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γ-ALKYLATION OF α'-(PHENYLSULFONYL)-α,β-UNSATURATED KETONES:

THE TRIANION IMPERATIVE

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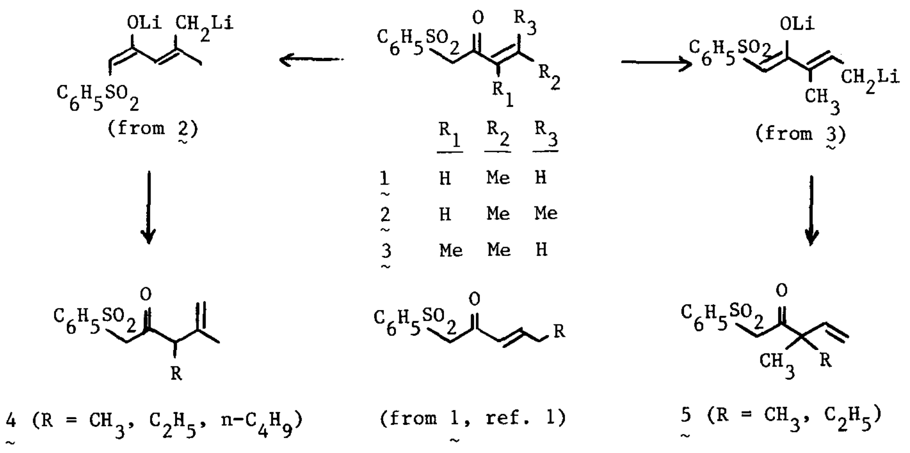
Abstract: γ-alkylation of the title compounds with primary alkyl iodides is possible only when both α'-protons are first ionized with excess lithium diisoproylamide.

We have reported[1] that β-ketosulfone 1 undergoes three-fold ionization (α',α',γ) and that monoalkylation of the resulting trianion with several primary alkyl iodides occurs predominantly at the γ-position.[2] Upon extending this investigation to β-ketosulfones 2 and 3[3] (Scheme I) we find that comparable trianion formation, following the initial first α'-deprotonation, does not occur (using up to 5 eqs. of LDA). The second deprotonation of 2 occurs at the syn-γ-methyl group[4] ("proximity control"[5]) and the resulting α',γ-dianion undergoes α-alkylation[6] (including CH_3I), corresponding to the results of Cooke[7a] and van der Gen[7b] with similar α',γ-dianions. β-Ketosulfone 3, with the sterically demanding α-methyl group, presumably first forms the Z-enolate (initial E-enolates are expected[8] from 1 and 2), in which case the second α'-hydrogen is trans to the enolate lithium-oxygen bond and thus inaccessible for proximity-controlled ionization.[5] Instead, only a γ-proton is removed and alkylation again takes place at C_α.[6] A typical procedure[1] follows:

Scheme I



	R_1	R_2	R_3
1	H	Me	H
2	H	Me	Me
3	Me	Me	H

4 (R = CH_3, C_2H_5, n-C_4H_9)

(from 1, ref. 1)

5 (R = CH_3, C_2H_5)

Seventy-five mg (0.315 mmole) of 2 dissolved in 1 ml of tetrahydrofuran (THF) was slowly added, under argon, to 0.63 mmol of freshly-prepared LDA in 4 ml THF-hexane at -78°. After 1 h, n-C_4H_9I (61 mg; 0.33 mmol) was added; warming to 25° (1.5 h) was followed by quenching into 10% HCl, then standard workup. Silica gel chromatography afforded 89 mg (96%) of 4 (R=n-Bu) as an oil (R_f = 0.82, 1:1 hexane-ether): IR (neat) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) AB quartet at δ 4.23 (2H, J_{AB} = 14 Hz); 4.9, 5.0 (s, $>=CH_2$); Anal. ($C_{16}H_{22}SO_3$) C, H. Using 5 eqs. of LDA gave identical results. Substituting n-butyl bromide, ethyl bromide and methyl iodide as alkylating agents gave ca. 50-90% yields of 4 (R=n-Bu, ethyl, methyl).

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References and Footnotes

1. P. T. Lansbury, G. E. Bebernitz, S. C. Maynard and C. J. Spagnuolo, *Tetrahedron Lett.*, 26, 169 (1985).

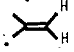
2. In contrast, methyl iodide reacts only at the doubly-ionized α'-position of the trianion, while other iodides are too hindered to alkylate there.

3. Keto-sulfone 2, mp 101-2°, was prepared (86% yield) from $C_6H_5SO_2CHLi_2$ and methyl senecoiate (cf. J. D. White *et al*, J. Am. Chem. Soc., 105, 6517 (1983)): $IR_{(CHCl_3)}$ 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9-7.4 (m, 5H), 6.25 (s, 1H), 4.15 (s, 2H), 2.1 (s, 3H), 1.9 (s, 3H); Anal. ($C_{12}H_{14}SO_3$) C, H.

   Keto-sulfone 3, mp. 73-4°, was prepared (75% overall) by adding $C_6H_5SO_2CH_2Li$ to tiglic aldehyde and oxidizing the crude carbinol with MnO_2 in methylene chloride: IR (CCl_4) 1675 cm^{-1}; ^1H NMR: Υ 7.9-7.4 (m, 5H), 6.80 (q, J=7 Hz, 1H), 4.42 (s, 2H), 1.89 (d, J=7, 3 H), 1.74 (s, 3H); Anal. ($C_{12}H_{14}SO_3$) C, H.

4. a) F. L. Harris and L. Weiler, *Tetrahedron Lett.*, 25, 1333 (1984).
   b) M. Majewski, J. R. Dreen and V. Snieckus, *ibid.*, 27, 531 (1986).

5. P. Beak, J. H. Hunter and Y. M. Jun, *J. Am. Chem. Soc.*, 105, 6350 (1983).

6. α-alkylation products from 2 and 3 were characterized[1] mainly by IR (deconjugated carbonyl stretch at ca. 1715 cm^{-1}) and ^1H NMR: diastereotopic α'-CH_2 protons as AB quartets centered at ca. δ 4.2 (J_{AB} ~ 14 Hz) and terminal  in 4 (δ 4.8-5.0, broad "singlets") or vinyl groups in 5 (ABX patterns at δ 5.0-5.9).

7. a) M. Cooke and R. Goswami, *J. Am. Chem. Soc.*, 99, 642 (1977).
   b) J. A. M. van den Goorbergh and A. van der Gen, Rec. Trav. Chim., 102, 393 (1983).

8. a) A. S. Narula, *Tetrahedron Lett.*, 22, 4119 (1981).
   b) R. E. Ireland, R. H. Mueller and A. K. Williard, *J. Am. Chem. Soc.*, 98, 2868 (1976).

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