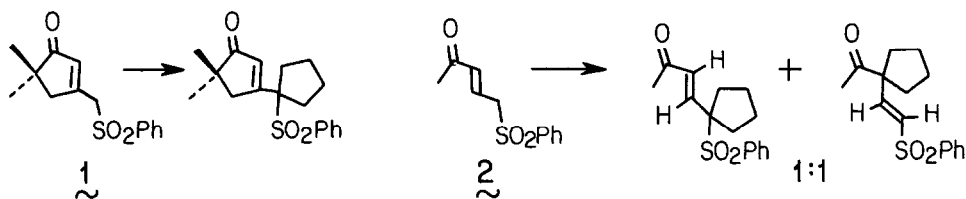


γ -ALKYLATION OF α,β -UNSATURATED KETONES: α' -PHENYLSULFONYL GROUPS AS
REGIOSELECTIVE CONTROL ELEMENTS

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Abstract: The α' -phenylsulfonyl derivative of E-3-penten-2-one (3) undergoes predominant γ -alkylation with a variety of alkyl iodides when first converted into a trilithiated intermediate with excess lithium diisopropylamide in tetrahydrofuran-hexane.

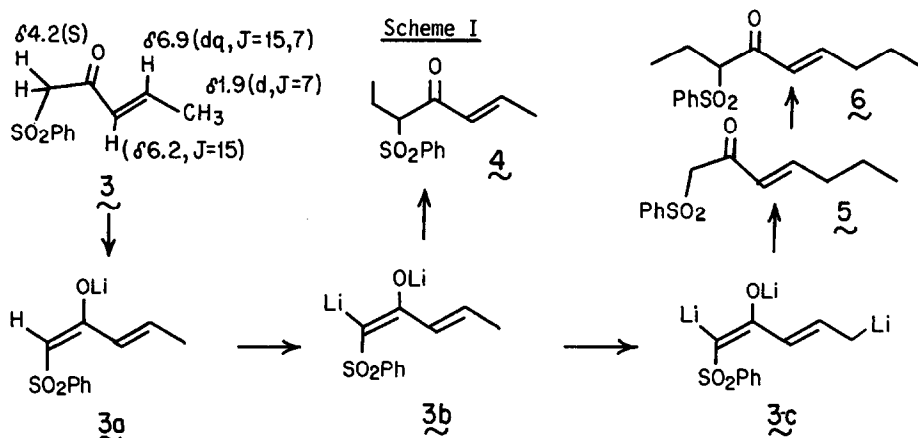
The thermodynamic dienolates of α,β -unsaturated aldehydes and ketones undergo intermolecular alkylation mainly at the α -position, even when steric hindrance is present.¹ Some time ago, we reported an approach for directing such alkylations to the γ -position.² This entailed temporary placement of a phenylsulfonyl substituent at C_{γ} of α,β -unsaturated ketones, which led to "cross-bred" allyl anions that gave varying degrees of γ -regioselectivity depending on substrate and alkyl halide structure.^{1,2} Useful γ/α ratios for most alkyl halides other than methyl iodide were found only in substrates where steric hindrance at C_{α} compensated for the counter-productive bulk of the γ -sulfone substituent. Similar results were obtained in step-wise annulations of monoanions from enone-sulfones 1 and 2 with α,ω -dihalides, using sodium hydride in N,N-dimethylformamide,³ e.g.



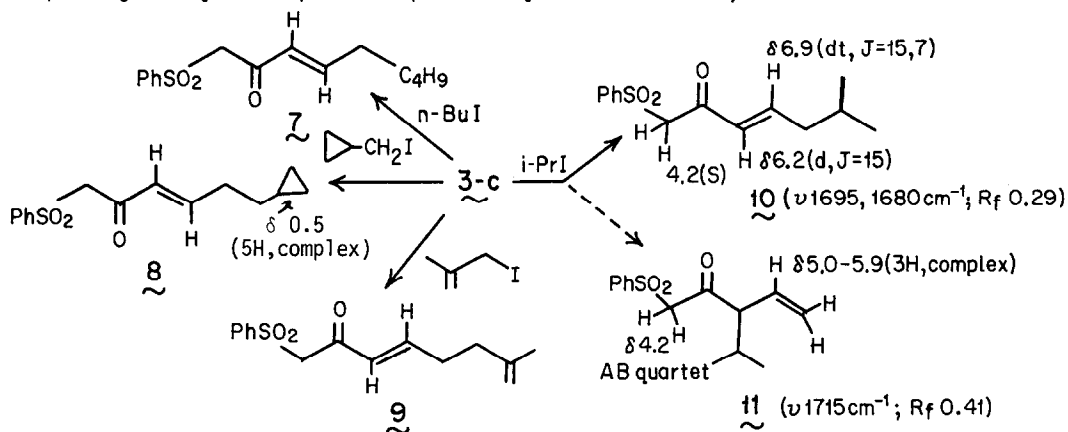
Excellent yields of γ,γ -annulation products (three- to six-membered rings) were obtained with 1, in part due to the gem-dimethyl steric effect near the α -position.³ As before,¹ γ -selectivity fell off sharply when the α - and γ -positions of dienolate nucleophile are sterically more equivalent (as in 2). Clearly, a different strategy for γ -selective alkylation of α,β -unsaturated ketones was needed, in particular one which would not increase steric hindrance at C_{γ} while modifying substrate behavior.

α,β -Unsaturated carboxylic acids⁴ and secondary amides⁵ undergo γ -alkylation via their dianions and one can anticipate that similar polyionized species could also be generated

from α' -phenylsulfonyl enones. Accordingly, we assembled^{6a} the keto-sulfone **3**, derivable from E-3-penten-2-one, and carried out stepwise ionizations with LDA, followed by ethyl iodide (15 min, 0°). Scheme I summarizes the results.

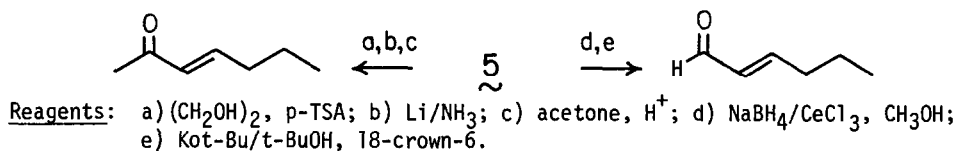


The substantial acidity of β -ketosulfones⁷ assures that enolate **3a** is first generated, presumably as the E-isomer.⁸ Additional ionization of **3a** was possible a priori at either C _{α'} ⁹ or C _{γ} ¹⁰. When **3** was treated with ca. 2.5 eq of LDA, followed by C₂H₅I (0°/15 min) only **4** was isolated, showing that the α',α' -dianion **3b** had been produced in kinetic preference^{9a,11} to α',γ . Most significantly, when **3** was exposed to 4-5 eqs of LDA (yellow→burgundy red solution), followed by 2 eqs of C₂H₅I, γ -ethylated products **5** and **6** (the latter from further alkylation of the α',α' -dianion of **5**) were isolated^{6b} in high yield (42% and 30%, respectively). Thus trianion **3c** can be generated and monoalkylated regioselectively, especially without surplus alkylating agent (see experimental procedure). With this encouraging development, a variety of other alkyl iodides (1-1.5 eqs) were reacted with **3c**, giving comparable results. Compounds **7-9** were formed in $\geq 5:1$ excess over the corresponding α -alkylation products (combined yields ca. 40-65%).



Such product mixtures were separated chromatographically (on silica gel with 1:1 hexane-ethyl acetate or ether), with the γ -alkylation products eluting after the α -isomers. Compounds 5-10 uniformly displayed split conjugated carbonyl bands in their IR spectra at ~ 1695 - 1675 cm^{-1} (for s-cis and s-trans conformers), whereas the α -isomers showed unconjugated carbonyl bands at $\sim 1715\text{ cm}^{-1}$. Proton NMR spectra (illustrated in full for isomers 10 and 11) of γ -alkylation products were as expected for E-enones ($J_{\text{vinyl}} \sim 15\text{ Hz}$), with the β -vinyl proton appearing as a doublet of triplets ($J_{\beta,\gamma} \sim 7\text{ Hz}$), instead of overlapping quartets (in 3). With isopropyl iodide, the ratio of 10 to 11 was only 2:1. Surprisingly, when ethyl, n-butyl and cyclopropylcarbonyl bromides were reacted with 3c, the γ -alkylation products (6-8 above) were minor products and α -alkylation prevailed ($>4:1$). This remarkable leaving group effect on regioselectivity is not yet understood. The hypothesis that alkyl iodides react via a single electron transfer (SET) mechanism¹³ seems weakened by noting the retention of the cyclopropylcarbonyl residue in product 8 when 3c was alkylated with cyclopropylcarbonyl iodide. Ring opening of cyclopropylcarbonyl free radicals is a very facile process,^{14a} but geminate coupling might be even faster.^{14b}

Several exploratory sequences carried out with 5 show that such γ -alkylated products can be converted back to desulfonylated α,β -unsaturated ketones and aldehydes.^{15,16}



Thus, the overall process of γ -alkylation is formally completed.

We are attempting to optimize the γ -alkylation of 3 and related systems with alkyl iodides, and seeking information on scope,¹⁷ limitations and mechanism. These studies will be reported in due course.

A typical experimental procedure follows:

Fifty milligrams (0.223 mmols) of 3 in 1 ml THF was added to 1.12 mmol of freshly-prepared LDA in THF-hexane at -78° under N_2 . After 2 h ethyl iodide (0.02 mL, 0.245 mmol) was added at 0° and 15 min later the reaction mixture was quenched into 10% HCl , followed by standard workup. The crude, oily product (44 mg) was chromatographed over silica gel (eluting with hexane to 1:1 ether-hexane), affording 6 mg (13%) of γ,α' -diethylation product 6 (R_f 0.48), MS (CI) m/e 281 ($\text{M}^+ + 1$), and 19 mg (44%) of γ -ethylation product 5 (R_f 0.40), MS (CI) m/e 253 ($\text{M}^+ + 1$); IR (neat) $1695, 1680\text{ cm}^{-1}$; $^1\text{H NMR}$ (CDCl_3) δ 7.9-7.4 (5H), 6.9 (1H, dt, $J=15,7$), 6.2 (1H, d, $J=15$), 2.2 (2H, q, $J=7$), 1.6-0.8 (5 H). In addition, 12 mg of 3 was recovered.

Acknowledgment: We are grateful to the National Science Foundation (Grant 8026526) for support of this research.

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b) The same methods as in ref. 6a were used to prepare authentic **5** (oil), substituting methyl E-2-hexanoate for methyl crotonate and E-2-hexanal for crotonaldehyde. Dianion alkylation of **5** (see text) led to an authentic specimen for comparison with **6** prepared from trianion **3c** with excess ethyl iodide. The compounds from these routes were identical in all respects with those from **3c**.
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(Received in USA 15 October 1984)