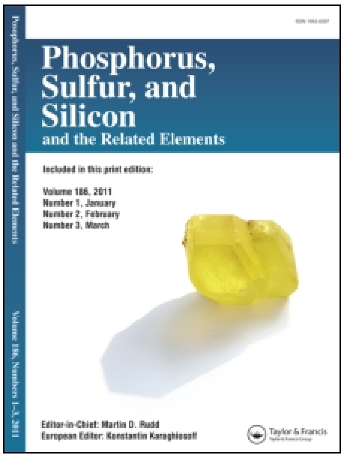

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The Synthesis of Unsymmetric and Symmetric Disulfides

Andrew L. Ternay Jr.[a]; Charles Cook[a]; Ewa Brzezinska[a]
[a] The Center for Medicinal Chemistry Research, Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington, Texas, U.S.A.

To cite this Article Ternay Jr., Andrew L. , Cook, Charles and Brzezinska, Ewa(1994) 'The Synthesis of Unsymmetric and Symmetric Disulfides', Phosphorus, Sulfur, and Silicon and the Related Elements, 95: 1, 351 — 352
To link to this Article: DOI: 10.1080/10426509408034234
URL: http://dx.doi.org/10.1080/10426509408034234

Phosphorus, Sulfur, and Silicon, 1994, Vol. 95-96, pp. 351-352
Reprints available directly from the publisher
Photocopying permitted by license only

THE SYNTHESIS OF UNSYMMETRIC AND SYMMETRIC DISULFIDES

ANDREW L. TERNAY, JR., CHARLES COOK AND EWA BRZEZINSKA
The Center for Medicinal Chemistry Research, Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington, Texas 76019, U.S.A.

Abstract The disulfide of 2-mercaptobenzothiazole is shown to be useful for the preparation of a wide variety of unsymmetric and symmetric disulfides.

INTRODUCTION

The synthesis of unsymmetric disulfides continues to be of interest, particularly because of their pharmaceutical value and biochemical importance. While numerous routes are available to such disulfides, reaction conditions may not be very mild, functional group incompatibilities may exist, reagents may be expensive and desired products may be difficult to isolate. Since symmetric disulfides often are easy to prepare, we have examined the use of symmetric disulfides in the preparation of unsymmetric disulfides. After evaluating several alternatives, we have elected to define the role and scope of the disulfide of 2-mercaptobenzothiazole $(BTS)_2$ in the preparation of both unsymmetric and symmetric disulfides. (The latter corresponds to direct oxidation of a thiol with $(BTS)_2$.)

RESULTS AND DISCUSSION

A variety of thiols (RSH) react with $(BTS)_2$ in a two step process. The first forms an unsymmetric disulfide, BT-S-S-R. These often are solids which can easily be purified by recrystallization. In turn, they can react with a second thiol (RSH or R'SH) to form either a symmetric (R-S-S-R) or an unsymmetric (R-S-S- R') disulfide. The first formed unsymmetric disulfide contains the BT fragment while the second does not.

The preparation of BT-S-S-R often can be accomplished in chloroform at 20-25 °C. Reaction is often complete within two hours. The by-product BTSH is then removed with a mild alkaline wash. Isolated yields of desired products generally range from 75-97%, with the majority of reactions affording products in > 85% yield. The purity of isolated products generally is greater than 98% as determined by hplc. Hplc analysis of crude reaction products indicates that crude reaction yields are generally > 95% with purities >95%. For systems where the RSH has little solubility in chloroform but significant water solubility, a mixed solvent system (often ethanol/chloroform/water) has proven valuable. Functional groups/fragments which have been found to be compatible with this scheme include the following: OH; O-alkyl; C=C; CO_2H; CO_2R; NHAc; CX_3; halogen; SO_3^-; and NH_2. (This list is not comprehensive.)

This first step has two minor drawbacks. First, it may produce lower yields when R is, itself, part of a heterocyclic thioamide. For example, yields are lower when RSH is 2-mercaptopyridine. This results from an obvious equilibration. Second, the presence of an amine hydrochloride (-NH_3^+ Cl^-) within R also lowers the yield and purity. This was demonstrated by, among other things, adding triethylammonium chloride to the reaction of p-methoxythiophenol and $(BTS)_2$ and noting a lowering of the isolated yield of the desired BT-S-S-$C_6H_4OCH_3$. (Symmetric disulfide amounts increase.) The reaction of $(BTS)_2$ with 1 mole of 2-mercaptoethylamine (MEA) hydrochloride produced only minor amounts of the desired BT-S-S-MEA HCl, the main product being the symmetric disulfide cystamine dihydrochloride.

The disulfides BT-S-S-R can be reacted with a second thiol, R'SH. This process can again be carried out in several solvents, depending upon the natures of R and R'. This second step may require as long as 18-24h, reflecting the relative weakness of the S-S bond in $(BTS)_2$ compared to BTSSR. As with the first step, this second displacement of BTSH generally occurs in excellent yields. It is not unusual to obtain overall isolated yields in the two steps which exceed 85%, and overall yields >90% have been observed.

The utility of these two processes can be emphasized by noting that several reactions produced analytically pure samples (C,H and S) after a simple wash was used to remove BTSH.

The procedure also can be used to create symmetric disulfides under rather mild conditions. One example involves the oxidation of MESNA, $HSCH_2CH_2SO_3^-$ Na^+. Attempted oxidation of MESNA with DMSO at 90 °C produced approximately 20% of the desired symmetric disulfide after 18h. An isolated yield of 98% of "di-MESNA" was obtained using $(BTS)_2$ at 20°C after 2h.

In order to prepare disulfides containing an NH_3^+ fragment in excellent yields and under mild conditions, we have employed the reaction of MeOC(O)S-R' with RSH. When the cationic fragment is located in R' the resulting salt can be stored for months in a freezer (≈ -10°C) and it reacts rapidly with RSH to give the desired R-S-S-R'.

SUMMARY

$(BTS)_2$ is an excellent reagent for the preparation of unsymmetric disulfides which either contain or lack the BT fragment. It also is well suited for the direct oxidation of a thiol to its symmetric disulfide.