



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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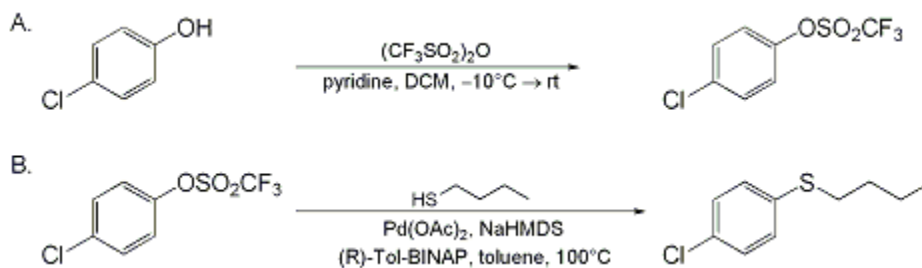
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

*Organic Syntheses, Coll. Vol. 10, p.147 (2004); Vol. 79, p.43 (2002).*

## PREPARATION OF **n**-BUTYL 4-CHLOROPHENYL SULFIDE



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Checked by Scott E. Denmark and Ramzi F. Sweis.

### 1. Procedure

*A. 4-Chlorophenyl trifluoromethanesulfonate*. A 250-mL, three-necked flask equipped with a Teflon-coated thermocouple, nitrogen bubbler, and septum is charged with a Teflon-coated magnetic stir bar, 4-chlorophenol (13.2 g, 102.5 mmol), and methylene chloride (125 mL) at room temperature (Note 1). Pyridine (9.1 mL, 112.5 mmol) is added to the solution via syringe, and the reaction mixture is cooled to  $-10^{\circ}\text{C}$  with an ice/methanol cooling bath (Note 2). Triflic anhydride (18.7 mL, 111.3 mmol) is added dropwise to the reaction mixture via syringe at a rate such that the temperature remains below  $-2^{\circ}\text{C}$  (Note 3). Upon completion of the addition, the reaction mixture is stirred for 1 hr at  $-10^{\circ}\text{C}$ , then allowed to warm to room temperature. When the reaction is complete, water (75 mL) is added to the mixture and the resulting two-phase mixture is stirred for 15 min (Note 4). In a 500-mL separatory funnel, the layers are separated and the organic (lower) layer is washed sequentially with 0.2 N hydrochloric acid (HCl), water, and brine (75 mL each). The final organic layer is concentrated to a yellow oil via rotary evaporation. The yellow oil is diluted with 25 mL of 5% ethyl acetate in hexanes and filtered through a bed of silica gel (63 g charged to a 150-mL filter funnel and prewetted with 5% ethyl acetate in hexanes, Note 5). The silica gel is washed with 5% ethyl acetate in hexanes until the desired triflate is no longer detected in the filtrate (250 mL). The filtrate is concentrated via rotary evaporation to give the desired triflate as a clear, colorless liquid (25.7 g, 96% yield)(Note 6).

*B. n-Butyl 4-chlorophenyl sulfide*. A 1-L, single-necked, pear-shaped flask, equipped with a Teflon-coated magnetic stir bar and septum, is charged with 4-chlorophenyl trifluoromethanesulfonate (17.6 g, 67.5 mmol), palladium acetate [Pd(OAc)<sub>2</sub>, (0.9 g, 4.1 mmol)], and toluene (425 mL), (Note 7). A nitrogen source is introduced through a 12-in., 16-gauge needle, which is punctured through the septum and submerged into the mixture. A second 16-gauge needle leading to a bubbler is punctured through the septum. The mixture is stirred while vigorously purging with nitrogen for 15 min (Note 8). The septum is opened briefly to introduce [(R)-Tol-BINAP, (3.1 g, 4.5 mmol, Note 9)], and the mixture is stirred for 15 min with continuous purging with nitrogen, yielding a homogenous orange solution.

A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, reflux condenser leading to a nitrogen inlet and a septum. A Teflon-coated thermocouple is introduced into the flask through the septum. The septum is removed and the flask is charged with toluene (515 mL). A second nitrogen source is introduced into the solution through a 12-in., 16-gauge needle, and the solution is vigorously purged with nitrogen for 5 min. To this mixture is immediately added via syringe 0.6 M sodium bis(trimethylsilyl)amide in toluene (157.5 mL, 94.5 mmol, Note 10). While the solution is stirred vigorously, 1-butanethiol (10.1 mL, 94.5 mmol) is added over the course of 3 min (Note 11). A gel-like solid forms and the internal temperature increases from  $21^{\circ}\text{C}$  to  $28^{\circ}\text{C}$ .

The solution containing the palladium catalyst and 4-chlorophenyl trifluoromethanesulfonate in toluene is transferred via a cannula to the mixture containing sodium 1-butanethiolate (Note 12). The mixture is heated to  $100^{\circ}\text{C}$  and stirred at this temperature for 12 hr (Note 13). The mixture is cooled to

ambient temperature and transferred to a 2-L extraction funnel. The organic phase is washed with 2 N sodium hydroxide (125 mL), 2 N hydrochloric acid (100 mL) and an aqueous saturated solution of sodium chloride (50 mL). The organic phase is dried over sodium sulfate and concentrated on a rotary evaporator, yielding a heterogeneous mixture. The mixture is triturated with hexanes (150 mL) and stored at 0°C overnight (Note 14). The mixture is filtered through a sintered-glass funnel, washing with hexanes. The filtrate is concentrated on a rotary evaporator, and the concentrate is transferred to a 35-mL, pear-shaped flask equipped with a Teflon-coated magnetic stir bar, a 12-cm Vigreux column and a short-path distillation apparatus. The oil is distilled at reduced pressure (0.3 mm), discarding the fractions that boil at 55-91°C (Note 15). The fraction boiling at 92°C is collected, to yield *n*-butyl 4-chlorophenyl sulfide as a colorless oil (11.2 g, 83% yield) (Notes 16 and 17).

## 2. Notes

1. An atmosphere of nitrogen is maintained throughout the course of the reaction. 4-Chlorophenol and dichloromethane were purchased from Aldrich Chemical Company, Inc. , and used without further purification.
2. Unless otherwise noted, all temperatures refer to internal temperatures measured with Teflon-coated thermocouples. Pyridine was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
3. Triflic anhydride was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
4. The course of the reaction was followed by TLC (95:5 ethyl acetate/hexanes, Silica Gel 60 F254, 2.5 × 7.5 cm, 250 μ thickness, UV visualization at 254 nm), monitoring for the disappearance of 4-chlorophenol : TLC:  $R_f$  (4-chlorophenol) = 0.09,  $R_f$  (4-chlorophenyl trifluoromethanesulfonate) = 0.56.
5. Silica Gel 60 (230-400 mesh) was purchased from EM Science .
6. The physical properties are as follows:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.24 (m, 2 H, J = 9.0, 3.4, 2.2), 7.44 (m, 2 H, J = 8.9, 3.4, 2.1) ;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 118.7 (q, J = 316.8), 122.6, 130.2, 134.2, 147.8, ppm; IR (neat)  $\text{cm}^{-1}$ : 1208, 1139, 880 . Anal. Calcd for  $\text{C}_7\text{H}_4\text{ClF}_3\text{O}_3\text{S}$ : C, 32.26; H, 1.55. Found: C, 32.25; H, 1.65.
7.  $\text{Pd}(\text{OAc})_2$  was purchased from Strem Chemical Co. and toluene was purchased from EM Science .
8. Most of the solids dissolve within 15 min.
9. (R)-Tol-BINAP [(R)-(+)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl] was purchased from Strem Chemical Co. , and used without further purification.
10. The 0.6 M solution of sodium bis(trimethylsilyl)amide in toluene was purchased from Aldrich Chemical Company, Inc. , and used as received.
11. 1-Butanethiol was purchased from Aldrich Chemical Company, Inc., and stored over 4Å molecular sieves . An excess of thiol is employed because of the formation of the disulfide as a competing side reaction.
12. The color of the mixture becomes bronze.
13. The submitters followed the course of the reaction by HPLC, monitoring for the disappearance of 4-chlorophenyl trifluoromethanesulfonate . HPLC conditions were as follows: 0.46 × 7.5 cm Eclipse-XDB column, gradient elution (10:80 → 85:15 acetonitrile/10 mM pH 6.3 phosphate buffer over 8.5 min, flow rate = 1.5 mL/min, detection = 210 nm).  $R_T$  (4-chlorophenyl trifluoromethanesulfonate) = 6.25 min,  $R_T$  (*n*-butyl 4-chlorophenyl sulfide) = 7.10 min.
14. Triturating the mixture with hexanes and storing overnight at 0°C induces the precipitation of solid (R)-Tol-BINAP, which is then removed by filtration.
15. Distillation is required to remove the primary side-product, di-*n*-butyl disulfide . Purification by silica gel chromatography gave inferior results because of similar retention times of the two compounds. The initial distillate fractions are turbid, indicating the presence of di-*n*-butyl disulfide . The absence of turbidity in the higher boiling fraction indicates distillate that is predominantly the desired *n*-butyl 4-chlorophenyl sulfide , containing only small amounts of *n*-butyl disulfide .
16. The isolated oil contains 0.5 mol% *n*-butyl disulfide . Additional *n*-butyl 4-chlorophenyl sulfide remains in the distilling flask, but is not recovered. The physical properties are as follows:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.94 (t, 3 H, J = 7.3), 1.43-1.48 (m, 2 H), 1.59-1.65 (m, 2 H), 2.90 (t, 2 H, J = 14.6), 7.27 (br s, 4 H) ;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.6, 21.9, 31.1, 33.5, 128.9, 130.2, 131.6, 135.6 ; IR (neat)  $\text{cm}^{-1}$ : 1096, 810 . Anal. Calcd for  $\text{C}_{10}\text{H}_{13}\text{ClS}$ : C, 59.84; H, 6.53. Found: C, 59.62; H, 6.76.

17. The checkers employed rac-BINAP purchased from Strem Chemical Company and used it in place of (R)-Tol-BINAP.<sup>2</sup> The same procedure was followed, except that 3 equiv of lithium chloride was added to the complete reaction mixture immediately prior to heating to 100°C. The reaction was run on one-half the scale used for (R)-Tol-BINAP and the product was obtained as before after two distillations (5.07 g, 75% yield). Anal. Calcd for C<sub>10</sub>H<sub>13</sub>ClS: C, 59.84; H, 6.53. Found: C, 59.85; H, 6.75. The initial dissolution of rac-BINAP is not complete because of the lower solubility of this ligand compared with (R)-Tol-BINAP.

### Waste Disposal Information

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

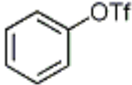

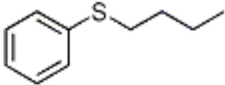
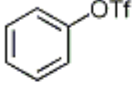

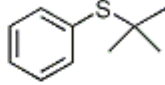
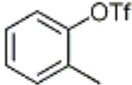

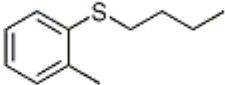
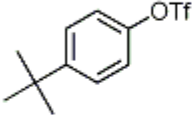

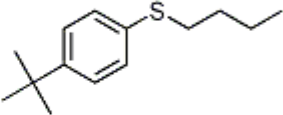
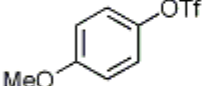

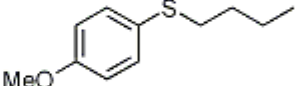
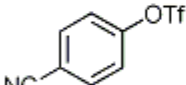

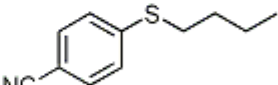
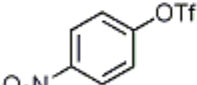

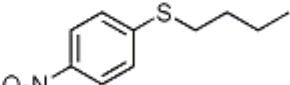
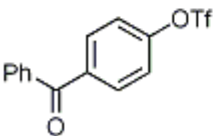

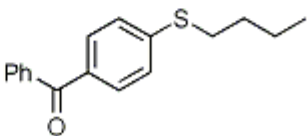
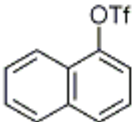

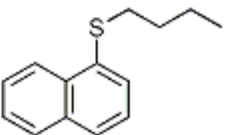
### 3. Discussion

This procedure describes the preparation of *n*-butyl 4-chlorophenyl sulfide starting from 4-chlorophenol. The intermediate 4-chlorophenyl trifluoromethanesulfonate highlights the chemoselectivity of this procedure, which overwhelmingly favors coupling at the carbon bearing the triflate functionality. As a consequence, the product contains a handle for additional functionalization by any one of the newly developed methods for coupling nucleophiles to aryl chlorides.<sup>3</sup> This procedure also highlights a modification of the originally described protocol, in which sodium *tert*-butoxide had been employed as the base.<sup>2</sup> Since the submitters' initial disclosure, they have discovered that the use of sodium bis(trimethylsilyl)amide decreases the amount of phenol by-product formed during the course of the reaction. In head-to-head experiments with sodium *tert*-butoxide versus bis(trimethylsilyl)amide, greater amounts of phenol were observed with the former base. This recent development allows the use of higher reaction temperatures and shorter reaction times if desired. The same yield of *n*-butyl 4-chlorophenyl sulfide was obtained when the reaction was conducted at 80°C, but a longer reaction time was required. Furthermore, the commercially available solutions of bis(trimethylsilyl)amide in toluene can be used directly, obviating the usual difficulties encountered with handling hygroscopic solids.

The preparations of aryl sulfides typically employ aryl halides as starting materials.<sup>4</sup> The procedure described here makes use of the ubiquitous class of commercially available phenolic compounds in the form of aryl triflates, which expands the range of readily accessible aryl sulfides. Prior to this disclosure, the use of aryl triflates in a palladium-catalyzed process for the formation of aryl alkyl sulfides was unprecedented.<sup>5</sup> This procedure appears to be general with regard to electronically neutral or electron-deficient aryl triflates (Table 1). The yields in Table I correspond to the initially disclosed procedure employing sodium *tert*-butoxide as the base. Lower yields were obtained with the 4-nitro-substituted triflate, and in the case of the electronically enriched substrate containing a 4-methoxy group.

Table 1

TABLE 1. PREPARATION OF ALKYL ARYL THIOETHERS

Aryl Triflate	Thiol	Product	Yield (%)
			93
			66
			79
			92
			54
			82
			60
			91
			95

## References and Notes

- Merck & Co., Inc., P.O. Box 2000, RY800-C362, Rahway, NJ 07065.
- Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, III, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606.
- For examples, see: (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989; (b) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677; (c) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053.
- (a) For recent examples, see reference 2b and additional references cited therein; (b) For a general review on sulfides, see: "Comprehensive Organic Chemistry"; Jones, D. N., Ed; Pergamon Press: Oxford, 1979; Vol. 3, pp 33-103; (c) For a review of transition-metal catalyzed carbon-heteroatom bond formation, see: Baranano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287.
- (a) A nickel-catalyzed process employing aryl mesylates and thiophenols has been described:

Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895; (b) For the preparation of aryl silyl sulfides from aryl triflates and trialkylsilylanethiolates, see: Arnould, J. C.; Didelot, M.; Cadilhac, C.; Pasquet, M. J. *Tetrahedron Lett.* **1996**, *37*, 4523.

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

4-Chlorophenyl trifluoromethanesulfonate:  
Methanesulfonic acid, trifluoro-, p-chlorophenyl ester (8);  
Methanesulfonic acid, trifluoro-, 4-chlorophenyl ester (9); (29540-84-9)

4-Chlorophenol: TOXIC:  
Phenol, p-chloro- (8);  
Phenol, 4-chloro- (9); (106-48-9)

Pyridine (8, 9); (110-86-1)

Triflic anhydride:  
Methanesulfonic acid, trifluoro-, anhydride (8, 9); (358-23-6)

Palladium acetate:  
Acetic acid, palladium(2+) salt (8, 9); (3375-31-3)

(R)-(+)-2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl: STREM CHEMICALS: (R)-Tol-BINAP:  
Phosphine, [1,1'-binaphthalene]-2,2'-diylbis[bis(4-methylphenyl)-, (R)- (11); (99646-28-3)

Sodium bis(trimethylsilyl)amide:  
Disilazane, 1,1,1,3,3,3-hexamethyl-, sodium salt (8);  
Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, sodium salt (9); (1070-89-9)

1-Butanethiol (8, 9); (109-79-5)

rac-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl: rac-BINAP:  
Phosphine, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl]- (11); (98327-87-8)