Desulfurization/α-Alkylation of β-Keto Sulfones

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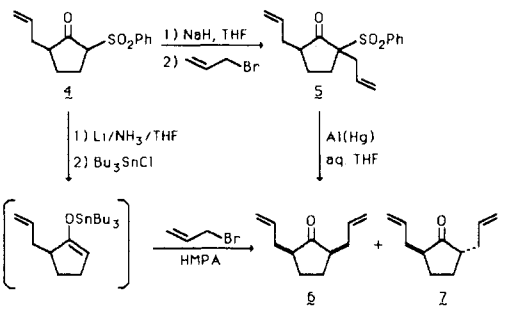
A one-pot procedure for the reductive alkylation of β-keto sulfones is described. The method proceeds by a lithium in liquid ammonia desulfurization of the starting β-keto sulfone, resulting in regiospecific generation of an intermediate enolate. Subsequent admixture of tributyltin chloride followed by addition of the alkylating agent in HMPA generates the C(α)-alkylated product in good yield and with excellent regiocontrol. Thus, 2-(phenylsulfonyl)-5-(2-propenyl)cyclopentanone gives 2,5-di(2-propenyl)cyclopentanone in 71% isolated yield with <1% of 2,2-di(2-propenyl)cyclopentanone detected in the crude reaction mixture. Experiments are presented which underscore the advantages of this procedure over traditional α-alkylation/desulfurization protocols.

The β-keto sulfone moiety is readily available from a variety of precursor functionalities[1] and displays a broad range of synthetic versatility.[2] One particularly well-recognized application[3] of the β-keto sulfone moiety in synthesis is in α-alkylation with subsequent reductive desulfurization. In this sequence, the sulfone group, which often plays a pivotal role in construction of the substrate to be alkylated (1)[1c,4] serves as a temporary activating group that secures regioselective α-alkylation of an unsymmetrical ketone. Enolate formation has been effected with a variety of bases, including sodium hydride,[5] lithium diisopropylamide,[6] sodium hydroxide,[7] and potassium amide.[8] Desulfurization is typically accomplished with aluminum amalgam in aqueous THF[9] (Figure 1).

However, the relative stability of the intermediate enolate and the significant steric requirements of the sulfone group[10] serve to limit the applicability of this two-step procedure. Typical difficulties include competitive O- vs. C-alkylation,[5-7] and due to the stability of the enolate, sensitive alkylating agents tend to decompose under the conditions required for alkylation. Prompted by these observations as well as a need in a total synthesis project to convert an unsymmetrical 3-[(4-methylphenyl)sulfonyl]octahydro-*as*-indacen-2(1*H*)-one to the corresponding α-alkylated octahydro-*as*-indacenone, a detailed study of the issues involved in the reductive alkylation of β-keto sulfones was undertaken. Herein the development of a one-pot desulfurization/α-alkylation protocol that proceeds with excellent regioselectivity is reported.

Scheme I



Results and Discussion

α-Alkylation/Desulfurization. Existing procedures for the reductive alkylation of β-keto sulfones proceed as two-pot operations: enolate formation/alkylation followed by desulfurization. Typically, the enolate of an α-substituted β-keto sulfone 1 ($R^2 \neq H$) reacts only sluggishly, even with allylic alkylating agents, requiring a polar solvent at elevated temperature (≥room temperature).[5] For example, allylation of β-keto sulfone **4** with allyl bromide required 3 h at 25 °C in THF and resulted in a 51% chromatographed yield of **5** (Scheme I). Subsequent desulfurization produced bisallylated cyclopentanones **6** and **7**[11] in a 3:2 ratio[12] in 41% overall yield from **4**. After studying a variety of β-keto sulfone/alkylating agent systems, it was found that the α-alkylation of cyclic β-keto sulfones requires 3–30 h at ≥25 °C and, after subsequent desulfurization, results in only modest yields of the α-alkylated cyclopentanone.

One-Pot Desulfurization/α-Alkylation. In order to improve on the overall yield for **1** → **3**, the possibility of a one-pot desulfurization/α-alkylation procedure was considered, reasoning that reductive desulfurization under aprotic conditions[13] would generate an intermediate enolate that could then be alkylated. Potential advantages of this protocol would include (i) streamlined logistics (one- vs. two-pot operation), (ii) avoidance of **2** (formation, isolation, and characterization), (iii) shorter reaction times

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(5) Trost, B. M.; Vincent, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5680–5683.

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(11) Onoue, H.; Moritani, I.; Murahashi, S.-I. *Tetrahedron Lett.* **1973**, 121–124.

(12) These stereoisomers proved readily separable by MPLC (see Experimental Section). Cis and trans stereochemical assignments were made by using tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) derivative in $CDCl_3$, where the *d,l*-trans isomer produces seven aliphatic multiplets in the presence of $Eu(hfc)_3$ and the meso-cis isomer produces only four aliphatic multiplets in the presence of $Eu(hfc)_3$.

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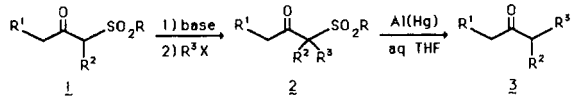
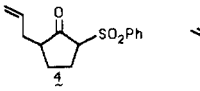
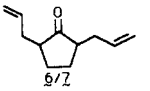
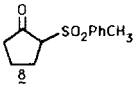
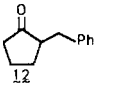
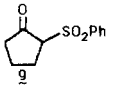
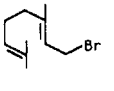
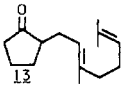
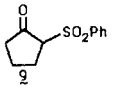
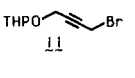
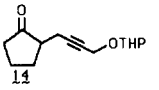
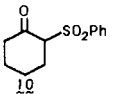
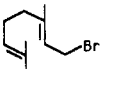
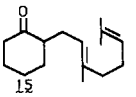


Figure 1.

Table I. Desulfurization/α-Alkylation of β-Keto Sulfones

entry	β-keto sulfone	alkylating agent	α-alkylated ketone	yield,[a] %
A				71
B		$PhCH_2Br$		59
C				64
D				83
E				52

[a] Yields refer to isolated, MPLC purified alkylation products.

for 1 → 3, and (iv) increased enolate reactivity. However, the first desulfurization/α-alkylation attempts were only moderately successful. For example, lithium in liquid ammonia reduction of 8 followed by one-pot admixture of benzyl bromide produced 2-benzylcyclopentanone[14] (12) in 36% isolated yield. A complex mixture of di- and tribenzylated cyclopentanones was also obtained (≈17% yield), indicating significant enolate equilibration under these alkylation conditions.

As previously noted by Tardella[15] and by Odic,[16] trialkylstannyl enolates offer significant advantage in the monoalkylation of ketones. In the present study, it was found that in the reductive alkylation of 8, addition of tributyltin chloride (1.5 equiv) to the intermediate lithio enolate prior to addition of benzyl bromide (1.5 equiv) in HMPA (2.6 equiv) resulted in a significant increase in the yield of 2-benzylcyclopentanone (36% → 59%). HPLC analysis indicated <1% of the di- and/or tribenzylated products in the crude reaction mixture. Thus, this operationally simple modification affords a vastly improved one-pot desulfurization/α-alkylation protocol that proceeds rapidly at low temperature (1 → 3 complete in 1.5 h at −78 to −50 °C). HMPA cosolvent is necessary to achieve this reactivity.[16] Inspection of Table I reveals the general applicability of this procedure for a variety of alkylating agents and cyclic β-keto sulfones.

Given the modest overall yield but complete regioselectivity of the two-pot α-alkylation/desulfurization of 4 → 6/7, the outcome of entry A was particularly pleasing (17:83 cis–trans). This result, which is outlined in Scheme I, not only demonstrates the improved efficiency of this desulfurization/α-alkylation procedure (71% vs. 41% for α-alkylation/desulfurization), but also provides evidence that the intermediate lithio and stannyl enolates are regiostable under the conditions of the reaction and do not equilibrate. That is, HPLC analysis revealed <1% of 2,2-di(2-propenyl)cyclopentanone in the crude reaction mixture.

In order to accurately contrast the relative efficiencies of α-alkylation/desulfurization vs. desulfurization/α-alkylation, 2-oxocyclopentyl phenyl sulfone[1a] (9) was subjected to both protocols. With propargylic bromide 11[17] as the alkylating agent, the sodio enolate of 9 required 30 h at room temperature for reaction completion (TLC) and resulted in a 61% isolated yield of the α-alkylated β-keto sulfone. Subsequent desulfurization with aluminum amalgam in aqueous THF produced cyclopentanone 14 in 56% overall yield from 9. In contrast, reductive alkylation of 9 with bromide 11 by the one-pot procedure was complete in 1.5 h and resulted in an 83% isolated yield of 14.

In conclusion, an operationally simple, one-pot desulfurization/α-alkylation procedure for the reductive alkylation of β-keto sulfones has been developed. The method provides regiocontrolled access to a variety of α-alkylated cycloalkanones in good yield. Application of this methodology in a synthesis of ikarugamycin[4] is currently under investigation.

Experimental Section

General. ^1H NMR spectra were taken on a Varian EM 390 spectrophotometer and are reported in ppm (δ units) downfield of internal tetramethylsilane. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Elemental analyses were performed by the University of California, Berkeley, analytical laboratories. MPLC refers to chromatography done at 10–50 psi through EM Lobar columns packed with LiChroprep Si60 (40–65 μm) with hexane/EtOAc eluent and monitored by refractive index detection. Chromatatron refers to preparative, centrifugally accelerated, radial, thin-layer chromatography with silica gel 60 PF as stationary phase and with hexane/EtOAc as eluent.

2-(Phenylsulfonyl)-5-(2-propenyl)cyclopentanone (4). A solution of 2-(hydroxymethylene)-5-(2-propenyl)cyclopentanone[18] (2.0 g, 13.1 mmol), $PhSSO_2Ph$ (3.28 g, 13.1 mmol), and potassium acetate (3.10 g, 31.6 mmol) in 50 mL of dioxane/water (1:1) was heated at 100 °C for 2 h. Upon cooling, the reaction mixture was extracted with ether (2×), and the combined organics were washed with 10% aqueous NaOH, water, and brine, dried (Na_2SO_4), and filtered. Concentration under reduced pressure yielded 2-(phenylthio)-5-(2-propenyl)cyclopentanone (2.98 g, 12.8 mmol, 98%) as a light yellow oil, which was used in the next step without further purification. An analytical sample of 2-(phenylthio)-5-(2-propenyl)cyclopentanone was purified by GLC (5% SE-30 on Chromasorb W at a column temperature of 200 °C): ^1H NMR (90 MHz, $CDCl_3$) δ 1.50–2.70 (m, 7 H), 3.35–3.70 (m, 1 H), 4.80–5.15 (m, 2 H), 5.70 (m, 1 H), 7.20–7.60 (m, 5 H); IR (CCl_4) 3090, 3020, 2990, 2950, 2890, 1735, 1635, 1585, 1475, 1440, 1150 cm^{-1}. Anal. Calcd for $C_{14}H_{16}SO$: C, 72.37; H, 6.94. Found: C, 72.32; H, 6.94.

To a solution of 2-(phenylthio)-5-(2-propenyl)cyclopentanone (1.90 g, 8.19 mmol) in methanol (40 mL) at 0 °C was added Oxone[1a] (7.54 g, 49.5% $KHSO_5$, 24.6 mmol) in water (40 mL). The resulting mixture was stirred at room temperature for 4 h, then diluted with water, and extracted with chloroform (2×). The combined organics were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by MPLC (1:1 hexane/EtOAc) gave 4 as a light yellow oil (1.96 g, 7.42 mmol, 90.6%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.30–2.80 (m, 7 H), 3.60–3.95 (m, 1 H), 4.85–5.15 (m, 2 H), 5.68 (m, 1 H), 7.40–7.95 (m, 5 H); IR ($CHCl_3$) 3090, 3050, 2995, 2960, 2900, 1745, 1645, 1445, 1310, 1140, 1080, 995, 920 cm^{-1}. Anal. Calcd for $C_{14}H_{16}SO_3$: C, 63.61; H, 6.10. Found: C, 63.45; H, 6.12.

α-Alkylation/Desulfurization: Preparation of *cis*- and *trans*-2,5-Di(2-propenyl)cyclopentanone (6 and 7).[11] To a suspension of NaH (18 mg, 0.78 mmol) in THF (1.5 mL) at room temperature was added 4 (200 mg, 0.78 mmol) in THF (200 μL).

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The mixture was stirred until hydrogen evolution ceased (20 min), at which time allyl bromide (200 μL, 2.3 mmol) was added, and the mixture was stirred at room temperature in the dark. After 3 h, water was added, and the mixture was extracted with ether (3×). The combined organics were washed with 10% aqueous NaOH, water, and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by chromatatron (3:1 hexane/EtOAc), yielding **5** as a light yellow oil (119 mg, 0.39 mmol, 51%): ^1H NMR (90 MHz, $CDCl_3$) δ 2.45 (d, J = 7.0 Hz, 2 H), 1.9–2.95 (m, 7 H), 4.8–6.0 (m, 6 H), 7.45–7.91 (m, 5 H); IR (neat) 3100, 2995, 2930, 1740, 1640, 1440, 1310, 1145, 1085 cm^{-1}.

A THF (0.3 mL) solution of sulfone **5** (117 mg, 0.39 mmol) was added to a suspension of Al(Hg) [from Al: 104 mg, 3.9 mmol] in THF/water (10 mL/1 mL). The resulting mixture was allowed to stir at room temperature, and the reaction progress was monitored by TLC. After 4 h, the mixture was filtered through a sintered glass funnel, and the solid residue was washed with ether (3×). The combined filtrates were washed with saturated aqueous $NaHCO_3$ and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by MPLC (95:5 hexane/EtOAc), yielding, in order of elution, **7** [(20 mg, 0.12 mmol, 31%) ^1H NMR (90 MHz, $CDCl_3$) δ 1.46 (m, 2 H), 2.05–2.20 (m, 6 H), 2.54 (m, 2 H), 4.98–5.10 (m, 4 H), 5.75 (m, 2 H); IR (CCl_4) 3100, 3020, 2980, 2950, 2890, 1735, 1640, 1435, 1155, 990, 910 cm[21]] and **6** [(31 mg, 0.19 mmol, 49%) ^1H NMR (90 MHz, $CDCl_3$) 1.50–2.60 (, 10 H), 4.90–5.20 (m, 4 H), 5.75 (m, 1 H); IR (CCl_4) 3100, 3020, 2980, 2960, 2895, 1735, 1640, 1440, 1150, 1115, 990, 915 cm^{-1}].

α-Alkylation/Desulfurization: Preparation of 2-[4-(Tetrahydro-2*H*-pyranyloxy)-2-butynyl]cyclopentanone (14). To a suspension of NaH (16 mg, 0.67 mmol) in THF (2 mL) at room temperature was added **9** (150 mg, 0.67 mmol) in THF (1 mL). The mixture was stirred until hydrogen evolution ceased (15 min), at which time a THF (1 mL) solution of propargylic bromide **11**[17] (230 mg, 1.0 mmol) was added, and the mixture was stirred at room temperature in the dark. After 30 h, TLC (2:1 hexane/EtOAc) indicated that the reaction was complete. Water was added, and the mixture was extracted with ether (3×). The combined organics were washed with 10% aqueous NaOH, water, and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by chromatatron (2:1 hexane/EtOAc), yielding the α-alkylated sulfone as a light yellow oil (155 mg, 0.41 mmol, 61%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.30–3.20 (m, 12 H), 2.70 (t, J = 3.0 Hz, 2 H), 3.30–3.95 (m, 2 H), 4.16 (t, J = 3.0 Hz, 2 H), 4.67 (s, 1 H), 7.45–7.91 (m, 5 H); IR ($CHCl_3$) 3040, 2980, 2950, 2890, 1745, 1585, 1450, 1310, 1140, 1080, 1025, 905 cm^{-1}.

A THF (0.3 mL) solution of this sulfone (150 mg, 0.40 mmol) was added to a suspension of Al(Hg) [from Al: 107 mg, 4.0 mmol] in THF/water (9 mL/1 mL). The resulting mixture was allowed to stir at room temperature, and the reaction progress was monitored by TLC. After 4 h, the mixture was filtered through a sintered glass funnel, and the solid residue was washed with ether (3×). The combined filtrates were washed with saturated aqueous $NaHCO_3$ and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by MPLC to give **14** (87 mg, 0.37 mmol, 92%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.35–2.60 (m, 15 H), 3.90–3.99 (m, 2 H), 4.22 (s, 2 H), 4.76 (s, 1 H); IR (CCl_4) 2960, 2890, 1745, 1115, 1025 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.42; H, 8.62.

Desulfurization/α-Alkylation without Added Bu_3SnCl: 2-Benzylcyclopentanone (12).[14] A THF (5 mL) solution of sulfone **8** (500 mg, 2.1 mmol) was added to a flask containing dry liquid ammonia (15 mL) and lithium (50 mg, 7.1 mmol) at −78 °C. About 2 min later, benzyl bromide (620 μL, 5.2 mmol) in THF (0.5 mL) was added, and the mixture was allowed to slowly warm to room temperature (1.5–2.0 h). Saturated aqueous ammonium chloride was added, and the mixture was extracted with 1:1 petroleum ether/ether (3×). The combined organics were washed with 10% aqueous HCl, water, saturated aqueous $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by MPLC (9:1 hexane/EtOAc) gave **12** as a colorless oil (131 mg, 0.75 mmol, 36%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.45–2.50 (m, 7 H), 2.61 (d, J = 9.0 Hz, 1 H), 3.13 (dd, J = 9.0, 3.0 Hz, 1 H), 7.25 (m, 5 H); IR (CCl_4) 3110, 3090, 3050, 2990, 2960, 2900, 1745, 1605, 1500, 1455, 1410, 1155, 915 cm^{-1}.

General Procedure for Desulfurization/α-Alkylation with Added Bu_3SnCl: 2-Benzylcyclopentanone (12).[14] A THF (5 mL) solution of sulfone **8** (500 mg, 2.1 mmol) was added to a flask containing dry liquid ammonia (10 mL) and lithium (48 mg, 6.9 mmol) at −78 °C. The solution was allowed to stir 2 min, and tributyltin chloride (0.74 mL, 2.7 mmol) was added, causing the color of the solution to go from light blue to milky white. After 5 min, benzyl bromide (0.30 mL, 2.5 mmol) in HMPA (1 mL) was added and the mixture was warmed to −50 °C and stirred for 1 h. Saturated aqueous ammonium chloride quench at −50 °C was followed by warming to room temperature, ammonia evaporation, and extration with 1:1 petroleum ether/ether (2×). The combined organics were washed with 10% aqueous HCl, water, saturated aqueous $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. MPLC (9:1 hexane/EtOAc) gave **12** as a colorless oil (214 mg, 1.2 mmol, 59%).

***cis*- and *trans*-2,5-Di(2-propenyl)cyclopentanone (6 and 7).**[11] Following the general procedure described above for the preparation of **12**, sulfone **4** (200 mg, 0.76 mmol) was alkylated [lithium (13 mg, 1.89 mmol); Bu_3SnCl (310 μL, 1.14 mmol); HMPA (300 μL); liquid ammonia/THF (5 mL/1.6 mL)] with allyl bromide (85 μL, 0.99 mmol). MPLC (95:5 hexane/EtOAc) gave, in order of elution, **7** (73 mg, 0.44 mmol, 59%) and **6** (15 mg, 0.091 mmol, 12%).

2-[4-(Tetrahydro-2*H*-pyranyloxy)-2-butynyl]cyclopentanone (14). Following the general procedure described above for the preparation of **12**, sulfone **9** (150 mg, 0.67 mmol) was alkylated [lithium (12 mg, 1.7 mmol); Bu_3SnCl (270 μL, 1.0 mmol); HMPA (300 μL); liquid ammonia/THF (5 mL/1.6 mL)] with propargylic bromide **11**[17] (190 mg, 0.80 mmol). MPLC (3:1 hexane/EtOAc) gave **14** as a colorless oil (131 mg, 0.55 mmol, 83%).

2-[(*E*)-3,7-Dimethyl-2,6-octadienyl]cyclopentanone (13).[19] Following the general procedure described above for the preparation of **12**, sulfone **9** (150 mg, 0.67 mmol) was alkylated [lithium (12 mg, 1.7 mmol); Bu_3SnCl (270 μL, 1.0 mmol); HMPA (300 μL); liquid ammonia/THF (4.8 mL/1.6 mL)] with geranyl bromide (200 mg, 0.92 mmol). MPLC (9:1 hexane/EtOAc) gave **13** as a colorless oil (95 mg, 0.43 mmol, 64%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.62 (s, 6 H), 1.71 (s, 3 H), 1.78–2.65 (m, 12 H), 5.08 (m, 2 H); IR (CCl_4) 3040, 2990, 2950, 2910, 2880, 1735, 1440, 1410, 1380, 1150, 1110, 910 cm^{-1}. No difficulties were encountered when this reaction was repeated on a larger scale: sulfone **9** (2.50 g, 11.1 mmol) giving **13** (1.37 g, 6.22 mmol) in 56% isolated yield.

2-[(*E*)-3,7-Dimethyl-2,6-octadienyl]cyclohexanone (15).[20] Following the general procedure described above for the preparation of **12**, sulfone **10**[4] (160 mg, 0.67 mmol) was alkylated [lithium (12 mg, 1.7 mmol); Bu_3SnCl (270 μL, 1.0 mmol); HMPA (300 μL); liquid ammonia/THF (4.8 mL/1.6 mL)] with geranyl bromide (174 mg, 0.80 mmol). MPLC (9:1 hexane/EtOAc) gave **15** as a colorless oil (82 mg, 0.35 mmol, 52%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.70 (s, 6 H), 1.76 (s, 3 H), 1.70–2.70 (m, 15 H), 5.14 (m, 2 H); IR (CCl_4) 3040, 2990, 2950, 2880, 1715, 1440, 1410, 1380, 1165 cm^{-1}.

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