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A GENERAL METHOD FOR γ-ALKYLATION OF α,β -UNSATURATED KETONES

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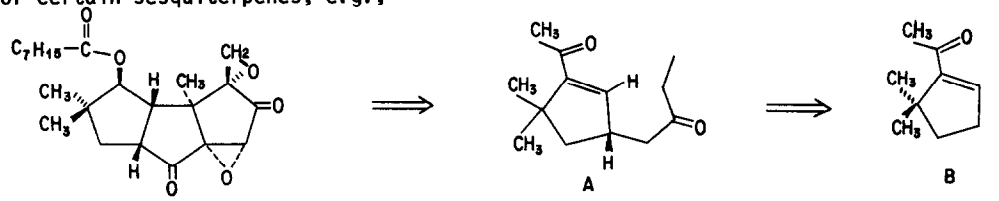
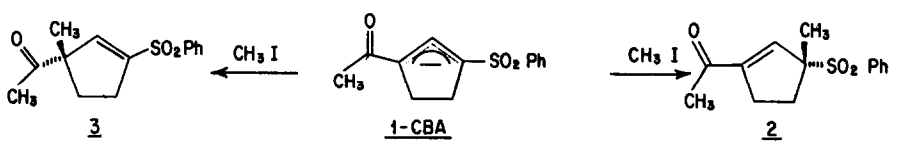
Kinetic and thermodynamic dienolates preparable from α,β-unsaturated ketones undergo α'- and α-alkylation, respectively[1]. Preferential intermolecular γ-alkylation has not been achieveable[2], although it is a sorely needed process. We have sought a general method for carrying out such γ-alkylations, especially to prepare 1-acetylcyclopentene synthons (i.e. A → B) for certain sesquiterpenes, e.g.,



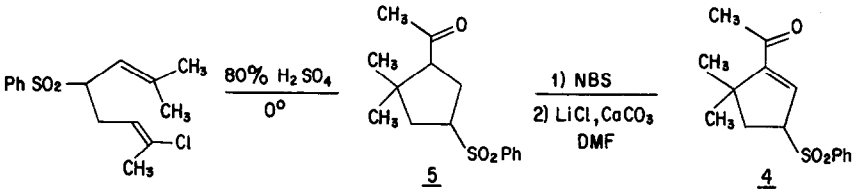
The temporary incorporation of an γ-arylsulfonyl substituent into the parent α,β-unsaturated ketones as a regiospecific control element during electrophilic alkylation and its subsequent removal comprises the essence of the approach reported herein.

Sulfonyl substituents were chosen for initial study[3] because of their proclivity to deconjugate from alkene groups during equilibration[4], in contrast with the conjugative tendencies of cyano and carbonyl-containing groups inter alia. We hypothesized that when dienolates and allyl sulfone anions (both α-alkylators by themselves) were cross-bred, the resulting "hybrid" anion (henceforth dubbed "CBA", for cross-bred anion) would alkylate more endothermically than the less conjugated progenitor anions. 1-Acetyl-3-phenylsulfonyl-cyclopentene (1) was selected for the first trial, since ionization would provide a symmetrically substituted CBA capable of undergoing only one alkylation. The Hammond postulate suggests that such endothermic reactions have "late", product-like transition states: hence 1-CBA might well prefer to alkylate at C_2 with developing enone (→ 2), rather than vinyl sulfone (→ 3), conjugation



3 1-CBA 2

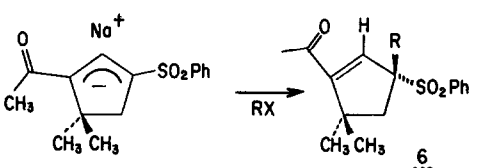
Insertion of the γ-sulfonyl group into an enone can be accomplished by N-bromosuccimide halogenation, followed by sodium benzenesulfinate (in DMF). Accordingly, 1[5], mp 110°, was readily synthesized from 1-acetylcyclopentene and methylated via the sodium salt (formed by NaH) in THF-HMPA at 0-25°. Nmr examination of the product mixture showed a 7:1 ratio of 2 to 3; the purified major isomer (2) was readily isolated in 62% yield, mp 101-3°, δ($CDCl_3$) 2.3 (3H,s), 6.4 (1H,m), ν_{film} 1674 cm^{-1} and λ_{max}^{EtOH} 242 nm (log ε 4). These are typical spectral features in all γ-alkylated derivatives of 1, 4 and 8, whereas α-alkylated compounds showed ir carbonyl bands at ca. 1700-1710 cm^{-1} and pertinent nmr signals at 2.1 (CH_3CO, 3H, s) and 6.8-7.0 ppm (β-vinylsulfone). With this demonstration of the desired regioselectivity[6] we began more extensive alkylation experiments for the coriolin synthon 4 (≡ A, above). This enone sulfone was prepared in ca. 50% overall yield by α-alkylation of phenyl prenyl sulfone with 1,3-dichloro-2-butene followed by chloroolefin annelation[7], leading to 5[5]. Ketone 5, obtained as a stereoisomeric mixture, was then brominated and HBr eliminated to generate the double bond required for CBA formation. Enone 4 did not equilibrate when treated with triethylamine; furthermore, quenching 4-CBA again resulted in 4, the apparent kinetic protonation



5 4

occurring at C_γ. Alkylation studies were undertaken with the sodium salt of 4 in THF-HMPA or DMF, usually at 0-25° for 3 hours, the predominant product (total yields were usually ≥ 85-90%) in every case being γ-alkyate. Product distributions and properties of purified γ-alkylation products are summarized in Table 1.

Table 1: Alkylation Products from 4-CBA



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RX	γ-R Product (6)	γ:α ratios† in THF-HMPA(3:1)	in DMF
CH_3I	a, mp. 117-8°	90:10	95:5
C_2H_5Br	b, mp. 129-130°	75:25	80:20
$CH_2{=}CHCH_2Br$	c, mp. 85- 86	80:20	85:15
$CH_3CH{=}CH{-}CH_2Br$	d, oil	80:20	----
$CH_2{=}CH(CH_2)_2Br$*	e, oil	----	80:20

(table 1 continued)

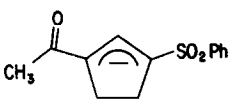
† Product ratios were estimated (to ca. ± 5%) by nmr integration of vinyl proton resonances (at 6.8-7.0 ppm (broad singlets) for α-alkylation products and at 6.3-6.5 ppm (sharp singlets) for γ-alkylation products).

* Ca. 50% starting material is recovered with this homoallylic halide, probably as a result of concomitant E_2 elimination.

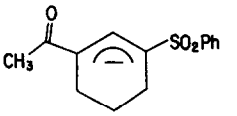
Removal of the phenylsulfonyl regiospecific control element, in order to complete the overall γ-alkylation sequence, has been accomplished in high yield with 6-a, using Zn/HOAc, Li/NH_3 or lithium dimethylcuprate[8], which invariably afforded the β,γ-unsaturated ketone[5] upon kinetic protonation and thence the conjugated isomer upon direct equilibration or otherwise[9].

At this point, further transformations of 6-c *inter alia* toward coriolin synthons (e.g. 8) were postponed in order to explore briefly the potential of this γ-alkylation strategy. A specific concern deals with what steric effect, if any, the gem-dimethyl grouping in 4 has on alkylation at the proximal α-position, compared with such steric hindrance at the more distant γ-position. Since 4 seems to be sterically biased[6] toward γ-alkylation (compared with the more symmetrical 1), other alkyl halides besides CH_3I were reacted with 1-CBA in DMF. A similar set of alkylation experiments were run with 1-acetyl-3-phenylsulfonylcyclohexene[5] (8), mp. 80-82°, prepared in the usual manner by NBS bromination of 1-acetylcyclohexene followed by benzenesulfinate displacement[10]. The γ/α ratios, determined by nmr are recorded in Table 2; overall yields of alkylation product were ≥ 90%.

TABLE 2: Alkylation Products* from 1- and 8-CBAs



1-CBA



1-CBA

RX	γ/α from 1	γ/α from 8
CH_3I	88:12 (in THF/HMPA)	72:28 (in THF/HMPA)
C_2H_5Br	57:43 (in DMF)	27:73 (in DMF)
$CH_2=CHCH_2Br$	68:32 (in DMF)	55:45 (in DMF)

* Product ratios were estimated (to ± 5%) by nmr integration of vinyl proton resonances. In products from 1, α-alkylate gave signals at 6.7-6.9 ppm and γ-alkylate gave signals at 6.3-6.5 ppm. The corresponding peaks in materials from 8 were at ca. 7.1 ppm (α-alkylate) and ca. 6.8 ppm (γ-alkylate). Total yields were ca. 90-95% based on virtual disappearance of the C_3-H signal at ca. 4.3 ppm in crude product.

These results show that the steric bulk of arylsulfonyl substituents can adversely interfere with their intrinsic γ-directive effect. Nevertheless the desired orientation of CBA's is being realized, especially when compensating steric effects operate near the carbonyl end of

the conjugated anion, as in 4. In contrast, unmodified dienolates, even when sterically hindered at C_α, invariably undergo α-alkylation[11,1b]. We are now studying ways to improve γ-selectivities by modifying the steric situation in CBAs derived from 1 and 8. The results of these studies, as well as progress toward coriolins, will be reported in the near future.

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References and Footnotes

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