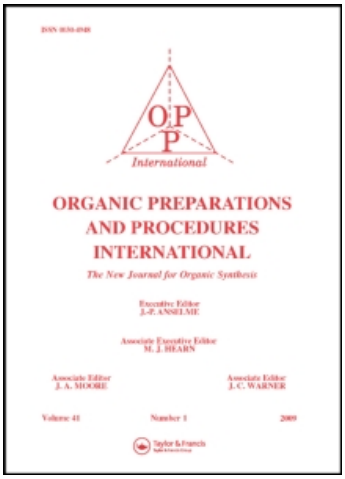

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A FACILE SYNTHESIS OF DISULFIDES BY OXIDATION OF THIOLS WITH *bis*(TRICHLOROMETHYL) CARBONATE AND TRIPHENYLPHOSPHINE OXIDE

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A FACILE SYNTHESIS OF DISULFIDES BY OXIDATION OF THIOLS WITH *bis*(TRICHLOROMETHYL) CARBONATE AND TRIPHENYLPHOSPHINE OXIDE

Submitted by (08/06/03)

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Disulfides are useful intermediates because of their use in a variety of chemical transformations.[1,2] They are also important organic compounds in their own right being incorporated in molecules of biological interest.[3] Numerous methods have been reported for the preparation of disulfides, such as the reaction of sodium disulfide with haloalkanes,[4] the oxidation of thiols,[5] oxidation of sodium alkyl thiosulfate by hydrogen peroxide,[6] reductive coupling of sulfonyl chlorides by piperidinium tetrathiotungstate,[7] sodium cyanoborohydride,[8] aluminium triiodide,[9] etc. However, these methods are commonly used in research laboratories and cannot be applied in industry because the reagents are expensive and/or the yields are low. Triphenylphosphine is used in the stoichiometric amount on an industrial scale in the Wittig reaction to prepare compounds such as vitamin A, and is thus oxidized to triphenylphosphine oxide. Since the extremely stable triphenylphosphine oxide has only few uses, and can be disposed of only with difficulty, there have been numerous attempts to reduce it to triphenylphosphine. Direct reduction using strong reducing agents such as alanates and silanes is too costly. Although chlorination of triphenylphosphine oxide with the less costly phosgene[10] gives triphenylphosphine dichloride, it is still an economically unsatisfactory process. In addition, phosgene is a highly toxic and dangerous gas and thus its transportation and storage pose considerable dangers.

bis(Trichloromethyl) carbonate (BTC), however, is a crystalline, stable solid (mp. 79-80°C, bp. 205-207°C, only slight decomposition to phosgene occurs at its boiling point[11]), which is easy to handle, transport and store. Here we report a new method for the preparation of disulfides by oxidation of thiols using BTC-triphenylphosphine oxide-triethylamine. It is not only a good method for the synthesis of disulfides but also a convenient means for the reduction of triphenylphosphine oxide to triphenylphosphine. *Table 1* shows that the oxidation of thiols using the BTC-triphenylphosphine oxide-triethylamine system is complete within 4-8 hrs and gives the disulfides, triphenylphosphine and triethylammonium chloride in good yields.

$$Cl_3COCOOCCl_3 + 3Ph_3PO \longrightarrow 3Ph_3PCl_2 + 3CO_2$$

$$Ph_3PCl_2 + 2RSH + 2Et_3N \longrightarrow Ph_3P + RSSR + 2Et_3N{\cdot}HCl$$

In conclusion, the work described herein provides a useful method for the preparation of disulfides and for the reduction of triphenylphosphine oxide. Further studies on applications of BTC are now in progress in our laboratory.

EXPERIMENTAL SECTION

Thiols were supplied by Zhejiang Shou & Fu Chemicals Ltd. Triphenylphosphine oxide, BTC, triethylamine and chloroform were obtained from commercial sources. Melting points were obtained on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC-80 spectrometer using $CDCl_3$ with tetramethylsilane as an internal standard.

General Procedure: To a solution of triphenylphosphine oxide (0.278 g, 1 mmol) in 1 mL chloroform in a three-neck 25 mL flask was added a solution of BTC (0.1 g, 0.33 mmol) in 1 mL chloroform at room temperature. After the mixture was magnetically stirred for an hour, the thiol (2 mmol) and triethylamine (2.2 mmol) were added in one portion to the mixture at room temperature respectively. Then the mixture was heated at reflux (see *Table 1*). After the reaction was complete, the mixture was washed with water (10 mL x 2) and triethylammonium chloride was obtained by evaporation of the aqueous phase. The organic phase was dried and the solvent was removed under reduced pressure. The crude products were purified by column chromatography on silica gel (20:1 cyclohexane-ethyl acetate as eluent) led to the disulfides and triphenylphosphine respectively.

Table 1. Disulfides by Oxidation of Thiols[a]

RSSR R	Yield[b] (%)	mp. (°C)	Lit.mp. (°C)	Time (hrs)	Ph_3P [b] (%)	Et_3N•HCl[b] (%)
C_6H_5	80	59-60	60[12]	6	65	92
2-ClC_6H_4	83	86-87	87-88[13]	4	68	93
4-ClC_6H_4	82	70-71	72[8]	4	67	91
2-$CH_3C_6H_4$	90	35-36	37-38[13]	7	72	96
4-$CH_3C_6H_4$	85	45-46	48[8]	7	70	93
4-$CH_3OC_6H_4$	86	118-119	120[13]	6	71	94
2-BrC_6H_4	83	97	97-98[13]	8	70	90
4-BrC_6H_4	84	93-95	94[8]	8	72	93
2,4,6- $(CH_3)_3C_6H_2$	82	124-126	125[14]	8	71	90
$C_6H_5CH_2$	76	70-72	71[14]	8	66	91

a) All reactions were carried out at the same molar ratio, RSH: BTC: Ph_3PO:Et_3N = 6: 1.05: 3:6.
b) Yields based on starting thiols, triphenylphosphine oxide and triethylamine respectively.

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A MILD AND EFFICIENT METHOD FOR RACEMIZATION OF α-AMINO ESTERS

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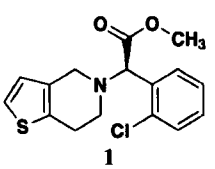
Racemization is an important reaction, whose importance is often overlooked. In industry, a number of enantiomerically pure compounds are produced by diastereomeric salt crystallization, leaving 50% of the undesired isomer. Racemization of this unwanted isomer followed by further kinetic resolution when repeated can lead to the maximum obtainable yield approaching 100%.[1] We became interested in the racemization of clopidogrel (**1**),[2] a tertiary amino ester, which is used to inhibit platelet-aggregation and for its anti-thrombotic effect; the *dextro* rotatory (*S*) form of the compound is marketed as its hydrogen sulfate salt. After separation of the (*S*) enantiomer as a diastereomeric salt, the remaining (*R*) enantiomer has to be recycled. There is no reported method for carrying out this process other than separation of the (*R*) enantiomer as its diastereomeric salt from the (*R*)-enriched mixture.[3]

A survey of methods for the racemization of α-amino esters showed that those having primary amino group have been racemized *via* Schiff base formation when heated in presence of ketones.[4] There are also reports of this reaction having been performed in presence of carboxylic acids[5] or with tertiary amines.[6] However, this methodology is not applicable to tertiary amines such as clopidogrel. If a strong base such as sodium hydride or sodium ethoxide is used, then special care needs to be exercised to prevent hydrolysis and transesterification.[7-8]



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