

Studies of the Condensation of Sulfones with Ketones and Aldehydes.

Michael E. Garst[†], Lloyd J. Dolby, Shervin Esfandiari, Rachel A. Okrent, Alfred A. Avey*

Organic Consultants, Inc., 132 E. Broadway, Suite 107, Eugene, Oregon

[†] Allergan Inc., 2525 DuPont Drive, Mail Code RD3D, Irvine, CA 92612

Orgcon2@Mindspring.com

Methyl 1,2,3,4,5,6,7,8-octahydro-2-naphthoate.	2
1,2,3,4,5,6,7,8-Octahydro-2-naphthoic Acid (2a).	2
Reaction of Cyclohexanone with Dimethyl Sulfone and Potassium <i>t</i>-Butoxide in DMAC.	3
2-Methylcycloheptanone.	3
1,2-Dimethylenecycloheptane (1b)	4
5-Oxatricyclo[7.5.0.0<3,7>]tetradec-1(9)-ene-4,6-dione (2b).	4
2,3-Dimethyl-1,3-butadiene (3)	5
2-Methyl-1,3-butadiene (5) from 2-Butanone.	5
1-Methylnaphthalene (6).	6
2'-Methyl-<i>p</i>-terphenyl (8).	6
Reaction of Acetophenone with Dimethyl Sulfone and Potassium <i>T</i>-Butoxide in DMAC.	7
Reaction of α-Tetralone with Diethyl Sulfone.	7
2-Methyl-1,3-butadiene (5) from Isobutyraldehyde.	8
Reaction of Benzaldehyde with Benzyl Phenyl Sulfone in DMAC.	8
Reaction of Benzaldehyde with Benzyl Phenyl Sulfone in THF.	10

Methyl 1,2,3,4,5,6,7,8-octahydro-2-naphthoate. A mechanically stirred solution of 2-methylcyclohexanone (208 g, 1.86 mol) and dimethyl sulfone (419.5 g, 4.28 mol) in DMAC (2750 mL) was heated on a steambath to 75 °C. Powdered potassium t-butoxide (500 g, 4.46 mol) was added all at once. The inside temperature rose to 98 °C upon addition and heating continued for 2 hr. The G.C. analysis of the reaction showed the reaction to be complete. The reaction was cooled to room temperature in an ice bath, diluted with water (2 L) and extracted with toluene (3 x 1 L). The organic phases were combined and washed with saturated sodium chloride (2 x 750 mL) filtered through 1PS paper and transferred to a 12L flask. Methyl acrylate (480 g, 5.58 mol) was added to the flask and the reaction was heated on a steam bath overnight. The solvent was removed in vacuo to give 291 g (80%, 79% purity by GC analysis) of the crude ester.

1,2,3,4,5,6,7,8-Octahydro-2-naphthoic acid (2a). To a solution of crude methyl 1,2,3,4,5,6,7,8-octahydro-2-naphthoate (20 g, 0.1 mol) in ethanol (100 mL) was added a 20% sodium hydroxide solution (75 mL) and the resulting mixture was refluxed on steam bath for 2 hr. The reaction mixture after cooling to room temperature was concentrated under reduced pressure. The resulting residue was diluted with water (150 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were back washed with water (1 x 50 mL). The combined aqueous layers were cooled in an ice-water bath and acidified with conc. HCl to pH around 3 to 4. After stirring for 1 hr, solid was collected, washed with water (100 mL) and air dried to give 16 g (49% for three steps) 1,2,3,4,5,6,7,8-octahydro-2-naphthoic acid (**2**). GC analysis showed a purity of 95%.

Reaction of Cyclohexanone with Dimethyl Sulfone and Potassium *t*-Butoxide in DMAC. A mechanically stirred solution of cyclohexanone (9.8 g 0.1 mol) and dimethyl sulfone (21.6 g, 0.23 mol) was heated under nitrogen on a steam bath to an internal temperature of 70 °C. To this solution was added potassium *t*-butoxide (26.9 g, 0.24 mol) in one portion. After all of the solid potassium *t*-butoxide dissolved a new solid began to form and the internal temperature of the reaction rose to 100 °C. The reaction mixture was stirred and heated on steam bath overnight. After which time, the reaction was cooled to room temperature, diluted with water (200 mL), and extracted with 2-methylbutane (2 x 100 mL). The combined organic layers were washed with water (1 x 100 mL) and dried over anhydrous magnesium sulfate. Distillation at atmospheric pressure gave a fraction boiling at 108-110 °C (4.7 g). GC/MS analysis of this fraction showed four peaks with M/e of 94 amu (C₇H₁₀) indicating four isomeric products. UV analysis showed three peaks at 202, 233, and 262 nm.

2-Methylcycloheptanone.ⁱ Sodium methoxide was generated by adding sodium metal (7.1 g, 0.31 mol) in 1-2 g portions to anhydrous methanol (400 mL) with stirring over 50 min at room temperature. Methyl 2-oxo-1-cycloheptanecarboxylate (50.0 g, 0.29 mol) was added over a period of 10 min. Iodomethane (62.5 g, 0.44 mol) in an equal volume of methanol (27 mL) was added dropwise over 20 min. The reaction mixture was covered with a dark cloth and stirred overnight at room temperature. The reaction was concentrated under reduced pressure and the residue (59 g) was dissolved in DMAC (400 mL). To this solution was added lithium chloride (61.1 g, 1.45 mol) followed by warming to 157 °C over 7 hr. After this time, the reaction was cooled to room temperature. The reaction mixture was diluted with water (1 L) and extracted with

CH₂Cl₂ (2 x 200 mL and 1 x 100 mL). The combined organic phases were: washed with water (2 x 500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The product was distilled 80-100 Torr, bp 105-117 °C. The distillate was diluted with water (600 mL) and extracted with *n*-pentane (2 x 250 mL) to remove remaining DMAC. The combined organic layers were washed with water (2 x 200 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 25.7g (69%) of 2-methylcycloheptanone as a colorless liquid. GC analysis showed a purity of 97%. ¹H NMR (CDCl₃, 60 MHz) δ: 2.75-2.30 (m, 3H), 3.01-2.25 (m, 8H), 1.12 (d, *J* = 5 Hz, 3H).

1,2-Dimethylenecycloheptane (1b).^{1e.g} To a solution of 2-methylcycloheptanone (12.0 g, 0.10 mol) and dimethyl sulfone (21.5 g, 0.23 mol) in DMAC (200 mL) was added potassium *t*-butoxide (28.2 g, 0.25 mol). The solution was stirred on a steam bath for 2 hr. GC analysis showed the reaction to be complete. The reaction mixture was cooled in an ice bath for 20 min and partitioned between 2-methylbutane (200 mL) and water (1 L). The layers were separated and the organic phase was washed with water (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The product diene was vacuum transferred to a receiving flask cooled in an ethanol-dry ice bath at 1/2 Torr over 3.5 hr. The solidified product melted, upon warming to room temperature, to give 5.14 g (42%, 74% pure by GC) of 1,2-dimethylenecycloheptane (**1b**) as a colorless liquid.

5-oxatricyclo[7.5.0.0<3,7>]tetradec-1(9)-ene-4,6-dione (2b). Compound **1b** (5.14 g, 0.042 mol) and maleic anhydride (4.12 g, 0.042 mol) were stirred in toluene (115 mL) on a steam bath for 2.5 hr and cooled in the refrigerator overnight. The toluene was

evaporated under reduced pressure. The product was recrystallized from hexanes, producing large white shiny crystals (6.64 g, 72% yield). A second recrystallization of 0.16 g of **2b** gave the analytical sample showing a purity of 99.0% by GC and mp 118.5-120 °C. ¹H NMR (CDCl₃, 60 MHz) δ: 3.4-3.1 (m, 2H), 2.6-2.0 (m, 8H), 1.8-1.2 (M, 6H). Anal. Calcd for CH: C, 70.89; H, 7.32. Anal. found: C, 71.23; H, 7.21; N.

2,3-Dimethyl-1,3-butadiene (3). A mechanically stirred solution of 3-methyl-2-butanone (17.2 g, 0.2 mol) and dimethyl sulfone (43.24 g, 0.46 mol) in DMAC (250 mL) was heated to 50 °C, under argon, on a steambath. To this solution was added powdered potassium *t*-butoxide in one portion. After 3 hr, the reaction was cooled to 20 °C, diluted with 400 ml of water, and extracted with toluene (2 x 100 mL). The combined organic phases were washed with saturated aqueous sodium (1 x 50 mL), dried over anhydrous magnesium sulfate, filtered through 1PS filter paper, and diluted with toluene to make 400 ml of solution. To a portion of this solution (200 mL) was added methyl acrylate (25.8 g, 0.3 mol). After heating on a steam bath overnight, distillation of the reaction yielded 16.8 g (36%) of methyl 3,4-dimethylcyclohex-3-ene-carboxylate⁴ (**4**).

2-methyl-1,3-butadiene (5) from 2-butanone. A 500 mL 3-necked flask fitted with a distillation head with efficient condenser, mechanical stirrer, and thermometer was charged with 2-butanone (14.4 g, 0.2 mL), dimethyl sulfone (43.24 g, 0.46 mol), potassium *t*-butoxide (53.76 g, 0.48 mol), and DMAC (125 mL). The solution was heated on a steam bath. When the internal temperature reached 90 °C a distillate began to collect in the receiving flask, which was cooled in an ice-methanol bath. Distillation was complete after 1 hr. The distillate (10 g) was washed with ice cold water (2 x 10

mL), dried over sodium sulfate, and filtered through a plug of cotton to give 3.5 g of 2-methyl-1,3-butadiene (**5**, 26%).

1-Methylnaphthalene (6). α -Tetralone (14.6 g, 0.1 mol), dimethyl sulfone (21.6 g, 0.23 mol), and DMAC (125 mL) were combined and heated under argon on a steam bath to 70 °C. To this solution was added potassium *t*-butoxide (26.9 g, 0.24 mol) all at once and the heating continued over night. The reaction was monitored by G.C. and dimethyl sulfone (9.8 g, 0.1 mol) and potassium *t*-butoxide (11.2 g, 0.1 mol) were added. The reaction was stirred on steam bath for another 5 hr when more dimethyl sulfone (11.8 g, 0.12 mol) and potassium *t*-butoxide (15.7 g, 0.14 mol) were added. The reaction was heated on the steam bath overnight and then cooled to room temperature, poured into water (150 mL) and extracted with hexanes (3 x 75 mL). The organic layers were combined, washed with 1 M hydrochloric acid (1 x 100 mL), saturated sodium bicarbonate (1 x 100 mL), saturated sodium chloride (1 x 100 mL), and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was distilled at atmospheric pressure. The product was distilled at 20 Torr, bp. 135-140 °C, to give 12.1 g (*ca.* 85%) of product. GC analysis of this fraction showed 90% 1-methyl naphthalene (**6**) and 10% naphthalene (**7**).

2'-Methyl-*p*-terphenyl (8).⁶ A solution of propiophenone (13.4 g, 0.1 mol) and dimethyl sulfone (21.6 g, 0.23 mol), in DMAC (125 mL) was heated on a steam bath under argon to a temperature of 70 °C. To this solution potassium *t*-butoxide (26.9 g, 0.24 mol) was added all in one portion. The reaction was stirred overnight on the steam bath. Analysis of the reaction by G.C. showed the reaction to be 45% product and 42% starting material. To the reaction mixture was then added dimethyl sulfone (21.6 g, 0.23

mol) and potassium *t*-butoxide (26.9 g, 0.24 mol) and the reaction continued overnight. To the reaction mixture after cooling to room temperature was added water (300 mL). The solid was collected and washed with water (50 mL) to give 7.4 g (61%) of 2'-methyl-*p*-terphenyl (**8**).

Reaction of Acetophenone with Dimethyl Sulfone and Potassium *t*-Butoxide in DMAC. A solution of acetophenone (12.0 g, 0.1 mol) and dimethyl sulfone (21.6 g, 0.23 mol), in DMAC (125 mL) was heated on a steam bath under argon to a temperature of 70 °C. To this solution potassium *t*-butoxide (26.9 g, 0.24 mol) was added all in one portion. The reaction was stirred overnight on the steam bath. The reaction was cooled in an ice-water bath and diluted with water (100 mL) and brine (50 mL). The reaction was then extracted with ethyl acetate (2 x 150 mL). A solid developed in the extraction and the phases were filtered. The organic phases were combined, washed with 1:2 brine:water (2 x 150 mL), brine (1 x 150 mL), and filtered through 1PS filter paper. The solvent was removed on a rotary evaporator and the residue was triturated with 50/50 hexanes /ethyl acetate to give 0.9 g (9%) of *p*-terphenyl (**9**)⁷. The filtrate was purified on a 100 g flash silica gel column eluting with ethyl acetate/hexanes. Column fractions containing product were combined, the solvent removed in *vacuo*, and the residue was recrystallized from hexanes to give 5.2 g (44%) of 1,4-diphenyl-3-penten-1-one (**10**)⁸ mp 72-74°. ¹H NMR (CDCl₃, 300 MHz) δ: 8.05-8.00 (m, 2H), 7.62-7.21 (m, 8H), 6.14 (tq, *J* = 6.9, 1.4 Hz, 1H), 3.93 (dq, *J* = 6.9, 0.9 Hz, 2H), 2.15 (dt, *J* = 1.4, 0.9 Hz, 3H).

Reaction of α-Tetralone with Diethyl Sulfone. α-Tetralone (7.3 g, 0.05 mol), diethyl sulfone (22 g, 0.18 mol), potassium *t*-butoxide (23.2 g, 0.19 mol) and DMAC (75 mL) were combined and heated under argon at 150 °C over night. The reaction was

cooled to room temperature, and water (250 mL) was added. The solid was collected, washed with water (250 mL) and air dried to give 5 g (87%) of naphthalene (**7**).

2-Methyl-1,3-butadiene (5) from Isobutyraldehyde. A 500 mL 3-necked flask fitted with a distillation head with efficient condenser, mechanical stirrer, and thermometer was charged with dimethyl sulfone (43.2 g, 0.46 mol), potassium *t*-butoxide (53.76 g, 0.48 mol), and DMAC (200 mL). The solution was then heated on a steam bath. When the internal temperature reached 90 °C, a solution of isobutyraldehyde (14.4 g, 0.2 mol) in DMAC (50 mL) was added dropwise over a period of 30 min. Volatile product began to collect in the receiving flask, which was cooled in an ice-methanol bath. Distillation was complete after 1 hr. The distillate (8 g) was washed with ice cold water (1 x 5 mL), 1M HCl (1 x 5 mL), and filtered through 1PS paper to give 1.0 g of 2-methyl-1,3-butadiene (**5**) (7.5%).

Reaction of Benzaldehyde with Benzyl Phenyl Sulfone in DMAC. To a solution of benzyl phenyl sulfone (0.93 g, 4 mmol) in 20 mL of DMAC was added solid potassium *t*-butoxide (0.57 g, 5 mmol) all at once. The solution turned light reddish orange almost immediately. Benzaldehyde (0.36 g, 3.4 mmol) was then added all at once and the reaction stirred at room temperature for 30 min. Analysis of the reaction mixture by G.C. indicated a new compound (46%) and benzyl phenyl sulfone (53%) and no benzaldehyde. The reaction was then charged with fresh benzaldehyde (0.18 g, 1.7 mmol) and the reaction continued another 30 min at room temperature. After this time G.C. analysis showed only product (50%) and benzyl phenyl sulfone (28%). Benzaldehyde (0.54 g, 5.1 mmol) was added and the reaction stirred at room temperature for an additional 30 min after which time G.C. analysis indicated a composition of 92% product 8% benzyl phenyl

sulfone. Additional benzaldehyde (0.36 g, 3.4 mmol, 1.4 g, 12.6 mmol total) was added and the reaction continued for an additional 15 min after which time it was diluted with 50 mL of 4:1 water: saturated sodium chloride. The mixture was then extracted with ethyl acetate (2 x 50 mL). The combined organic phases were: washed with 50 mL of brine, filtered through 1PS paper, and concentrated in *vacuo* to give a yellow solid. The solid was triturated with 1:9 ethyl acetate: hexanes (30 mL) and collected to give 1g of solid. This solid was recrystallized from 15 mL of acetone to give 0.4 g of the tri adduct **14** (25%) as a mixture of diastereomers. The diastereomers (50 mg) were separated on a C18 reverse phase column eluted with 2 L of a linear gradient of 30 to 65% methanol/water (96 fractions, 21 mL each). The short retention time diastereomer eluted in fractions 29-34 which were combined and stripped to give 18 mg of one diastereomer as a white solid. The solid was recrystallized from 1.5 mL of methanol. mp 212-214 °C, MS *m/z* 407, ¹H NMR (300 MHz, CDCl₃) δ 7.6-7.1, (m, 15 H), 4.66 (d, *J* = 8.4 Hz, 1 H), 4.41 (m, 1 H), 2.92 (dd, *J* = 3.9, 15.3 Hz), 2.76 (s, 6H) 2.65 (dd, *J* = 9.6, 15.3 Hz), Anal. Calculated C, 70.73; H, 6.18; N, 3.44; S, 7.87. Found C, 70.96; H, 6.08; N, 3.46; S, 7.76. The other diastereomer eluted in fractions 39-44 which were combined and stripped to give 20 mg of product as a white solid. The product was recrystallized from 1.5 mL of methanol. mp 194-196 °C; MS *m/z* 407, ¹H NMR (300 MHz, CDCl₃) δ 7.6-6.8, (m, 15 H), 4.91 (d, *J* = 9.3 Hz, 1 H) 4.48 (m, 1 H), 3.46 (dd, *J* = 5.1, 15.9 Hz), 3.15 (dd, *J* = 7.8, 15.9 Hz), 2.92 (s, 6H).. Anal. Calc. C, 70.73; H, 6.18; N, 3.44; S, 7.87 Found: C, 70.69; H, 5.76; N, 3.26; S, 7.55. The acetone mother liquors and the solution from trituration were combined, the solvent removed in *vacuo*, and loaded onto a 10 g flash silica gel column. The column was eluted with 50ml fractions of hexanes/ethyl acetate. The 1,2-

diphenyl-1-phenylsulfonylethylene (**12**)¹⁰ came off the column in fractions 8-22 (5%-15% ethyl acetate in hexanes). The solvent was removed on a rotary evaporator and the residue (0.25 g) was recrystallized from 5 mL ethyl acetate to give 0.1 g of adduct **12** (7.8%). Column fractions 25-35 (25%-50% ethyl acetate in hexanes) were combined and concentrated in *vacuo* to give an oil which crystallized on standing. The solid was triturated with 15 ml of hexanes filtered and recrystallized from 7.5 mL ethyl acetate to give 0.4 g of dimethyl cinnamamide (**13**, 57%)¹¹.

Reaction of Benzaldehyde with Benzyl Phenyl Sulfone in THF. To a solution of benzyl phenyl sulfone (0.23 g, 1 mmol) in THF (5 mL) was added potassium *t*-butoxide (0.17 g, 1.5 mmol) followed by benzaldehyde (0.21 g, 2 mmol). After 30 min no benzaldehyde was evident by G.C. analysis of the reaction. More benzaldehyde (0.21 g, 1.5 mmol) was added and the reaction continued at room temperature for an additional 2 hr. Analysis of the reaction mixture showed the reaction was not complete. The reaction was then refluxed for 30 min. After which time G.C. analysis showed the reaction to be incomplete. Additional potassium *t*-butoxide (0.17 g, 1.7 mmol) was added and refluxing was resumed for 30 min longer. After which time the reaction was shown to be complete by G.C. analysis. The reaction was allowed to cool to room temperature and then poured into 50 mL of water and extracted with ethyl acetate (75 mL). The organic layer was washed with water (1 x 50 mL), brine (1 x 50 mL), filtered through 1PS filter paper and concentrated under reduced pressure to give 0.25 g (78%) of the 1,2-diphenyl-1-phenylsulfonylethylene (**12**)¹⁰ as a white solid.

(i)Marshall, J. A.; Partridge, J. J. *J. Org. Chem.* **1968**, 33, 4490.