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A NOVEL METHOD FOR SYNTHESIS OF UNSYMMETRICAL SULFIDES FROM ALCOHOLS AND THIOLS BY UTILIZING AMINOPHOSPHONIUM SALTS

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Sulfides have been received much attention because of its potential utilities,[1] and various methods for synthesis of sulfides have been explored.[2] Their major processes require halides which are often derived from alcohols, however, halides bearing allyl, cyclopropyl, and propargyl groups are hardly accessible, since such functional groups are liable to rearrange during a course of halogenation of alcohols.[3]

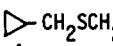
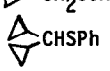
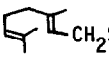
We now wish to report a novel and efficient method for synthesis of unsymmetrical sulfides from alcohols and thiols in a single step by utilizing N,N-methylphenylaminotriphenylphosphonium iodide $Ph_3P^+N(CH_3)Ph\ I^-$ (1)[4] as depicted in eq 1, where the reaction proceeds with complete inversion of configuration.

$$R^1OH \xrightarrow[2.\ Ph_3P^+N(CH_3)Ph\ I^-\ (1),\ R^2SH]{1.\ NaH} R^1SR^2 \qquad \text{(eq 1)}$$

In a typical procedure, to a solution of sodium cis-cinnamyl alcoholate prepared on treatment of cis-cinnamyl alcohol (0.67 g, 5.0 mmol) with sodium hydride (50 % in mineral oil, 0.24 g, 5.0 mmol) in dry dimethylformamide (10 ml) was added a solution of aminophosphonium salt 1 (2.48 g, 5.0 mmol) and ethanethiol (0.31 g, 5.0 mmol) in DMF (20 ml) in one portion at room temperature. After the reaction mixture was stirred for additional 8 hr, water (30 ml) and ether (50 ml) were added. The organic layer was washed twice with 0.1 N-HCl solution (50 ml) and dried ($MgSO_4$). After the bulk of the solvent was removed, light petroleum ether (10 ml) was added to the residue. Removal of the precipitated triphenylphosphine oxide followed by distillation under reduced pressure gave ethyl cis-cinnamyl sulfide[5] (0.75 g, 4.2 mmol) in 84 % yield.

Typical synthetic examples of unsymmetrical sulfides are shown in the Table.

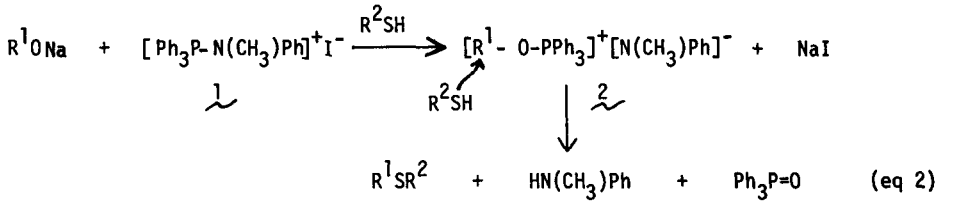
TABLE Synthesis of Unsymmetrical Sulfides (R^1SR^2) from Reactions of Alcohols (R^1OH) with Thiols (R^2SH) by Utilizing Aminophosphonium Salt 1[a]

Run	R^1OH R^1	R^2SH R^2	Product[5]	Isolated Yield %
1	C_2H_5	$PhCH_2$	$C_2H_5SCH_2Ph$	80
2		$PhCH_2$		77
3		Ph		81[b]
4	cis-PhCH=CH-CH_2	C_2H_5	cis-PhCH=CH-$CH_2SC_2H_5$[c]	84
5	trans-PhCH=CH-CH_2	C_2H_5	trans-PhCH=CH-$CH_2SC_2H_5$[c]	90
6		Ph		88
7	CH_2=CH-$CH(CH_3)$	$(CH_3)_3C$	CH_2=CH-$CH(CH_3)SC(CH_3)_3$[c]	64
8	CH_2=CH-$CH(CH_3)$	CH_2=CH	CH_2=CH-$CH(CH_3)SCH$=CH_2[c]	52
9	Ph-C≡C-CH_2	C_2H_5	Ph-C≡C-$CH_2SC_2H_5$	88

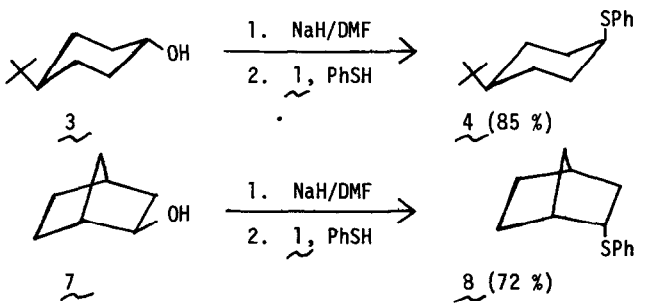
[a] The reaction was carried out in DMF at room temperature for 8 hr. [b] Glpc yield, distillation gave a mixture of dicyclopropylcarbinyl and 1-cyclopropyl-but-3-enyl phenyl sulfides. [c] Isomeric purity was 100 % by glpc (CW-20M).

This method is applicable to various thiols such as alkyl, benzyl, phenyl, t-butyl and vinyl thiols. Cyclopropyl (run 2) and dicyclopropylcarbinyl (run 3) alcohols were converted into the corresponding sulfides in good yields. Further, cis- and trans-cinnamyl alcohols (run 4 and 5) and geraniol (run 6) led to the corresponding cis- and trans-cinnamyl sulfides and geranyl sulfide with retention of configuration. Any allylic rearrangement could not be detected during the reactions of allyl and propargyl alcohols (run 4-9).

These results can be rationalized by assuming that alkoxyphosphonium salt 2[6] would be a key intermediate, which we recently proposed in the synthetic reaction of amines from alcohols by utilizing 1[4]. Nucleophilic attack of added thiols (R^2SH) at the carbon of the alkoxy group of 2 would afford sulfides (R^1SR^2) along with triphenylphosphine oxide and N-methylaniline as shown in eq 2.



Nucleophilic displacement of an alkoxyphosphonium salt by a counter thiolate ion has recently been documented by Downie[6] and Hata[7]; however, in this reaction the counter ion of N,N-methylphenylamide initially formed is apparently innert, and added thiols react with salt 2 exclusively. To gain further insight into this reaction, we investigated the steric course of the present reaction using isomers of 4-t-butylcyclohexanol and 2-norbornanol. When trans-4-t-butylcyclohexanol (3) was allowed to react with 1 and thiophenol in DMF at 60° for 4 hr, phenyl cis-4-t-butylcyclohexyl sulfide[8] (4) was obtained stereospecifically in 85 % yield, while cis-alcohol 5 gave trans-sulfide[9] 6 in 90 % yield. 2-Norbornanol can also be converted into the corresponding sulfide stereospecifically. Thus, treatment of exo-2-norbornanol (7) with 1 and thiophenol at 25° for 4 hr afforded phenyl endo-2-norbornyl sulfide[10] (8) in 72 % yield, while endo-2-norbornanol (9) afforded exo-2-norbornyl sulfide[11] 10 in 87 % yield. endo-Norbornyl sulfides are hardly accessible, since norbornyl skeleton is liable to rearrange[3,12]; therefore, Diels-Alder reactions have been employed for selective synthesis of endo-norbornyl sulfides.[13]



3 4 (85 %)

7 8 (72 %)

These stereochemical results clearly indicate that the sulfuration proceeds with complete inversion of configuration via nucleophilic attack[14] of an added thiol at the carbon of alkoxyphosphonium salt.

REFERENCES AND NOTES

1) (a) D. Seebach, Angew. Chem. internat. Edit., 8, 639 (1969); D. Seebach and M. Kolb, Chem. and Ind., 687 (1974); (b) C. R. Johnson and J. E. Keiser, Org. Syn., 46, 18 (1966); (c) E. J. Corey and M. Jautelat, Tetrahedron Lett., 5787 (1968); (d) H. Kwart and T. J. George, Chem. Commun., 433 (1970).

2) (a) nucleophilic subsutitution: M. E. Peach, "The Chemistry of the Thiol Group," S. Patai, Ed., Interscience, New York, N. Y., 1974, p 725; P. A. Grieco, Chem. Commun., 486 (1972),

(b) alkylation of sulfenyl chlorides: M. S. Kharash and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, 1954, p 1274; (c) desulfuration of disulfides: C. G. Moore and B. R. Trego, J. Chem. Soc., 4205 (1962).

3) P. de Mayo, "Molecular Rearrangements," John Wiley & Sons, Inc., New York, N. Y., 1963, Chapter 2,3,4.

4) Y. Tanigawa, S.-I. Murahashi, and I. Moritani, Tetrahedron Lett., 471 (1975).

5) All products exhibited satisfactory spectral and analytical data.

6) Recently, Downie isolated tris(dimethylamino)alkoxyphosphonium hexafluorophosphates, which react with potassium thiophenoxides to give thiophenylethers. [I. M. Downie, H. Heaney, and G. Kemp, Angew. Chem. internat. Edit., 14, 370 (1975), see also B. Castro, Y. Chapleur, and B. Gross, Tetrahedron Lett., 2313 (1974).]

7) Recently, Hata reported a method for synthesis of sulfides from alcohols and disulfides by utilizing phosphines. [I. Nakagawa and T. Hata, Tetrahedron Lett., 1409 (1975).]

8) The nmr spectrum of 4 [bp 112-115°/2.5 mm, mass (m/e) 248] included 5 phenyl H at 7.10-7.37 (m), 1 equatorial methyne H attached to sulfur atom at 3.50-3.67 (m), 1 methyne and 8 methylene H at 1.22-2.10 (m) and 9 methyl H at 0.87 (s) ($CDCl_3$,δ), respectively.

9) The nmr spectrum of 6 [bp 120-125°/2.0 mm, mass (m/e) 248] was as follows ($CDCl_3$,δ): 5 phenyl H at 7.10-7.43 (m), 1 axial methyne H attached to sulfur atom at 2.83-3.17 (m), 1 methyne and 8 methylene H at 0.93-2.33 (m) and 9 methyl H at 0.80 (s), respectively. The homogeneity of 4^8 and 6 was indicated by glpc analysis (CW-20M).

10) The nmr spectrum of 8 [bp 118-121°/2.0 mm, mass (m/e) 204] was as follows (CCl_4,δ): 5 phenyl H at 7.04-7.40 (m), 1 exo-methyne H attached to sulfur atom at 3.50 (d-d-d, J=11, 6 and 4 Hz) and 2 methyne and 8 methylene H at 0.92-2.44 (m), respectively.

11) The nmr spectrum of 10 [bp 122-124°/2.0 mm, mass (m/e) 204] was as follows (CCl_4,δ): 5 phenyl H at 7.00-7.28 (m), 1 endo-methyne H attached to sulfur atom at 3.10 (d-d-d, J=8, 5 and 2 Hz) and 2 methyne and 8 methylene H at 1.02-2.40 (m), respectively. The homogeneity of 8^{10} and 10 was indicated by glpc analysis (CW-20M).

12) Weinberg reported that endo-2-norbornylbromide was prepared only to an extent of 11.9 % yield by the reaction of exo-2-norbornanol with triphenylphosphinedibromide in triglyme. [J. P. Schaefer and D. S. Weinberg, J. Org. Chem., 30, 2639 (1965).]

13) D. I. Davies and P. J. Rowley, J. Chem. Soc. C, 1832 (1968).

14) O. Mitsunobu, M. Wada, and T. Sano, J. Amer. Chem. Soc., 94, 679 (1972).