reduced nucleophilicity when compared to lithium diisopropylamide alone.[9]

Construction of a wide variety of 2,6-dialkylated cyclohexenone derivatives should be possible by consecutive alkylation of 2-thioalkoxyenones. For example, methylation of enone **5** (methyl iodide, potassium *tert*-butoxide in *tert*-butyl alcohol) gave dialkylated enone **7** [88% yield, bp 100° (~0.3 Torr), *m/e* 226].

Acknowledgment.—This work was supported by an E. I. du Pont de Nemours and Co. Young Faculty Grant.

(6) R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973).
(7) G. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).
(8) Methylation studies with **3** and analogs using secondary amide bases under a variety of conditions always resulted in recovery of 15–30% thioalkoxyenone.
(9) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).

DEPARTMENT OF CHEMISTRY
CORNELL UNIVERSITY
ITHACA, NEW YORK 14850

ARTHUR G. SCHULTZ*
DAVID S. KASHDAN

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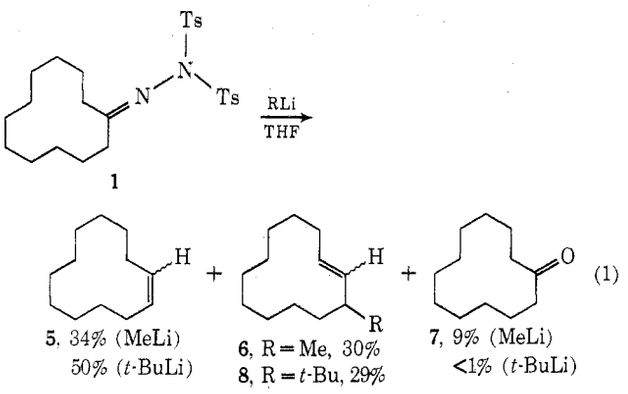
N,N-Ditosylhydrazones. Synthesis and Some Unique Reactions with Alkyllithium Reagents

Summary: Several *N,N*-ditosylhydrazones have been synthesized and converted into either 3-alkyl olefins or simple alkylated hydrocarbons by reaction with methyl- and *tert*-butyllithium.

Sir: The reactions of tosylhydrazones with alkyllithium reagents and other bases are well known, providing useful synthetic routes from ketones to a variety of compounds including olefins, allenes, acetylenes, diazo compounds, and carbenes.[1] This paper describes the preparation of several members of a new class of compounds, the *N,N*-ditosylhydrazones, and the reaction of representative members with methyl- and *tert*-butyllithium. While yields have not been optimized in any of the experiments described below, we consider the transformations sufficiently novel to report them at this time.[2]

Using Baumgarten's[3] procedure for the preparation of *N,N*-ditosylamines, a dry DMF solution of cyclododecanone monotosylhydrazone, mp 154–156°, prepared by the method of Bamford and Stevens,[4] was treated at 25° (N_2) with 1.2 equiv of sodium hydride followed by 1.0 equiv of toluenesulfonyl chloride. After water work-up cyclododecanone *N,N*-ditosylhydrazone (**1**), mp 152–153°, was obtained in 49% yield. The *N,N*-ditosylhydrazones listed in Table I were similarly prepared.

Reaction of ditosylhydrazone **1** with 2.5 equiv of methyllithium (2.0 *M* in hexane) in THF at 0° (N_2) followed by a water quench and ether extraction led to the mixture of products shown in eq 1 which was separated by preparative vpc.



(1)

The products were identified by direct comparison with authentic samples. Cyclododecene[5,6] (**5**) was prepared by reaction[1] of cyclododecanone monotosylhydrazone with methyllithium. Authentic 3-methylcyclododecene[5,7] (**6**) was prepared by treating 2-methylcyclododecanone monotosylhydrazone[7] with methyllithium.

The formation of 3-methylcyclododecene (**6**) in this reaction was quite unexpected, suggesting that the reaction of ditosylhydrazones with other alkyllithium reagents might constitute a new 3-alkyl olefin synthesis. We were particularly intrigued by the use of *tert*-butyllithium since few examples of the direct introduction of a *tert*-butyl group into a molecule are known.[8]

(1) See, *inter alia*, L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley-Interscience, New York, N.Y., Vol. 2, 1969, pp 417–423, and Vol. 3, 1972, p 293; A. M. Foster and W. C. Agosta, *J. Org. Chem.*, **37**, 61 (1972).
(2) See paragraph at end of paper regarding supplementary material.
(3) P. J. DeChristopher, J. P. Adamek, G. D. Lyon, J. J. Galante, H. E. Haffner, R. J. Boggio, and R. J. Baumgarten, *J. Amer. Chem. Soc.*, **91**, 2384 (1969).
(4) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).
(5) A mixture of cis and trans isomers.
(6) V. Prelog and M. Speck, *Helv. Chim. Acta.*, **38**, 1786 (1955).
(7) J. Casanova and B. Waegell, *Bull. Soc. Chim. Fr.*, 1289 (1971).
(8) See, for example, G. H. Posner and J. J. Sterling, *J. Amer. Chem. Soc.*, **95**, 3076 (1973).