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STEREOSPECIFIC DISPLACEMENT OF SULFUR FROM CHIRAL CENTERS. ACTIVATION VIA THIAPHOSPHONIUM SALTS.

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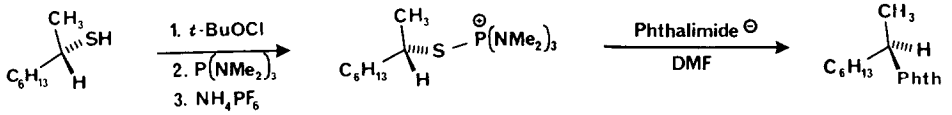
Summary: The first general method for direct displacement of sulfur from chiral carbon centers has been developed. Chiral mercaptans are readily converted to the corresponding thiaphosphonium salts by treatment with t-butyl hypochlorite and hexamethylphosphorous triamide. Metathesis with ammonium hexafluorophosphate provides stable, isolable, crystalline salts which undergo clean nucleophilic diplacement with a variety of heteroatom and carbon based nucleophiles, affording products in which the stereochemistry has been inverted.

Organosulfur chemistry has played an important role in the development of new synthetic methodology for controlling selective carbon-carbon bond formation and the introduction of various functionality.[2] Chiral sulfoxides have been employed to transfer chirality from sulfur to adjacent carbon centers,[3] however, this methodology has been limited by the inability to stereospecifically remove the sulfur auxiliary from the chiral carbon center which has been created. We have developed mild, efficient and general methodology for activating chiral carbon-sulfur bonds towards nucleophilic diplacement with a variety of nucleophiles, in order to effectively elaborate molecules into which chirality has been introduced.

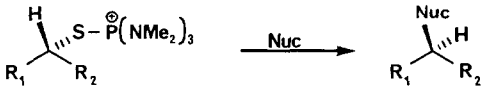
We have found that mercaptans can be converted easily to the corresponding thiaphosphonium salts[4] by successive treatment with t-butyl hypochlorite and tris-(dimethylamino)phosphine, followed by metathesis with ammonium hexafluorophosphate or sodium tetrafluoroborate (eq. 1).[5] These thiaphosphonium salts readily dissolve in organic solvents (e.g. THF, CH_2Cl_2, DMF) and in most instances, cleanly participate in nucleophilic displacement reactions.[6]

(eq.1) 

$[\alpha]_D^{20} = -22.5°$ lit. $[\alpha]_D^{20} = -24.9°$

The displacement reactions[7] occur for a variety of primary and secondary thiaphosphonium salts, proceeding with inversion of stereochemistry. For example, phthalimide cleanly displaces tris-(dimethylamino)phosphine sulfide from the (S)-2-octyl salt, providing (R)-2-phthalimidooctane (eq 1). A broad range of other nucleophiles participate in this displacement reaction, including halides, thiocarboxylate anions, stabilized carbanions, and certain copper and hydride reagents. Representative displacement reactions are presented in Table I.

Table 1



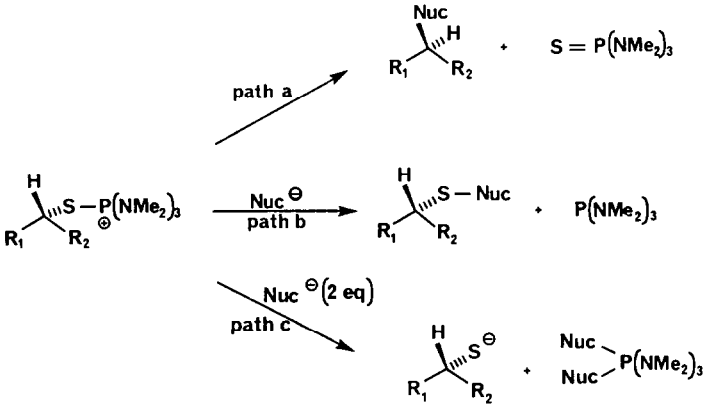
Entry	R1	R2	Nucleophile	Yield (%)[a,b]
1	Ph	H	Phthalimide	79
2	C_7H_{15}	H		83
3	C_6H_{13}	CH_3		79 (66[c])
4	cyclohexyl			<15
5	Ph	H	Br^-	98
6	C_7H_{15}	H		96
7	C_6H_{13}	CH_3		88
8	cyclohexyl			<15
9	CO_2Et	H		95
10	C_7H_{15}	H	N_3^-	79[c]
11	Ph	H	$-CH(CO_2Et)_2$	68
12	C_7H_{15}	H		72
13	C_6H_{13}	CH_3		81 (55[c])[d]
14	Ph	H	Me_2CuLi	93
15	C_7H_{15}	H		77
16	Ph	H	$LiBH_4$	81
17	C_7H_{15}	H		28
18	C_7H_{15}	H	CH_3COS^-	89[c]

[a]Yields were determined by gpc unless otherwise noted.
[b]All products were correlated with authentic material.
[c]Isolated yields. [d]See footnote #8.

Several entries in Table I warrant additional comment. The cyclohexylthiaphosphonium salt gave lower yields of displacement products due to competing elimination. Efficient displacement reactions at carbon with organometallic reagents were limited to MeCu and Me_2CuLi. More elaborate alkyl, aryl or vinyl copper reagents and the higher order, mixed cuprates $R_2Cu(CN)Li_2$ all participated preferentially in sulfenylation reactions (vide infra). $LiBH_4$ was the most effective hydride reagent. More reactive hydride reagents ($LiEt_3BH$) resulted in rapid formation of $(Me_2N)_3P{=}S$, but provided poor yields of displacement products.

These thiaphosphonium salts manifest apparent electrophilic reactivity at three contiguous sites, as illustrated in Scheme I. In addition to the desired displacement mode (path **a**) in which nucleophilic attack occurs at carbon, we have observed formation of sulfides and phosphine (path **b**) for reactive nucleophiles such as alkyl lithium reagents, and formation of the original mercaptans (path **c**) for reactions involving fluoride, cyanide, alkoxides or ketone enolates as nucleophiles. Path **b** may involve direct sulfenylation of the alkyl lithium nucleophiles, or may proceed via attack at phosphorus, generating a phosphorane intermediate[9] which suffers reductive elimination to form sulfide. It is likely that path **c** also involves the intermediacy of a phosphorane, which subsequently expels mercaptide.[10]

Scheme I



Current efforts are focusing on elucidation of mechanistic aspects of these reactions and on exploitation of this methodology in asymmetric synthesis of important chiral molecules.

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References and Notes.

1. Recipient of an American Cancer Society Junior Faculty Research Award, 1983-1986.

2. See for example: B. M. Trost, Acc. Chem. Res. **1978**, 11, 453; E. Vedejs and G. A. Krafft, Tetrahedron **1982**, 38, 2857. E. Vedejs, Acc. Chem.Res. **1984**, 17, 358-64.

3. See for example: a. G. Solladie, Synthesis **1981**, 185; b. G. Solladie in "Asymmetric Synthesis", Vol. 2, p. 184, (J. D. Morrison and J. W. Scott, eds.), Academic Press, New York, **1984**; c. G. H. Posner in "Asymmetric Synthesis", Vol. 2, p. 225, (J.D. Morrison and J.W. Scott, eds.), Academic Press, New York, **1984**; d. M. R. Barbachyn and C.R. Johnson in "Asymmetric Synthesis", Vol. 4, p. 227, (J. D. Morrison and J. W. Scott, eds.), Academic Press, New York, **1984**.

4. Thiaphosphonium salts of HMPT and PPh_3 have been prepared previously. See for example: a. D. N. Harpp and J. G. Gleason, J. Amer. Chem. Soc. **1971**, 93, 2437-2445; b. J. R. Corfield and S. Tripett, J. Chem. Soc.(C) **1971**, 334-336; c. H. Ohmori, S. Nakai, M. Sekiguchi and M. Masui, Chem. Pharm. Bull. **1980**, 28, 910-916.

5. A typical experimental procedure for the formation of the thiaphosphonium salt derived from ethyl-2-mercaptoacetate illustrates the ease of salt formation. Ethyl 2-mercaptoacetate (220 μL, 240 mg, 2.0 mmol) was dissolved in 7mL THF, cooled to -40°C under nitrogen and treated with t-butyl hypochlorite (250 μL, 230 mg, 2.1 mmol). After stirring for 10 min., freshly distilled tris(dimethylamino)phosphine (360 μL, 325 mg, 2.0 mmol) was added. After stirring for an additional 4 min., a white precipitate was observed. The solution was poured into 5 mL H_2O, the aqueous layer washed with diethyl ether (2x5 mL), and then treated with $NaBF_4$ (440 mg, 4.0 mmol) dissolved in 5 mL H_2O. The solution remained homogeneous and was extracted with CH_2Cl_2 (3x5 mL). The combined extracts were washed with 5 mL H_2O, dried over Na_2SO_4, and evaporated. Recrystallization from CH_2Cl_2/Et_2O gave 600 mg (81%) of the thiaphosphonium salt as colorless plates. M.P. 81-82° C. I.R. (nujol): 1740, 1190, 1150, 1050, 990, 755, 680 cm^{-1}. NMR ($CDCl_3$) 1.33 (t, 7 Hz, 3H), 2.88 (d, 12 Hz, 18H), 3.70 (d, 16 Hz, 2H), 4.22 (q, 7 Hz,2H).

6. Displacement reactions involving analogous thiaphosphonium intermediates that were not isolated have been noted in several instances. a. R. G. Weiss and E. I. Snyder, J. Chem. Soc. Chem. Comm. **1968**, 1358-1359; D. H. R. Barton, G. Page and D. A. Widdowson, J. Chem. Soc. Chem. Comm. **1970**, 1466; b. D. N. Harpp and B. A. Orwig, Tetrahedron Lett. **1970**, 31, 2691-2694; c. D. N. Harpp, J. Adams, J. G. Gleason, D. Mullins and K. Stelieu, Tetrahedron Lett. **1978**, 42, 3989-3992.

7. A typical displacement reaction was carried out as follows:
Diethyl malonate (455 μL, 480 mg, 3.0 mmol) was added to a slurry of degreased sodium hydride (144 mg, 50%, 3.0 mmol) in 10 mL dry DMF. After hydrogen evolution was complete, the 1-octyl BF_4 salt (395 mg, 1.0 mmol) was added and the mixture stirred under nitrogen at 60°C for 6 hr. The mixture was cooled, treated with 15 mL H_2O and extracted with diethyl ether (3 x 10 mL). The combined ether extracts were washed with H_2O (2x5 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on a silica gel column, eluting with 18:1:1 hexanes, CH_2Cl_2, Et_2O, providing 152 mg (66%) of Diethyl octylmalonate.

8. The stereochemistry of this product was determined by decarboxylative conversion to (R)-3-methylnonanoic acid. $[\alpha]_D^{20}$ = +4.70; lit, $[\alpha]_D^{20}$ = +5.10. A. I. Meyers, J. Slade, R. K. Smith, E. Mihelich, F. M. Hershenson and C. D. Liang, J. Org. Chem., **1979**, 44, 2247-2249.

9. Corfield and Tripett (Reference 4b) reported that treatment of Et-S-$\overset{+}{P}Ph_3$ with tolyl lithium gave both Et-S-Ph and Et-S-Tolyl, implicating an intermediate phosphorane in this process.

10. Barton and co-workers (D. H. R. Barton, D. P. Manly and D. A. Widdowson, J. Chem. Soc. Perkin I **1975**, 1568-1574) reported that $Bu_3\overset{+}{P}$-S-Me + $PhCH_2O^- \rightarrow PhCH_2SMe + Bu_3P{=}O$, presumably via $Bu_3P(SMe)OCH_2Ph$, expulsion of MeS^- and subsequent nucleophilic attack by MeS^- at the benzylic carbon.

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