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### ONE-STEP SYNTHESIS OF UNSYMMETRICAL SULFIDES BEARING HEXAFLUOROCUMYL MOIETY

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#### **GRAPHICAL ABSTRACT**



**Abstract** A facile and convenient one-pot synthesis of novel unsymmetrical sulfides, 2'-alkylthio- and 2'-arylthio-1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-oles 1a-k, is presented. Physicochemical characterization; IR infrared; <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR; and mass spectral analyses of the obtained compounds are discussed as well.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications<sup>®</sup> for the following free supplemental resource(s): Full experimental and spectral details.]

Keywords Alkyl-aryl sulfides; diaryl sulfides; hexafluorocumylalcohol; ortholithiation; unsymmetrical sulfides

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#### A. ZAJĄC AND J. DRABOWICZ

#### INTRODUCTION

Physicochemical properties of unsymmetrical sulfides make them very interesting divalent organosulfur derivatives. Some of them are biologically and pharmacologically active.<sup>[1-3]</sup> Therefore they are used as pesticides,<sup>[4]</sup> antioxidants,<sup>[5]</sup> and germicidal agents.<sup>[6]</sup> Other ones have applications in the formation of self-assembling monolayers with interesting physical properties.<sup>[7,8]</sup> First of all, these compounds are very useful in organic synthesis as precursors of higher-valent sulfur compounds, for example, sulfoxides,<sup>[1,2,4,9–11]</sup> sulfones, and sulfonium salts.

During the years a number of methods for the synthesis of these compounds have been described in the literature. Probably the most commonly used route is based on an alkylation of thiols<sup>[1,5,12,13]</sup> or thiolates<sup>[4,7,14]</sup> with alkyl or aryl halides in various conditions. Other protocols include aziridine ring opening with thiols,<sup>[15]</sup> palladium-catalyzed cross-coupling reaction of compounds containing sulfur–boron single bonds with organic electrophiles (Suzuki reaction),<sup>[16]</sup> sulfenylation of arenes with arenesulfenyl chlorides,<sup>[6,17]</sup> reduction of thiolesters,<sup>[18]</sup> and metal-catalyzed reductive coupling of disulfides with organic halides<sup>[3,19–22]</sup> or organoboronic acids.<sup>[23,24]</sup>

#### DISCUSSION

The ortholithiation reaction of 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol and subsequent treatment with various electrophiles as a method of synthesis of the corresponding *ortho*-substituted derivativeshas been known for a long time<sup>[25]</sup> but is still fruitfully used.<sup>[26-30]</sup> Nevertheless, usage of symmetrical disulfides as precursors of an electrophile in this process has not been presented until now.

Here we report a facile protocol that allows the one-pot synthesis of unsymmetrical sulfides bearing hexafluorocumyl moiety, 2'-alkylthio- or 2'-arylthio-1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-oles 1a-k (except described elsewhere but obtained by other methods, such as compounds  $1a^{[31]}$  and  $1f^{[32]}$ ). It is based on the use of commercially available 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (hexafluorocumyl alcohol) 2 as a substrate. It reacts with *n*-butyllithium in the presence of tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) under nitrogen with the formation of the dilithiated derivative 3. The generated dilithium salt was allowed to react with the corresponding disulfide 4a-k in THF for 24 h and gave, after standard work up, the expected unsymmetrical sulfides listed in Scheme 1. The isolated crude residues were purified by column chromatography to afford the corresponding pure products 1a-k in good yields. The products are colorless liquids, except 1f and 1i-k, which are colorless solids with low melting points. They are stable at room temperature under a laboratory atmosphere.



Scheme 1. Synthesis of sulfides 1a-k.



Scheme 2. Attempts of synthesis of the sulfide 1e.

Generally, the yield strongly depends on the surroundings of the carbon atom attached to the divalent sulfur atom. Thus, the yields are comparable for substituents containing primary or secondary carbon atoms and decrease dramatically for di-tbutyl disulfide. The fact can be easily explained by the increase of bulkiness of the substituents. It should also be noted that for ethyl sulfide **1b** the yield is surprisingly less than for *n*-propyl analoge **1c**. The fact is reproductible and remains unexplained. The isolated yields for naphthyl and aza-aromatic analogs are lowest, which is most likely due to more complex purification process in comparison with other analogs, although yields established by NMR measurements were good. Because the yield of the reaction is extremely poor for 1e, where R = t-Bu we attempted to use S-tbutyl methanethiosulfonate 5 instead of disulfide 4e (Scheme 2). It should be more active because of the presence of a better leaving group, the methanesulfonyl moiety. Unfortunately, all attempts failed and furnished only unchanged substrate 2 in almost quantitative yield. The use of N-(t-butylsulfanyl)phthalimide 6 was ineffective either (Scheme 2) and results in some other product, which will be described elsewere. Considering physicochemical properties of the newly prepared unsymmetrical sulfides it is interesting to note that coefficient of light refraction for liquid products increases with increasing of a number of carbon atoms, and for aryl analogs 1 g and h is considerably greater than for alkyl compounds 1a-d.

#### **EXPERIMENTAL**

The melting points were measured on capillary apparatus and were not corrected. For column chromatography, silica gel 60 (70-to 230-mesh ASTM) was used. For preparative thin-layer chromatography (TLC), silica-gel  $60 F_{254} 200 \times 200 \times 2$  mm preparative thin-layer chromatography (PLC) glass plates were used. The NMR spectra were obtained using 200-MHz and 500-MHz spectrometers. The infrared (IR) spectra were recorded using Fourier transform infrared (FTIR) spectrometer by the thin film and KBr tablet methods. The mass spectra and

high-resolution mass spectrometry (HRMS) were measured using a double-focusing (BE geometry) mass spectrometer utilizing chemical ionization (CI) with isobutane as an ionizating agent or electron ionization (EI) technique. The coefficients of light refraction were measured using Abbe's type refractometer.

Disulfides were synthesized by a previously published method.<sup>[31]</sup>

### 2'-Alkylthio- or 2'-Arylthio-1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ols (1a–k): General Procedure

A solution of n-BuLi in hexane (10 mL, 2.5 M, 25 mmol) was transferred using a syringe into dry round-bottom two-neck flask previously flushed out with nitrogen, placed on a magnetic stirrer, and sealed with two rubber septa under nitrogen at rt. TMEDA ( $0.57 \,\mathrm{mL}$ ,  $3.75 \,\mathrm{mmol}$ , 15% mol with respect to *n*-BuLi) was then added dropwise to the stirred solution using a syringe. The solution became cloudy in a while. After additional stirring (30 min) the reaction mixture was cooled to ca.  $-10^{\circ}$ C on an acetone / dry ice bath, and a solution of alcohol 2 (2.08 g, 8.5 mmol) in dry THF (3 mL) was added dropwise using syringe during 10 min. After the addition the mixture became clear. Then the reaction mixture was allow to reach rt and was stirred for the next 24 h. After that, the mixture was cooled to ca.  $-10^{\circ}$ C on an acetone / dry ice bath again, and the corresponding disulfide **4a–k** (8.5 mmol) was added dropwise using a syringe over 10 min. After reaching rt the solution was stirred for 24 h, and the resulting solution was then transferred into a separation funnel and quenched with an equal volume of  $H_2O$  and ca. 5% solution of  $H_2SO_4$  (5 mL). The two-phase system was then shaken for 1 min and extracted with  $CH_2Cl_2$  (3 × 30 mL). The combined organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (CHCl<sub>3</sub>), furnishing the corresponding pure products **1a-k**.

#### 2'-Methylthio-1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (1a)

Colorless liquid; yield: 2.09 g (85%);  $n_D^{25} = 1.4613$ ;  $R_f = 0.8$  (CHCl<sub>3</sub>). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 2.54$  (s, 3H), 7.39–7.50 (m, 2H), 7.62–7.84 (m, 2H), 8.70 (s, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 22.1$ , 80.9 (h, <sup>2</sup> $J_{C-F} = 29.7$  Hz), 122.8 (q, <sup>1</sup> $J_{C-F} = 288.3$  Hz), 128.9, 129.3 (h, <sup>3</sup> $J_{C-F} = 2.8$  Hz), 130.1, 130.6, 134.7, 138.3. <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>):  $\delta = -73.80$ . IR (thin film): 3166 (O-H stretch), 1114 (C-F stretch), 707 (C-S stretch) cm<sup>-1</sup>. MS (EI, 70 eV): m/z (%) = 124.1 (11), 151.1 (19), 290.1 (100) [M]<sup>+</sup>. HRMS-EI: m/z [M]<sup>+</sup>calcd. for C<sub>10</sub>H<sub>8</sub>OSF<sub>6</sub>: 290.0200; found: 290.0197 ( $\Delta$  1,15696).

#### CONCLUSION

We developed a convenient protocol for the synthesis of 2'-alkylthio- or 2'-arylthio-1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-oles 1a-k from hexafluorocumyl alcohol 2 and the corresponding disulfides 4a-k and fully characterized the new products. They can be considered as convenient precursors of optically active higher-valent sulfur compounds.

#### SUPPORTING INFORMATION

Full experimental details, and <sup>1</sup>H and <sup>13</sup>C NMR spectra can be found via the Supplementary Content section of this article's Web page.

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#### REFERENCES

- Vijaikumar, S.; Pitchumani, K. Simple, solvent free syntheses of unsymmetrical sulfides from thiols and alkyl halides using hydrotalcite clays. J. Mol. Catal. A: Chem. 2004, 217, 117–120.
- Cremlyn, R. J. An Introduction to Organosulfur Chemistry; John Wiley & Sons: Chichester, 1996.
- Kumar, S.; Engman, L. Microwave-assisted copper-catalyzed preparation of diarylchalcogenides. J. Org. Chem. 2006, 71, 5400–5403.
- Russavskaya, N. V.; Korchevin, N. A.; Alekminskaya, O. V.; Sukhomazova, E. N.; Levanova, E. P.; Deryagina, E. N. New preparation of chloroalkyl sulfides. *Russ. J. Org. Chem.* 2002, *38*, 1445–1448.
- Pinko, P. I.; Terakh, E. I.; Gorokh, E. A.; Nikulina, V. V.; Prosenko, A. E.; Grigor'ev, I. A. Synthesis and antioxidant properties of unsymmetrical sulfides based on ω-(3,5-di-*tert*butyl-4-hydroxyphenyl)alkanethiols. *Russ. J. Appl. Chem.* 2002, 75, 1660–1664.
- Foss, N. E.; Dunning, F.; Jenkins, G. L. Some unsymmetrical aryl sulfides. J. Am. Chem. Soc. 1934, 56, 1978–1980.
- Troughton, E. B.; Bain, C. D.; Whitesides, G. M.; Nuzzo, R. G.; Allara, D. L.; Porter, M. D. Monolayer films prepared by the spontaneous self-assembly of symmetrical and unsymmetrical dialkyl sulfides from solution onto gold substrates: structure, properties, and reactivity of constituent functional groups. *Langmuir.* 1988, 4, 365–385.
- Zhang, M.; Andeerson, M. R. Investigation of the charge transfer properties of electrodes modified by the spontaneous adsorption of unsymmetrical dialkyl sulfides. *Langmuir* 1994, 10, 2807–2813.
- Kraus, G. A.; Maeda, H. The synthesis of α-acetoxy sulfides and their Lewis acidmediated reactions. *Tetrahedron Lett.* 1995, 36, 2599–2602.
- Metzner, P.; Thuillier, A. In Sulfur Reagents in Organic Synthesis; A. R. Katritzky, O. Meth-Cohn, and C. W. Rees (Eds.); Academic Press: San Diego, CA, 1994.
- 11. Trost, B. M.; Fleming, I. Comprehensive Organic Synthesis, vol. 6; Pergamon Press: New York, 1991.
- 12. Yin, J.; Pidgeon, C. A simple and efficient method for preparation of unsymmetrical sulfides. *Tetrahedron Lett.* **1997**, *38*, 5953–5954.
- Sandler, S. R.; Karo, W. Organic Functional Group Preparations; Academic Press: New York, 1968.
- Arguello, J. E.; Schmidt, L. C.; Peneory, A. B. "One-Pot" Two-Step Synthesis of Aryl Sulfur Compounds by Photoinduced Reactions of Thiourea Anion with Aryl Halides. Org. Lett. 2003, 5, 4133–4136.

- Turk, S. D.; Louthan, R. P.; Cobb, R. L.; Bresson, C. R. Direction of ring opening in the reaction of episulfides with amines. J. Org. Chem. 1964, 29, 974–975.
- Ishiyama, T.; Mori, M.; Suzuki, A.; Miyaura, N. The palladium-catalyzed cross-coupling reaction of 9-organothio-9-borabicyclo[3.3.1]nonanes with organic electrophiles: Synthesis of unsymmetrical sulfides. J. Organomet. Chem. 1996, 525, 225–231.
- Bottino, F.; Fradullo, R.; Pappalardo, S. Convenient synthesis of unsymmetrical aryl sulfides. J. Org. Chem. 1981, 46, 2793–2795.
- Eliel, E. L.; Daignault, R. A. A convenient synthesis of branched unsymmetrical sulfides. J. Org. Chem. 1964, 29, 1630–1631.
- Taniguchi, N. Alkyl- or arylthiolation of aryl iodide via cleavage of the S-S bond of disulfide compound by nickel catalyst and zinc. J. Org. Chem. 2004, 69, 6904– 6906.
- Ranu, B. C.; Mandal, T. Indium(I) iodide–promoted cleavage of diaryldiselenides and disulfides and subsequent condensation with alkyl or acyl halides: One-pot efficient synthesis of diorganylselenides, sulfides, selenoesters, and thioesters. J. Org. Chem. 2004, 69, 5793–5795.
- 21. Ajiki, K.; Hirano, M.; Tanaka, K. Rhodium-catalyzed reductive coupling of disulfides and diselenides with alkyl halides, using hydrogen as a reducing agent. *Org. Lett.* **2005**, 7, 4193–4195.
- Tang, R.-Y.; Zhong, P.; Lin, Q.-L. A convenient conversion of pyrazolyl disulfide to sulfides by sodium dithionite and synthesis of sulfoxide. *J. Fluorine Chem.* 2006, 127, 948–953.
- 23. Taniguchi, N. Convenient synthesis of unsymmetrical organochalcogenides using organoboronic acids with dichalcogenides via cleavage of the S-S, Se-Se, or Te-Te bond by a copper catalyst. J. Org. Chem. 2007, 72, 1241–1245.
- Hrabalek, A.; Pus, L.; Baranek, V.; Kunes, J.; Palat, K. Synthesis of unsymmetrical sulfides derived from tetrazole-5-thiols. *Chem. Heterocycl. Compds.* 2002, 38, 183–189.
- Perozzi, E. F.; Michalak, R. S.; Figuly, G. D.; Stevenson, IIIW. H.; Dess, D. B.; Ross, M. R.; Martin, J. C. Directed dilithiation of hexafluorocumyl alcohol—formation of a reagent for the facile introduction of a stabilizing bidentate ligand in compounds of hypervalent sulfur (10-S-4), phosphorus (10-P-5), silicon (10-Si-5), and iodine (10-I-3). *J. Org. Chem.* **1981**, *46*, 1049–1053.
- Kojima, S.; Doi, Y.; Okuda, M.; Akiba, K.-Y. First stereochemical characterization of configurationally stable diastereomers of hypervalent stiboranes (10-Sb-5) and acceleration of intramolecular permutation by donor solvents. *Organometallics* 1995, 14, 1928–1937.
- Yamamoto, Y.; Sakaguchi, A.; Ohashi, N.; Akiba, K.-Y. Synthesis, stability, and reactions of 10-Sn-5 tin ate complexes bearing four tin-carbon bonds. J. Organomet. Chem. 1996, 506, 259–263.
- Gliga, A.; Klare, H.; Schumacher, M.; Soki, F.; Neudörfl, J. M.; Goldfuss, B. New umpolung catalysts: Reactivity and selectivity of terpenol-based lithium phosphonates in enantioselective benzoin-type couplings. *Eur. J. Org. Chem.* 2011, 256–263.
- 29. Gliga, A.; Goldfuss, B.; Neudörfl, J. M. Lithium phosphonateumpolung catalysts: do fluoro substituents increase the catalytic activity? *Beilstein J. Org. Chem.* 2011, 7, 1189–1197.
- Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. Ethynyl benziodoxolones for the direct alkynylation of heterocycles: Structural requirement, improved procedure for pyrroles, and insights into the mechanism. *Chem. Eur. J.* 2012, *18*, 5655–5666.
- 31. Boeré, R. T.; Esser, D. E.; Willis, C. J.; Stephan, D. W.; Obal, T. W. Complexes of hybrid ligands: The synthesis of a thioanisole-substituted fluoro alcohol and its complexes with

Pd2+ and Pt2+: The structure of a palladium(II) complex containing alkoxide, phosphine, thio ether, and chloride donors. *Can. J. Chem.* **1987**, *65*, 798–803.

- Kawashima, T.; Ohno, F.; Okazaki, R. Synthesis, structure, and thermolysis of a tetracoordinate 1,2-λ<sup>4</sup>-oxathietane. *Angew. Chem. Int. Ed. Engl.* 1994, 33, 2094–2095.
- Drabowicz, J.; Mikołajczyk, M. A simple procedure for the oxidation of thiols to disulfides by means of bromine/aqueous potassium hydrogen carbonate in a two-phase system. *Synthesis* 1980, 32–34.