Tetrahedron Letters No. 45, pp 3955 - 3958, 1974. Pergamon Press. Printed in Great Britain.

ALKYLATION AND REDUCTION-ALKYLATION OF α-PHENYLTHIO KETONES AND ALDEHYDES

Robert M. Coates (1a), H. Dale Pigott, and Janet Ollinger (1b)

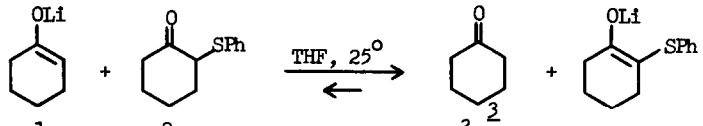
Department of Chemistry, University of Illinois, Urbana, Illinois 61801

(Received in USA 27 June 1974; received in UK for publication 1 October 1974)

At present there exist relatively few synthetic procedures for effecting regiospecific geminal dialkylation at a methylene group adjacent to a carbonyl function (2), a transformation type which is useful in the formation of quaternary carbon centers. We wish to report that α-phenylthio ketones and aldehydes, now available by direct enolate sulfenylation (3), may be alkylated at carbon bearing sulfur and further that the sulfide function of the alkylated phenylthio ketones may be regiospecifically replaced by an alkyl substituent through reduction-alkylation (4,5).

While it is abundantly clear that the alkyl- or arylthio group enhances both the kinetic and thermodynamic acidity of the proton on carbon bearing sulfur of sulfides (6), the extent of such acidification in β-ketosulfides or related compounds has not, to our knowledge, been determined. We have therefore measured the position of equilibrium established between the lithium enolate of cyclohexanone (generated by methyllithium cleavage of the trimethylsilyl enol ether) (7) and 2-phenylthio cyclohexanone (2) by trapping with trimethylsilyl chloride (7) and subsequent glc and nmr analysis. That the rate of silylation exceeds the rate of enolate equilibration was demonstrated by quantitative silylation of 1 upon inverse addition to a mixture of trimethylsilyl chloride and 2 at 25°.

Since log K is identical to the ratio of the pKa's of 2 and 3 (under the conditions of this experiment), the phenylthio group increases the acidity of cyclohexanone by at least 3 pK units (8).



1 2 3

$K \geq 2.3 \pm 0.1 \times 10^3$

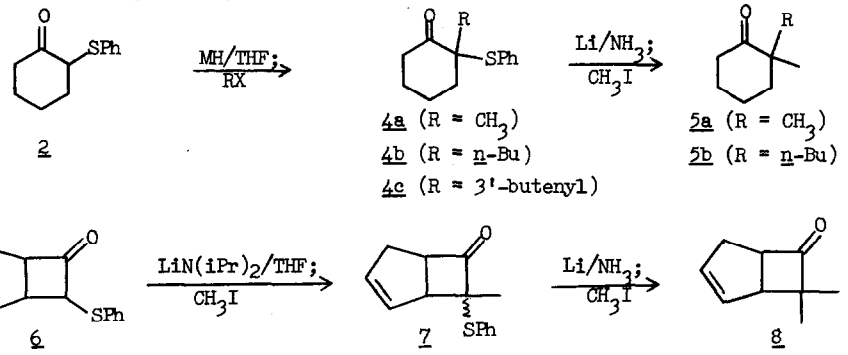
For preparative purposes the enolate anions of α-phenylthio ketones 2, 6, and 9 (9) were generated by reaction with sodium or potassium hydride (10)or lithium di-isopropyl amide in tetrahydrofuran, and subsequently allowed to react with the chosen alkyl halide (Table 1) (11). Although alkylation at carbon bearing sulfur generally occurs in excellent yield, the one

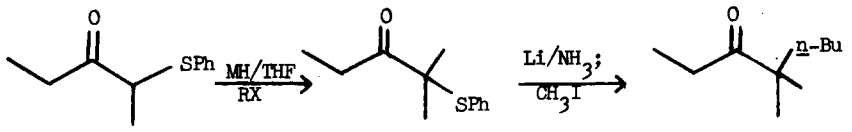
Table 1. Alkylation-Reduction-Alkylation of α-Phenylthio Ketones

Entry	α-Phenylthio Ketone	Metallation/Alkylation Conditions[a]	Product[b]	Reduction/Alkylation Conditions	Product[b]
1.	2	NaH/THF, 80°, 2 hr; 2 eq. CH_3I, 0°, 2 hr.	4a (93%)	10 eq. $Li/NH_3/Et_2O$, -33°; 15 eq. CH_3I, -33°, 30 min.	5a (69%)
2.	2	KH/THF, 25°, 5 min.; 1.6 eq. n-BuI, 25°, 24 hr	4b (91%)	as above	5b (84%)
3.	2	KH/THF; 1.1 eq. 4-bromo-1-butene, as above	4c (15%)		
4.	2	$C_6H_{11}NH_2$/PhH, molec. sieves, Δ; $LiN(iPr)_2$/THF, 25°, 10 min; 2.1 eq. 4-bromo-1-butene, 25°, 48 hr; 10% HCl, 1.3 hr	4c (38%)		
5.	6	$LiN(iPr)_2$/THF, 80°, 15 min; 3 eq. CH_3I, 25°, 2 hr	7 (76%)[c]	as above	8 (79%)
6.	9	NaH/THF, 25°, 5 min; 2 eq. n-BuI, 25°, 24 hr	10a (93%)	7 eq. $Li/NH_3/Et_2O$, -78°; 2.5 eq. CH_3I/THF, 25°, 15 hr[d]	11 (79%)
7.	9	NaH/THF, 25°, 5 min; 1.25 eq. allyl-Br, 0°, 1 hr	10b (84%)		

Footnotes: (a) Reaction time and/or temperature not necessarily minimal or optimal. (b) Products generally purified by column chromatography on silica gel. (c) 2:1 mixture of epimers. (d) Excess Li destroyed by titration with iPrI; NH_3 and ether removed prior to alkylation.

homoallylic halide tried (4-bromo-1-butene) gave a poor yield (17%), presumably owing to competing elimination. A substantial improvement (38%) was realized in this case by use of the metallo-enamine procedure (12). The alkylated α-phenylthio ketones 4a, 4b, 7 and 10a underwent reductive cleavage with lithium in liquid ammonia to the corresponding enolate which was in turn methylated by addition of methyl iodide.

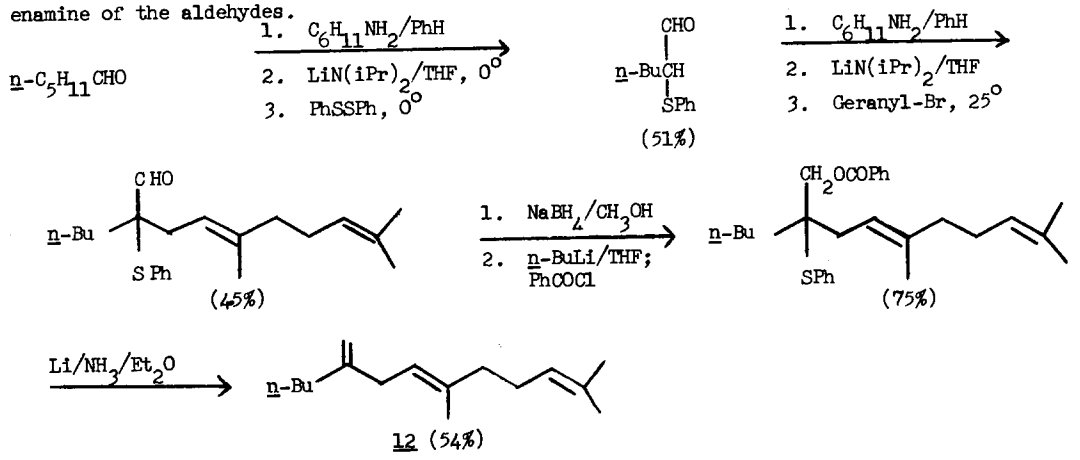




9 10a (R = n-Bu) 11
10b (R = Allyl)

Although the specific ketones (5a, 5b, 8, and 11) prepared in this work could, in principle, be synthesized by known methods for regiospecific geminal dialkylation, the approach presented here enhances the scope of this transformation. Thus, any two alkyl groups (within the usual constraints of enolate alkylation) may be introduced and in either order. The latter adds the capability of stereochemical control with sterically biased substrates.

The reaction sequence of electrophilic α-alkylation of α-phenylthio carbonyl compounds, hydride reduction of (or nucleophilic addition to) the carbonyl group, and finally reductive elimination of the vicinal hydroxy sulfide (13) should, in principle, provide a regiospecific olefin synthesis. To illustrate this method, which bears a conceptual resemblance to the Conforth olefin synthesis (14), we have prepared the triene 12 from n-hexaldehyde. This reaction scheme could serve as a prototype for a total synthesis of moenocinol, the C-25 lipid alcohol isolated from the hydrolysate from the antibiotics moenomycin and prasinomycin (15). In this case, sulfenylation and alkylation were carried out with the lithio cyclohexylenamine of the aldehydes.



Acknowledgment--We wish to thank the National Science Foundation and the National Institutes of Health for financial assistance. The high resolution mass spectrometer employed in this research was provided by NIH grants CA 11388 and GM 16864 from the National Cancer Institute and the National Institute of General Medical Sciences, respectively.

References

1. (a) A. P. Sloan Foundation Fellow 1971-1973; author to whom inquiries should be sent; (b) National Institutes of Health Trainee 1971-1973.

2. Some known methods include (a) the combination of regiospecific aldol condensation to an α,β-unsaturated ketone with reduction-alkylation - cf. H. O. House et al.; J. Amer. Chem. Soc., 95, 3310 (1973); Stork et al., ibid., 87, 275 (1965); (b) reduction-alkylation of α-n-butylthiomethylene ketones - R. M. Coates and R. L. Sowerby, ibid., 93, 1027 (1971); (c) alkyl transfer from trialkyl boranes to α-diasoketones or α,β-unsaturated ketones - D. J. Pasto and P. W. Wojtkowski, J. Org. Chem., 36, 1790 (1971); J. Hooz, and J. N. Bridson, J. Amer. Chem. Soc., 95, 602 (1973).

3. (a) B. Trost and T. N. Salzmann, ibid., 95, 6840 (1973); (b) D. Seebach and M. Teschner, Tetrahedron Lett., 5113 (1973).

4. Alkylation and reduction-alkylation of t-butylthio acetone, acetate, and acetonitrile has recently been reported by S. Kamata, S. Uyeo, N. Haga, and W. Nagata, Syn. Commun., 3, 265 (1973).

5. Isolated examples of alkylation of mono-alkylthio enolates have appeared in the recent literature: (a) A. G. Schultz and D. S. Kashdan, J. Org. Chem., 38, 3814 (1973); (b) P.A. Grieco and J. J. Reap, Tetrahedron Lett., 1097 (1974); (c) R. F. Romanet and R. H. Schlessinger, J. Amer. Chem. Soc., 96, 3701 (1974); (d) Reference 3a.

6. D. Seebach, Angew Chem. Intern. Ed., 8, 639 (1969).

7. (a) G. Stork and P. F. Hudrlik, J. Amer. Chem. Soc., 90, 4462, 4464 (1968); (b) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, J. Org. Chem., 34, 2324 (1969).

8. We cannot exclude the possibility that a slight degree of re-equilibration occurs during silylation, i.e., increasing the proportion of 1-OTMS and 2 actually isolated. To the extent that such re-equilibration has occurred, the true equilibrium constant K would be greater than 2.3×10^3.

9. Prepared by reaction of 2-chlorocyclohexanone, 7-chlorobicyclo[3.2.0]hept-2-en-6-one (W. T. Brady and E. F. Hoff, Jr., J. Amer. Chem. Soc., 90, 6256 (1968)) and 2-bromo-3-pentanone respectively, with sodium thiophenoxide in ether.

10. C. A. Brown, J. Org. Chem., 39, 1324 (1974).

11. The elemental composition of all new compounds (by either microanalyses or high resolution mass spectrometry was consistent with theoretical values. All compound gave appropriate ir and nmr spectra.

12. G. Stork and J. Benaim, J. Amer. Chem. Soc., 93, 5938 (1971).

13. R. M. Coates and R. L. Sowerby, J. Amer. Chem. Soc., 94, 5386 (1973).

14. J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, J. Chem. Soc., 112, 2539 (1959).

15. (a) R. Tschesche, F. X. Brock, and I. Duphorn, Tetrahedron Lett., 2905 (1968); Ann. Chem., 720, 58 (1968); (b) W. A. Slusarchyk and F. L. Weisenborn, Tetrahedron Lett., 659 (1969).