Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

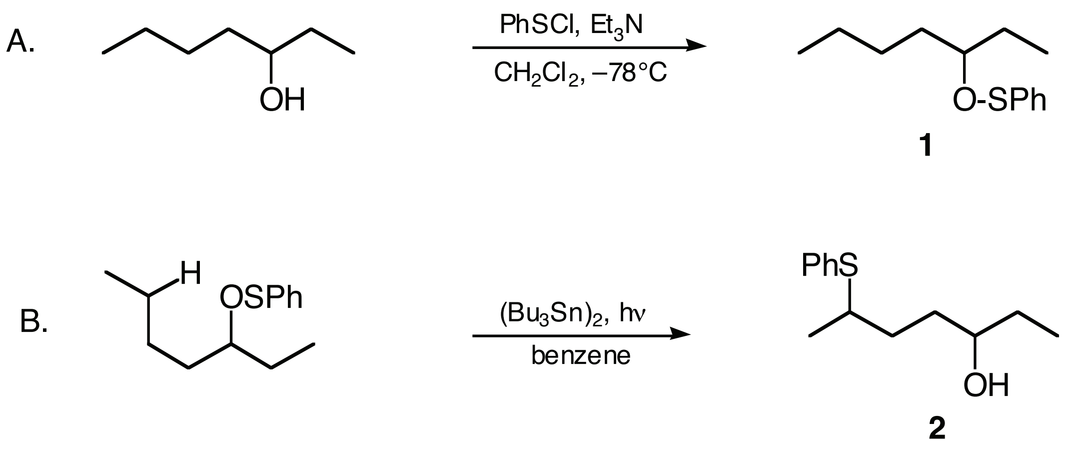
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Copyright © 2005 Organic Syntheses, Inc. All Rights Reserved

DOI:10.15227/orgsyn.081.0244
Organic Syntheses, Vol. 81, p. 244-253 (2005); Coll. Vol. 11, p. 121-127 (2009).

PHENYLSULFENYLATION OF NONACTIVATED δ-CARBON ATOM BY PHOTOLYSIS OF ALKYL BENZENESULFENATES: PREPARATION OF 2-PHENYLTHIO-5-HEPTANOL

(Heptane, 2-phenylthio-5-hydroxy)



Submitted by Goran Petrovic, Radomir N. Saicic and Zivorad Cekovic.[1]
Checked by Fangzheng Li and Marvin J. Miller.

1. Procedure

A. 3-Heptyl benzenesulfenate. A 1-L, three-necked, round-bottomed flask equipped with a 50-mL pressure-equalizing addition funnel fitted with an argon inlet, an internal thermometer, a drying tube, and a magnetic stir bar is charged with 10.0 g (86.1 mmol) of 3-heptanol (Note 1), 420 mL of anhydrous methylene chloride (Note 2), and 30 mL (22 g, 215 mmol) of freshly distilled triethylamine (Note 3). The flask is flushed with argon and the solution is cooled in a acetone/dry ice bath to an internal temperature of –72 °C. Benzenesulfenyl chloride (10.93 mL, 13.7 g, 94.73 mmol) (Note 4) is added over 20 min to the efficiently stirred solution. The reaction mixture is stirred at –72 °C for 45 min and then protected from light (Note 5) and allowed to warm to room temperature. The resulting mixture is diluted with 200 mL of methylene chloride and then washed successively with 200 mL of deionized water, 200 mL of 1.5M hydrochloric acid, 200 mL of deionized water, 200 mL of saturated aqueous sodium hydrogen carbonate solution, and 200 mL of deionized water. The organic solution is dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure from a flask wrapped with aluminum foil. The residual oil is purified by vacuum distillation (bp 131-132 °C, 3 mmHg) to give 17.2 g (89% yield) of the title compound **1** as a green-yellow oil (Notes 6, 7, 8).

B. 2-Phenylthio-5-heptanol. A photochemical reactor consisting of a tubular pyrex flask, a magnetic stirbar, a water-cooled high pressure mercury lamp, and an argon inlet tube (Note 9) is charged with 12.3 g (54.8 mmol) of 3-heptyl benzenesulfenate, 1.6 g (2.8 mmol) of hexabutylditin (Note 10), and 220 mL of benzene (Note 11). The solution is purged with argon for 10 min to remove oxygen and then irradiated for 1 h with water cooling (Note 12). The solvent is then removed under reduced pressure to afford a pale yellow oil which is purified by dry flash chromatography on silica gel (Note 13). The fractions containing the desired product are combined and concentrated by rotary evaporation under reduced pressure to afford 6.5 g (53%) of 2-phenylthio-5-heptanol as a colorless oil (Note 14).

2. Notes

1. 3-Heptanol was purchased from Fluka Chemika and distilled (bp 155 °C) before use. The checkers purchased 3-heptanol from Aldrich Chemical Company and used it without purification.

2. Methylene chloride was distilled from phosphorus pentoxide and stored over activated molecular sieves (4Å).

3. Triethylamine was purchased from the Merck & Company, Inc. and distilled from calcium hydride. The checkers used triethylamine purchased from Aldrich Chemical Company.

4. Benzenesulfenyl chloride was prepared from the reaction of thiophenol with sulfuryl chloride in the presence of triethylamine in petroleum ether (bp 35-50 °C) according to the procedure of Barrett, A. G. M.; Dhanak, D.; Graboski, G. G.; Taylor, S. J. *Org. Synth. Coll. Vol. VIII*, **1993**, 550. This reagent was stored under argon in a refrigerator and protected from light, under which conditions it can be stored for one month without significant change (G. Zelčans, *Encyclopedia of Reagents for Organic Synthesis,* Ed. L. A. Paquette, Wiley, New York, 1995, Vol. 1, p. 272).

5. Alkyl benzenesulfenates are sensitive to light and their preparation should be carried out in a darkened hood.

6. The crude product is sufficiently pure for use in the next step. The submitters preferred to perform the distillation at a lower pressure (89 °C, 0.3 mmHg) in order to minimize decomposition and obtained the product in 91% yield. The checkers obtained the product in 84-89% yield in several runs.

7. The preparation of alkyl benzenesulfenates is accompanied by the formation of products of higher oxidation states of sulfur. These products have higher boiling points and are separated by careful distillation of the product under reduced pressure.

8. The product exhibits the following spectroscopic properties: IR (KBr) cm^{-1}: 3061, 2960, 2934, 2874, 2000-1600, 1583, 1477, 1464, 1439, 1113, 1069, 1024, 943, 916, 893, 811, 737, 690; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 7.5 Hz, 6H), 1.24-1.31 (m, 4H), 1.56-1.70 (m, 4H), 3.52 (q, *J* = 5.7 Hz, 1H), 7.16-7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.5, 14.1, 22.9, 26.9, 27.5, 33.5, 89.3, 125.3, 128.9, 141.8.

9. The reaction apparatus used by the submitters for irradiation on a 12-g scale was 18 cm high and 6 cm in diameter and had a 55/50 joint at the top for an immersion well. The apparatus is fitted with an argon inlet tube and water-cooled condenser which is connected to a mineral oil bubbler. The light source was a 125W high pressure Hanovia mercury lamp. The checkers used a tubular pyrex flask 15 cm high and 7.5 cm in diameter. The light source was a 450W high pressure ACE mercury lamp (7825-34 lamp) with filter to provide 250 nm light.

10. Hexabutylditin was purchased from Aldrich Chemical Company, Inc. and used without purification.

11. Anhydrous benzene was purchased from Aldrich Chemical Company and used without purification.

12. The course of the reaction was followed by TLC (silica gel 60 A, 2.5 x 7.5 cm plates, elution with 95:5 ethyl acetate/hexane, visualization with 50% sulfuric acid followed by heating) by monitoring the disappearance of benzenesulfenate starting material **1**.

13. A chromatography column of 4.5-cm diameter was charged with 250 g of silica gel (ICN Silica 10/18 60 A). The viscous oily crude product is dissolved in 10 mL of methylene chloride, 10 g of silica gel is added, and the solvent is evaporated. The resulting dry powder is applied on the top of the column which is then successively eluted with petroleum ether, 95:5 petroleum ether/acetone, and 90:10 petroleum ether/acetone.

14. The submitters obtained the product in 61% yield; the checkers isolated the purified product in 53-56% yield in several runs. The product exhibits the following spectroscopic properties: IR (KBr) cm^{-1}: 3400, 3074, 2961, 2930, 2874, 2000-1600, 1584, 1480, 1458, 1439, 1376, 1303, 1263, 1178, 1092, 1068, 1025, 1000, 971, 923, 746, 692; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.5 Hz, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.40-1.80 (m, 6H), 3.22 (m, 1H), 3.48 (m, 1H), 7.18-7.29 (m, 3H), 7.37-7.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.9, 21.5, 21.5, 30.4, 30.4, 32.9, 33.1, 34.3, 34.5, 43.7, 43.8, 73.2, 73.3, 126.9, 128.9, 132.3, 135.7.

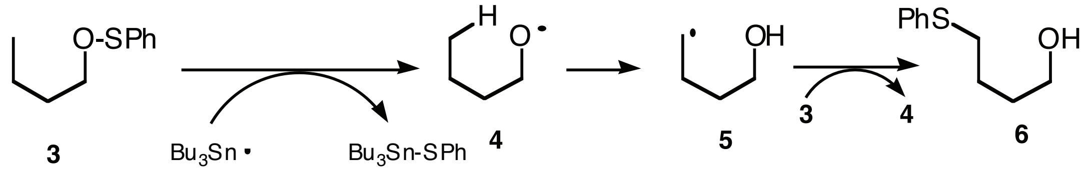
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The introduction of various functional groups onto a remote nonactivated carbon atom is of great synthetic importance.[2] The regioselective functionalization of a nonactivated δ-carbon atom involves a free radical 1,5-hydrogen transfer from δ-carbon atom to oxygen or nitrogen centered radicals.[3] Transposition of a radical center from oxygen or nitrogen to the remote carbon atom offers possibilities for introduction of different functional groups onto the nonactivated carbon atom or for formation of a new carbon-carbon bond. Diversity of this type of reaction offers possibilities for introduction of different oxygen,[2] nitrogen,[4] halogen,[5] and sulfur[6] functional groups as well as an olefinic bond[7] onto the δ-carbon atom. The present procedure is based on the original results[6] of the author and co-workers.

Formation of δ-phenylthio alcohols from alkyl benzenesulfenates **3** formally represents a simple interchange of the positions of δ-hydrogen and phenylthio group. The sequence of radical reactions is initiated by tributyltin radical and is based on its thiophilic addition to the sulfur of an alkyl benzenesulfenate.[6] The formed alkoxyl radical **4** upon intramolecular 1,5-hydrogen migration gives the δ-carbon radical **5**. In the absence of any other reactive species the carbon radical undergoes homolytic substitution at the sulfur atom in the alkyl benzenesulfenate **3** to give the δ-phenylthio alcohol **6** and to generate the alkoxyl radical **4** as a transfer radical which continues the chain (see Scheme 1).



Scheme 1

δ-Phenylsulfenylation is also conceivable in a tin-free variant; however, when alkyl benzenesulfenates were irradiated in the absence of hexabutylditin, the reaction proceeded at a lower rate and gave 10-15% lower yields of δ-phenylthio alcohols.[6]

This method for introduction of the thioether functional group tolerates the presence of a broad range of functional groups, such as alkene, ester, carbonyl, and cyano groups.

Introduction of the phenylthio group onto the δ-carbon atom of alcohols can have valuable synthetic applications. δ-Phenylthio alcohols can be oxidized to the corresponding δ-sulfoxides and sulfones (with their versatile reactivities) or they can be deprotonated by strong base converting the δ-carbon atom to a nucleophilic species. Conversion of δ-phenylthio alcohols to the corresponding δ-carbonyl compounds can be achieved via halogenation followed by subsequent hydrolysis. In this way an inversion of the reactivity of the δ-carbon atom may be accomplished and it can react as an electron acceptor.

The procedure of phenylsulfenylation of δ-carbon atom was applied to a variety of other substrates as summarized in Table 1.

1. Faculty of Chemistry, University of Belgrade, Studentski trg 16, PO Box 158, 11000 Belgrade, Serbia&Montenegro

2. (a) Heusler, K; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3,* 525; (b) Mihailovic, M. Lj.; Cekovic, Z. *Synthesis,* **1970**, 209; (c) Barton, D. H. R., *Pure and Appl. Chem.* **1968**, *16,* 1; (d) Feray, N.; Kuznetsov, P.; Renaud, P., in *Radicals in Organic Synthesis,* Eds. Renaud, P. and Sibi, M. P., Vol. 2. Ch. 3.6. p. 246, Wiley-VCH, Weinheim, 2001; (e) Cekovic, Z.,*Tetrahedron* **2003**, *59,* 8073

3. Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51,* 7095.

4. (a) Barton, D. H. R.; Parakh, S. I. *Half a Century of Free Radical Chemistry,* Cambridge University Press, Cambridge, 1993; (b) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640; (c) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 4076.

5. Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1961**, *83*, 2207;

6. Petrovic, G.; Saicic, R. N.; Cekovic, Z. *Tetrahedron Lett.* **1997**, *38*, 7107; (b) Petrovic, G.; Saicic, R. N.; Cekovic, Z. *Tetrahedron* **2003**, *59,* 187; (c) Petrovic, G.; Saicic, R. N.; Cekovic, Z. *Synlett,* **1999**, 635; (d) Pasto, D. J.; Cottard, F. *Tetrahedron Lett.* **1994**, *35*, 4303.

7. (a) Cekovic, Z.; Green, M. M. *J. Am. Chem. Soc.* **1974**, *96*, 3000; (b) Cekovic, Z.; Dimitrijevic, Lj.; Djokic, G.; Srnic, T. *Tetrahedron,* **1979**, *35*, 2021

Appendix
Chemical Abstracts Nomenclature (Registry Number)

2-Phenylthio-5-heptanol: 3-Heptanol, 6-(phenylthio); (198778-75-5)
3-Heptyl benzenesulfenate: Benzenesulfenic acid, 1-ethylpentyl ester; (198778-69-7)
3-Heptanol; (589-82-2)
Triethylamine: Ethanamine, N,N-diethyl-; (121-44-8)
Benzenesulfenyl chloride; (931-59-9)
Hexabutylditin: Distannane, hexabutyl; (813-19-4)
Thiophenol: Benzenethiol; (108-98-5)
Sulfuryl chloride; (7791-25-5)
Petroleum ether: Ligroine; (8032-32-4)

TABLE 1.
δ-PHENYLTHIO ALCOHOLS PREPARED BY PHOTOLYSIS OF ALKYL BENZENESULFENATES IN THE PRESENCE OF HEXABUTYLDITIN

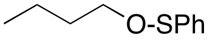
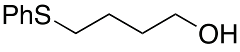
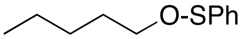
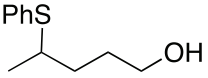
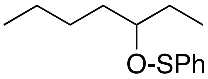
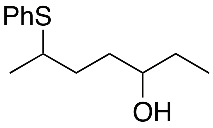
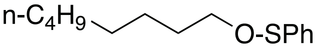
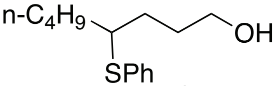
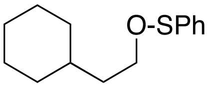
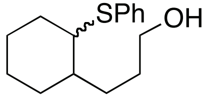
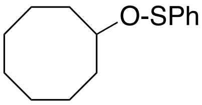
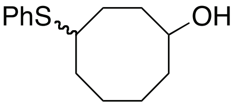
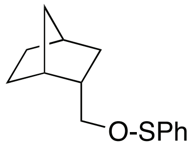
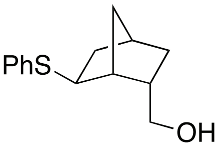
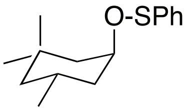
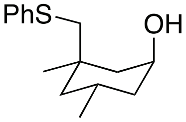
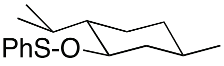
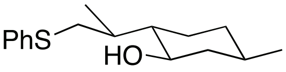
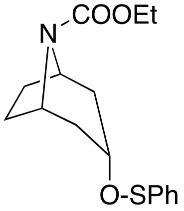
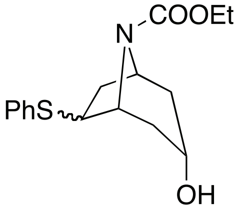
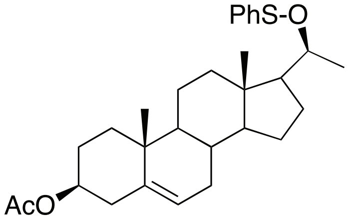
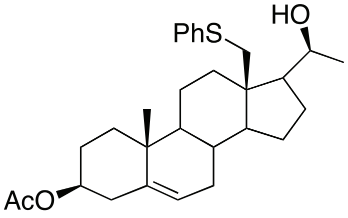
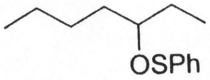
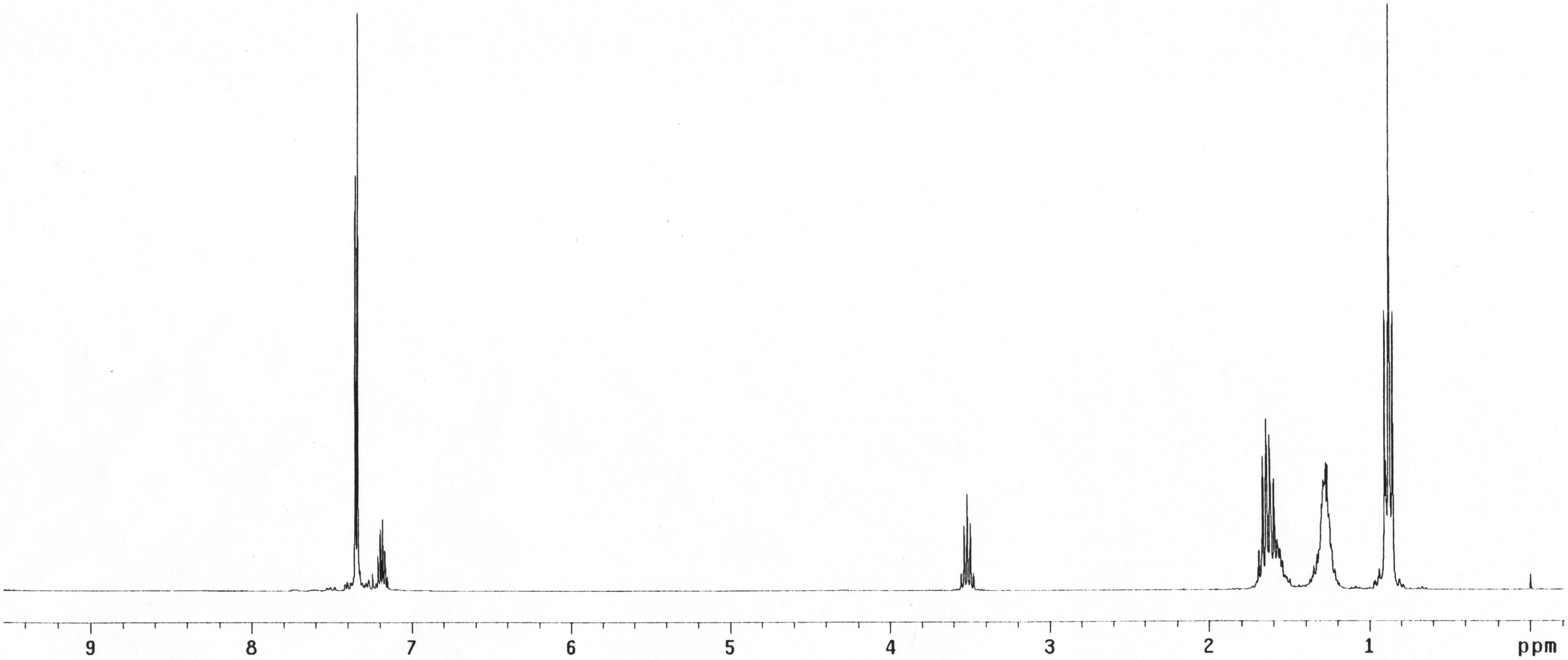
Alkyl benzenesulfenates	δ-Phenylthio alcohols	Yields (%)
		17
		80
		61
		47
		51
		35
		64
		62
		43

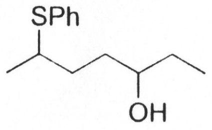
TABLE 1 (continued)
δ-PHENYLTHIO ALCOHOLS PREPARED BY PHOTOLYSIS OF ALKYL BENZENESULFENATES IN THE PRESENCE OF HEXABUTYLDITIN

Alkyl benzenesulfenates	δ-Phenylthio alcohols	Yields (%)
		45
		40



$C_{13}H_{20}OS$





$C_{13}H_{20}OS$