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High Pressure-Promoted Transformation of Alcohols into the Corresponding Phenylsulfides with Bu3P-PhSSPh[1]

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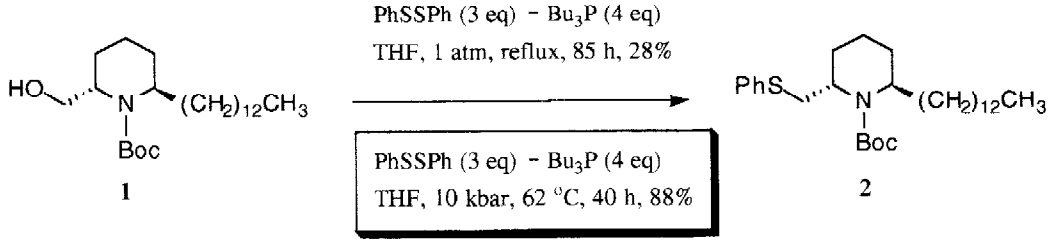
Key Words Phenylsulfides, High pressure reactions, Bu3P, PhSSPh, Steric hindrance

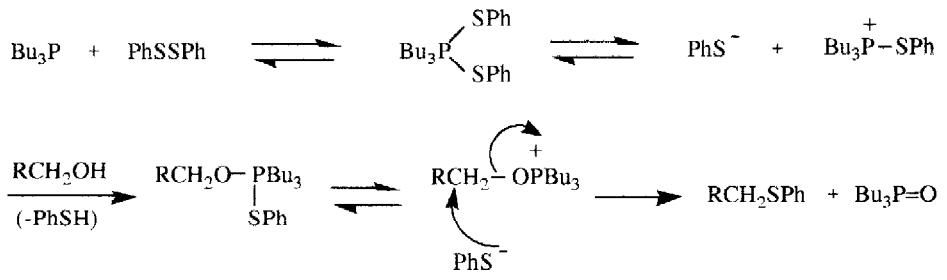
Abstract: Several sterically hindered primary and secondary alcohols are efficiently converted into the corresponding phenylsulfides by using Bu3P-PhSSPh system under high pressure conditions

Organosulfur compounds are generally known as versatile intermediates in synthetic chemistry [2] For example, the corresponding sulfoxide derivatives bearing acidic hydrogens readily undergo alkylation with several electrophiles providing useful methodology in modern organic synthesis. In certain cases organosulfur compounds are employed as convenient intermediates for the replacement of hydroxyl group by hydrogen or the reductive transformation of carbonyl function into methylene unit [3] Hence, development of practical methods to prepare these compounds is of great value. For the conversion of alcohols into the corresponding organic sulfides, one of the most straightforward approaches might be the use of a combination of organic disulfides and tertiary phosphines such as Bu3P-PhSSPh reagent system developed by Hata et al.[4]

In our separate work directed toward an enantioselective synthesis of solenopsin B, we required an efficient procedure for the convesion of alcohol **1** into the phenylsulfide derivative **2** as a crucial step (Scheme 1).[5] However, the usual reaction conditions employing 3 equiv of PhSSPh and 4 equiv of Bu_3P in refluxing THF resulted in a sparingly low yield (28%) even after prolonged heating; a considerable amount (55%) of unreacted starting material was recovered. This unexpected sluggish reactivity of **1** can be explained by the sterically hindered nature around the hydroxyl functionality. In order to overcome these problems we anticipated that the application of high pressure chemistry would be favorable.[6]



Scheme 1



Scheme 2

Survey of the literature reveals the mechanistic feature of this type of transformation as illustrated in Scheme 2, in which ionization process and bond-forming step play an important role.[7] As expected by our previous observations,[1, 8] these processes are significantly promoted by applying high pressure technique. Based on this consideration the above reaction was examined at 10 kbar pressure (Scheme 1). In accordance with our expectation the reaction was undoubtedly accelerated at elevated pressure furnishing the desired product **2** in much improved yield (88%). Encouraging with this success, further investigations were undertaken to elucidate the general scope of this synthetic procedure. In this Letter we wish to describe our powerful method for converting alcohols into the corresponding phenylsulfides which are inaccessible under normal conditions. The results are summarized in Table 1.[9]

Several aspects of this method are worthy of note. In every case the use of high pressure technique was found to enhance the rate of reaction, and hence good yields of phenylsulfides were realized. Since the reaction might proceed with an SN2 substitution mechanism (Scheme 10),[10] *tert*-alcohols such as *t*-BuOH showed no reactivity even at high pressure (Run 6).[4] In addition, on the basis of this reaction mechanism, we tentatively assigned the structure of **5** and **6**; only from the spectral evidence of ^{1}H NMR,[9] unfortunately, we could not clarify their relative stereochemistry. In view of the recent interest of thiosugar derivatives Run 14 demonstrates the utility of our method.[11]

In summary, several sterically hindered primary and secondary alcohols are efficiently converted into the corresponding phenylsulfide derivatives with Bu3P-PhSSPh system under high pressure conditions. In this study we could also reconfirm that high pressure chemistry is indeed effective to complete the reactions which involve ionization and bond-forming pathways.

Typical procedure for the preparation of 2: A mixture of alcohol **1** (100 mg, 0.25 mmol), PhSSPh (164 mg, 0.75 mmol), and Bu3P (202 mg, 1.0 mmol) in dry THF (1.2 mL) was placed in a Teflon reaction vessel and allowed to react at 10 kbar and 62 °C for 40 h. Thereafter the mixture was diluted with ether and washed with 2M NaOH and satd NaCl. After evaporation of the solvent, the crude product was purified by preparative TLC (hexane/CH_2Cl_2, 1 : 1) to give **2** (108 mg, 88%) as white crystals: mp 30.0-33.5 °C; $[\alpha]^{21}_D$ -0.92° (*c* 1.52, $CHCl_3$); IR (neat) 1688, 1584, 1392, 1174 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 0.88 (3H, t, *J*=6.0 Hz), 1.25 (20H, s), 1.44 (9H, s), 1.3-2.0 (10H, m), 2.94 (1H, dd, *J*=13.2, 9.1 Hz), 3.40 (1H, dd, *J*=13.2, 4.2 Hz), 3.65-3.95 (2H, m), 7.0-7.5 (5H, m). Found: *m/z* 489.3648. Calcd for $C_{30}H_{51}NO_2S$: M, 489.3641.

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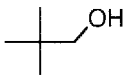
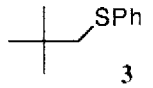
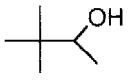
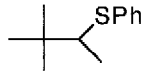
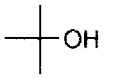
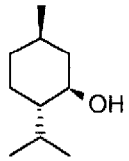
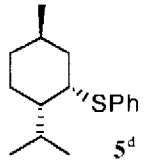
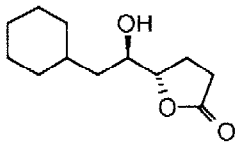
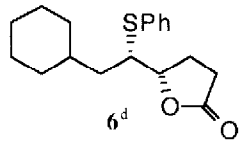
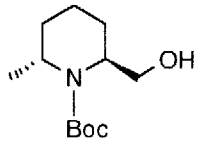
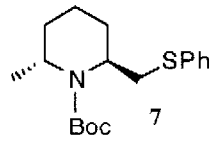
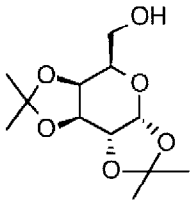
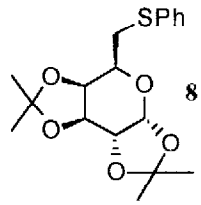
Table 1. Reaction of Alcohols with Bu3P-PhSSPh[a]

Run	Alcohol	Reaction Conditions	Product	Yield, %
1		1 atm, 16 h[c]	 **3**	90
2		10 kbar, 62 °C, 3 h[c]		100
3		1 atm, 50 h[c]	 **4**	~0
4		10 kbar, 62 °C, 20 h[c]		65
5		1 atm, 37 h[c]	no reaction	
6		10 kbar, 62 °C, 20 h[c]	no reaction	
7		1 atm, 40 h	 **5**[d]	42
8		10 kbar, 62 °C, 3 h		100
9		1 atm, 40 h	 **6**[d]	5
10		10 kbar, 62 °C, 10 h		64
11		1 atm, 40 h	 **7**	56
12		10 kbar, 62 °C, 20 h		92
13		1 atm, 36 h	 **8**	42
14		10 kbar, 62 °C, 5 h		100

[a]All reactions were carried out using 3 equiv of PhSSPh and 4 equiv of Bu3P in THF unless otherwise noted. The reaction at atmospheric pressure was conducted in refluxing THF. [b]Isolated yields [c]1.5 equiv of PhSSPh and 2 equiv of Bu3P were used. [d]Tentatively assigned structure See Text.

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9. Compound **3**: bp 110 °C/15 mmHg; IR (neat) 1582, 1479, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 1.03 (9H, s), 2.88 (2H, s), 7.0-7.4 (5H, m). Compound **4**: bp 120 °C/14 mmHg; IR (neat) 1584, 1479, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 1.06 (9H, s), 1.28 (3H, d, *J*=6.8 Hz), 3.05 (1H, q, *J*=6.8 Hz), 7.1-7.5 (5H, m). Compound **5**: bp 126 °C/1 mmHg; $[\alpha]^{20}_D$ +43.6° (*c* 1.0, $CHCl_3$); IR (neat) 1584, 1479, 1456, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 0.84 (3H, d, *J*=6.4 Hz), 0.93 (6H, d, *J*=6.6 Hz), 0.9-1.5 (3H, m), 1.5-2.2 (5H, m), 3.63 (1H, m), 7.1-7.5 (5H, m). Compound **6**: mp 77.0-78.0 °C; $[\alpha]^{23}_D$ -4.0° (*c* 0.3, $CHCl_3$); IR (KBr) 1765, 1586, 1574, 1454, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 0.8-2.0 (13H, m), 2.0-2.7 (4H, m), 3.44 (1H, ddd, *J*=8.9, 5.2, 3.8 Hz), 4.61 (1H, dt, *J*=7.4, 3.8 Hz), 7.1-7.5 (5H, m). Compound **7**: oil; $[\alpha]^{23}_D$ -5.9° (*c* 1.4, $CHCl_3$); IR (neat) 1688, 1584, 1392, 1365 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 1.21 (3H, d, *J*=6.8 Hz), 1.44 (9H, s), 1.4-2.0 (6H, m), 2.88 (1H, dd, *J*=13.0, 10.8 Hz), 3.34 (1H, ddd, *J*=13.0, 4.4, 0.4 Hz), 3.8-4.1 (2H, m), 7.1-7.5 (5H, m). Compound **8**: oil; $[\alpha]^{22}_D$ -39.9° (*c* 1.4, $CHCl_3$); IR (neat) 1584, 1483, 1439, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 1.24, 1.27, 1.34, 1.45 (each 3H, s), 3.16 (2H, d, *J*=7.0 Hz), 3.84 (1H, dt, *J*=7.0, 1.8 Hz), 4.26 (1H, dd, *J*=5.1, 2.2 Hz), 4.37 (1H, dd, *J*=7.9, 1.8 Hz), 4.59 (1H, dd, *J*=7.9, 2.2 Hz), 5.51 (1H, d, *J*=5.1 Hz), 7.0-7.5 (5H, m).
10. Suggested mechanism shows a quite resemblance to Mitsunobu reaction: O. Mitsunobu, *Synthesis*, **1981**, 1.
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