Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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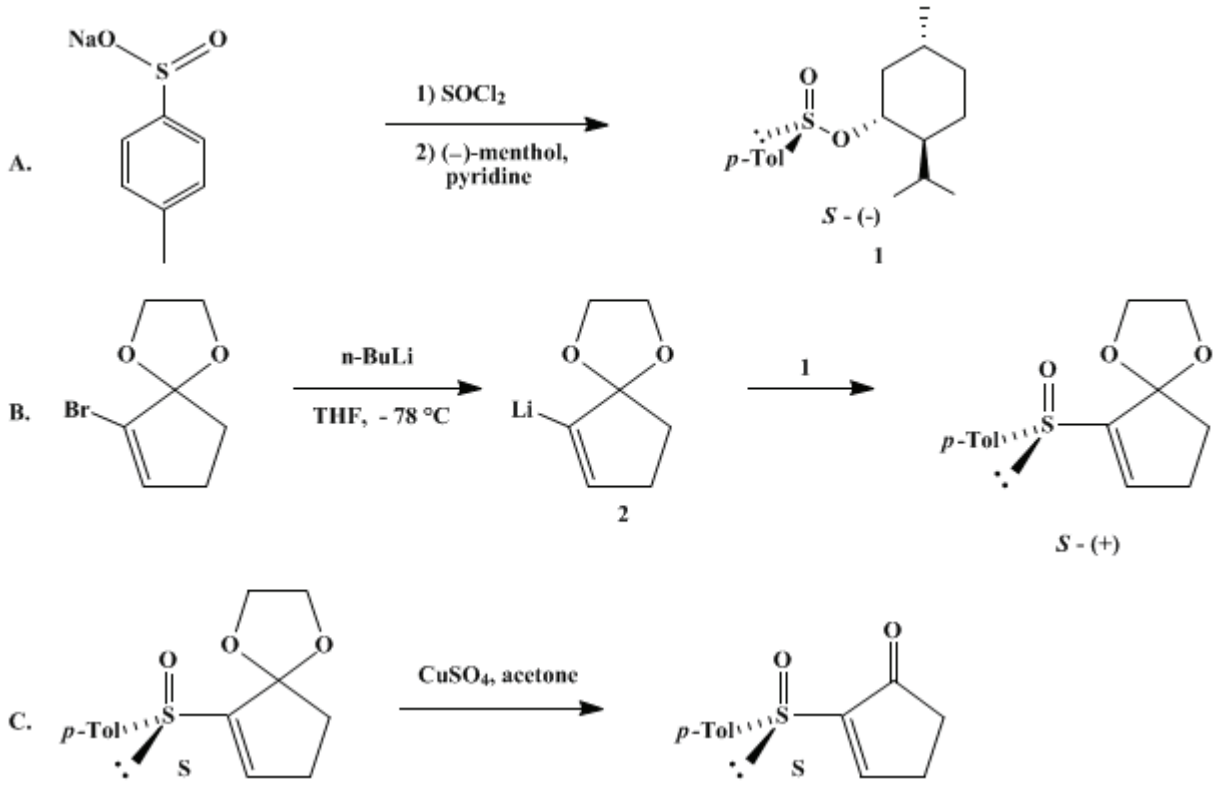
(*S*)-(+)-2-(*p*-TOLUENESULFINYL)-2-CYCLOPENTENONE: PRECURSOR FOR ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED CYCLOPENTANONES

[2-Cyclopenten-1-one, 2-[(4-methylphenyl)sulfinyl]-, (*S*)-]



Submitted by Martin Hulce, John P. Mallomo, Leah L. Frye, Timothy P. Kogan, and Gary H. Posner[1].
Checked by Ernest B. Clark, Michel Crevoisier, Han Young, and Robert M. Coates.

1. Procedure

Caution! Part A should be conducted in an efficient fume hood to avoid exposure to sulfur dioxide generated in the reaction. Benzene has been identified as a carcinogen; OSHA has issued emergency standards for its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. (*S*)-(−)-*Menthyl p-toluenesulfinate*. In a dry, 250-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet are placed a magnetic stirring bar and 65 g (40 mL, 0.55 mol) of thionyl chloride (Note 1). The liquid is stirred under a nitrogen atmosphere as 35.6 g (0.200 mol) of anhydrous sodium *p*-toluenesulfinate (Note 2) is added in portions over about 1 hr (Note 3). The solution immediately develops a yellow-green tinge as sulfur dioxide is liberated. After about three-fourths of the sulfinate has been added, 30 mL of benzene is added to facilitate stirring. The greenish slurry is stirred for another 1.5 hr, after which time 75 mL of benzene is added. The mixture is transferred to a 500-mL, round-bottomed flask, along with 75 mL of benzene used to rinse the flask. Excess thionyl chloride and benzene are removed by rotary evaporation and gentle heating. Four 150-mL portions of benzene are added to the residue, and each portion is evaporated to complete the removal of the thionyl chloride. The flask is equipped with a magnetic stirring bar and a 125-mL, pressure-equalizing dropping funnel. The crude *p*-toluenesulfinyl chloride, sodium chloride, and residual benzene are dissolved in 150

mL of anhydrous diethyl ether. The resulting ethereal suspension is stirred and cooled in an ice bath as 31.3 g (0.200 mol) of (−)-menthol (Note 1) in 25 mL of pyridine is added over ca. 2 min. The mixture is allowed to stir overnight, after which 70 g of ice is added. The layers are separated and the aqueous layer is extracted with one 100-mL portion of ether. The ethereal solutions are combined, washed three times with 50-mL portions of 20% aqueous hydrochloric acid, and dried with a mixture of anhydrous sodium sulfate and potassium carbonate. Filtration to separate the drying agents and rotary evaporation until a pressure of 3 mm is sustained leaves 57.5 g of crude methyl *p*-toluenesulfinate as a clear liquid admixed with white crystals. The less soluble (*S*)-(−) diastereomer (**1**) is isolated in several crops by crystallization from 1.2 volumes of reagent-grade acetone at −20°C. After the first crop has been collected, 3 drops of concd hydrochloric acid is added to the acetone mother liquor to effect equilibration of the sulfinate diastereomers. A total of 40.9–42.2 g of crystalline sulfinate is obtained in six crops. Recrystallization from acetone affords two crops of (*S*)-(−)-methyl *p*-toluenesulfinate, mp 105–106°C, $[\alpha]_D^{25}$ −199.4 (acetone, *c* 1.5), weighing 36.9–38.2 g (63–65%) (Note 4).

B. *(S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone ethylene ketal*. A 250-mL, three-necked, round-bottomed flask equipped with two rubber septa, a nitrogen inlet, 125-mL pressure-equalizing dropping funnel, and a magnetic stirring bar is flame-dried under nitrogen. After the apparatus cools to room temperature, the flask is charged with 70 mL of anhydrous tetrahydrofuran (Note 5) and cooled in an isopropyl alcohol–dry ice bath. Stirring is begun as 42 mL (60.8 mmol) of 1.45 *M* butyllithium in hexane (Note 6) is added slowly through the dropping funnel over 10–30 min. After another 10 min. a solution of 11.3 g (55.1 mmol) of 2-bromo-2-cyclopentenone ethylene ketal (Note 7) is added from the dropping funnel over 30 min. The colorless or pale-yellow solution is stirred and cooled at −78°C for 1.5 hr. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two rubber septa, and a stopcock connected to a bubbler gas exit is flushed with nitrogen and charged with 24.4 g (82.9 mmol) of (*S*)-(−)-menthyl *p*-toluenesulfinate and 460 mL of anhydrous tetrahydrofuran. The sulfinate suspension is stirred vigorously (Note 8) and cooled at −78°C as the vinyllithium reagent (**2**) in the first flask in then transferred into the second flask through a cooled cannula by means of nitrogen pressure (Note 9). As the 50-min transfer proceeds, the sulfinate suspension becomes yellow. The mixture is stirred for another 15 min at −78°C, the cooling bath is removed, and 125 mL of saturated aqueous sodium dihydrogen phosphate is added. When the contents have warmed to room temperature, the tetrahydrofuran is removed by rotary evaporation. The residue is partitioned between 300 mL of water and 200 mL of chloroform. The aqueous layer extracted with three 100-mL portions of chloroform. The chloroform extracts are combined and dried over anhydrous potassium carbonate. Filtration of the drying agent and evaporation of the chloroform gives 40–55 g of a viscous brown oil consisting of the sulfinyl ketal, menthol, menthyl sulfinate, minor by-products, and residual chloroform. The sulfinyl ketal is isolated by modified flash chromatography on 500 g of Woelm silica gel (32–64 μm) packed in dry diethyl ether in a 6.5-cm × 45-cm column (Note 10). The crude product is applied to the column in 25 mL of chloroform and the column is eluted with ether under sufficient compressed air pressure to achieve a flow of 60 mL per min. After thirty 60-mL fractions are collected, the solvent is changed to ethyl acetate, and another forty 60-mL fractions are collected and analyzed by thin-layer chromatography (Note 11). Combination and evaporation of fractions 40–60 provides 9.05–9.75 g (62–67%) of crude (*S*)-(+)-2-(*p*-toluenesulfinyl)-2-cyclopentenone ethylene ketal as a pale-yellow oil, $[\alpha]_D^{25}$ +78° ($CHCl_3$, *c* 0.25) (Note 12).

C. *(S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone*. A magnetic stirring bar, 100 g of anhydrous copper(II) sulfate, and a solution of 9.05–9.75 g of the sulfinyl ketal in 300 mL of acetone are placed in a 500-mL Erlenmeyer flask. The flask is flushed with nitrogen and stoppered. The suspension is stirred vigorously overnight, the copper sulfate is separated by filtration, and the filtercake is washed thoroughly with 500–700 mL of acetone. Concentration of the combined filtrates by rotary evaporation gives 7.36–7.58 g of tan crystals. Recrystallization is carried out by dissolving the product in a minimum volume of ethyl acetate (ca. 80 mL) at room temperature, treating with Norite, diluting with an equal volume of diethyl ether, and cooling to −20°C. After the resulting crystals are collected, the mother liquor is evaporated under reduced pressure at room temperature, and the procedure is repeated twice. The mother liquor is again evaporated and the residue (1.4–1.8 g) is purified by flash chromatography on 110 g of Woelm silica gel using ethyl acetate as eluant (Note 13). Combination of appropriate fractions, evaporation, and recrystallization affords two additional crops of crystalline product (0.4–0.7 g). The yield of (*S*)-(+)-2-(p-toluenesulfinyl)-2-cyclopentenone, mp 125–126°C, [α]

$_D$ + 148° ($CHCl_3$, *c* 0.11), is 6.02–6.60 g (50–54% based on bromo ketal) (Note 14) and (Note 15).

2. Notes

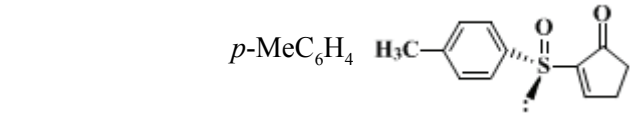
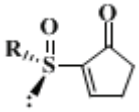
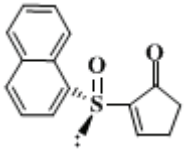
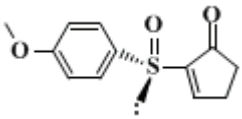
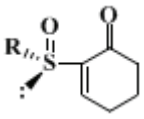
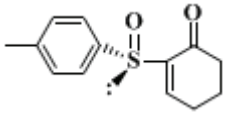
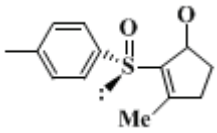
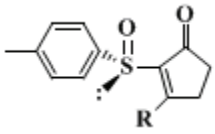
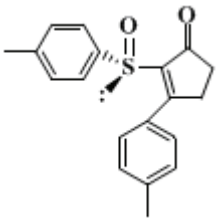
1. This reagent was purchased from Aldrich Chemical Company, Inc.
2. Sodium p-toluenesulfinate hydrate, purchased from Aldrich Chemical Company, Inc., was dried overnight in a vacuum oven at 140°C to remove the water of hydration. The weight loss amounts to 19–21%.
3. The checkers added the sodium sulfinate from a 100-mL, three-necked flask via a bent sidearm fitted to the reaction vessel. A stream of nitrogen flowing through the 100-mL flask prevented backflow of fumes from the reaction and caking of the sodium sulfinate powder.
4. The spectral properties of the (*S*)-(-) sulfinate are as follows: IR (CCl_4) cm^{-1}: 2958 (s), 2924 (s), 2870 (s), 1455 (m), 1135 (s), 961 (s), 919 (s), 853 (s); ^1H NMR (90 MHz, $CDCl_3$) δ: 0.72 (d, 3 H, *J* = 6, $CHCH_3$), 0.94 and 0.86 [2 d, 6 H, *J* = 7, CH $(CH_3)_2$], 2.37 (s, 3 H, $ArCH_3$), 4.08 (t of d, 1 H, *J* = 5, 10, $CHOSO_2$), 7.26 and 7.56 (2 d, 4 H, *J* = 8, ArH).
5. Tetrahydrofuran was dried by distillation from sodium–benzophenone ketyl before use.
6. Butyllithium in hexane is available from Aldrich Chemical Company, Inc. and Alfa Products, Morton Thiokol, Inc. The reagent was titrated with anhydrous diphenylacetic acid as described in the literature.[2]
7. 2-Bromo-2-cyclopentenone ethylene ketal was prepared according to a published procedure.[3] The compound is quite unstable and should be purified by distillation before use to remove impurities. The submitters stored the bromo ketal at −20°C over Linde 3Å molecular sieves and redistilled a portion in a Kugelrohr apparatus with an oven temperature of 38°C (0.1 mm) immediately before use. The checkers found it necessary to distill the bromo ketal a second time to increase its purity. The compound was stored at −20°C and used in Step B the next day.
8. The submitters caution that rapid stirring is essential to avoid local heating from the exothermic reaction and, as a consequence, diminished yields.
9. The checkers used a 61-cm, 16-gauge cannula with a single loop ca. 6 cm in diameter immersed in an isopropyl alcohol–dry ice bath. The submitters report that lower yields were obtained when the vinyllithium reagent was allowed to warm above −78°C briefly during the transfer.
10. The submitters purified the product by medium-pressure liquid chromatography on a 60-cm × 5-cm column packed with 230–400-mesh silica gel 60 purchased from E. Merck. Ethyl acetate was used as eluant at a flow rate of 4.0 mL per min. Fractions (20 mL) were collected and analyzed by thin-layer chromatography.
11. Thin-layer chromatograms were obtained with silica gel as absorbent and ethyl acetate as developing solvent. The order of elution and R_f values of the major components are as follows: menthyl sulfinate (0.65). menthol (0.59), sulfinyl ketal (0.30).
12. The ^1H NMR spectral characteristics of the ketal are as follows ($CDCl_3$) δ: 2.0–2.2 (m, 2 H, CH_2), 2.3–2.6 (m, 2 H, $C{=}CCH_2$), 2.37 (s, 3 H, CH_3), 3.7–3.9 (m, 4 H, OCH_2CH_2O), 6.67 (t, 1 H, *J* = 2, C=CH), 7.24 (2 d, 4 H, *J* = 8, aryl H).
13. Flash chromatography was carried out according to a procedure in the literature.[4]
14. The spectral properties of the sulfinyl enone are as follows: IR (CCl_4) cm^{-1}: 2924 (m), 1715 (s), 1287 (m), 1152 (s), 1083 (s), 1054 (s), 728 (m), ^1H NMR ($CDCl_3$) δ: 2.2–2.5 (m, 2 H, CH_2), 2.30 (s, 3 H, CH_3), 2.6–2.8 (m, 2 H, $C{=}CCH_2$), 7.19 and 7.58 (2 d, 4 H, *J* = 8, aryl H), 8.03 (t, 1 H, *J* = 2, C=CH); mass spectrum (70 eV), *m/z* (relative intensity): 220 (M^+, 30), 172 (100), 139 (48), 129 (72). The product was analyzed by the submitters: Anal. calcd. for $C_{12}H_{12}SO_2$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.53; H, 5.51; S, 14.72.
15. The submitters report that the sulfinyl ketone may be stored in vials in a desiccator at 0°C for more than 1 year without evidence of decomposition. Although storage under an inert atmosphere is not necessary, the checkers found that product exposed to the atmosphere at room temperature became discolored after several weeks.

3. Discussion

Enantiomerically pure β-substituted carbonyl compounds serve as useful intermediates in the synthesis of many chiral organic compounds. The enantioselective synthesis of acyclic β-substituted carboxylic acids has been reported by Meyers,[5,6] Mukaiyama,[7] and Koga.[8,9] However, no effective, general method for the enantio-controlled preparation of β-substituted cycloalkanones was available

prior to the investigations by the submitters.[10] For example, poor enantioselectivity was observed in conjugate additions of organometallic reagents to cyclic α,β-enones in the presence of optically active solvents[11] or chiral ligands.[12] In contrast, the submitters have found that conjugate addition to chiral cyclic α-sulfinyl α,β-enones occurs with high enantioselectivity.[13,14,15,16,17,18] Thus, the title compound is a useful intermediate for the synthesis of a variety of β-substituted cyclopentanones.

TABLE I
ENANTIOMERICALLY PURE α-SULFINYL-α,β-ENONES PREPARED FROM ETHYLENE KETALS OF α-BROMO-α,β-ENONES

Sulfinyl Enone	R	Product	Yield (%)	mp (°C)	$[\alpha]_D^{25}$
	p-MeC_6H_4		50–54	125–126	+142°
	1-Naphthyl		65	96.5–97.0	+292°
	p-$MeOC_6H_4$		76	120.5–121.5	+141°
	*p*-MeC_6H_4		66	101–102	+210°
	Me		38	90.5–91.0	+21.0°
	*p*-MeC_6H_4		35	132–133	−322°

The preparation of (*S*)-(−)menthyl *p*-toluenesulfinate described in Step A is based upon the procedure reported by Solladié.[19] 2-Bromo-2-cyclopentenone ethylene ketal is available from 2-cyclopentenone by the procedure of Smith and co-workers.[3] The present procedure has been used by the submitters to prepared analogous chiral α-sulfinyl α,β-enones (Table I).[13,14,15,16,17,18] The utility of these chiral synthons is enhanced by their stability, the facility of their conjugate addition reactions, and the capability of producing either enantiomeric β-substituted adduct by varying the reaction conditions.[20] Similar methodology has allowed conversion of some enantiomerically pure butenolide sulfoxides into the corresponding β-substituted butyrolactones.[21]

Both (*S*)-(−)- and (*R*)-(+)-menthyl 4-toluenesulfinates are now available from the Aldrich Chemical Company, Inc.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 47

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

benzophenone ketyl

sulfinyl ketal

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether,
diethyl ether (60-29-7)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

copper sulfate,
copper(II) sulfate (7758-98-7)

acetone (67-64-1)

pyridine (110-86-1)

sodium (13966-32-0)

Diphenylacetic acid (117-34-0)

menthol (15356-60-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

sodium sulfinate

hexane (110-54-3)

sodium dihydrogen phosphate (7558-80-7)

2-Cyclopentenone (930-30-3)

vinyllithium (917-57-7)

Menthyl p-toluenesulfinate,

Sodium p-toluenesulfinate hydrate (824-79-3)

menthyl sulfinate

2-Bromo-2-cyclopentenone ethylene ketal (68241-78-1)

methyl p-toluenesulfinate

Sodium p-toluenesulfinate

p-toluenesulfinate

2-Cyclopenten-1-one, 2-[(4-methylphenyl)sulfinyl]-, (S)-,
(S)-(+)-2-(p-TOLUENESULFINYL)-2-CYCLOPENTENONE (79681-26-8)

p-toluenesulfinyl chloride, sodium chloride

(S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone ethylene ketal (82136-15-0)