Stereoselective Synthesis of *trans*-2-Alkylthiane 1-Oxides

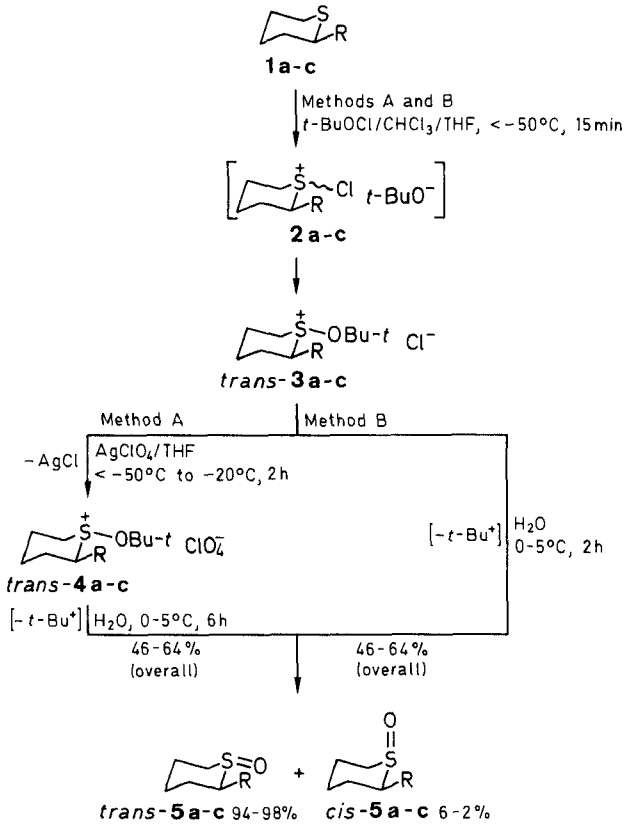
I. Jalsovszky,*[a] F. Ruff,[a] M. Kajtár-Peredy,[b] A. Kucsman[a]

[a] Institute of Organic Chemistry, Eötvös University, H-1518 Budapest 112, P.O. Box 32, Hungary

[b] Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, P.O. Box 17, Hungary

2-Alkylthianes react with *tert*-butyl hypochlorite to give *trans*-1-*tert*-butoxythianium salts which are hydrolyzed to trans-2-alkylthiane 1-oxides with high stereoselectivity.

tert-Butyl hypochlorite is known to be an excellent reagent for the conversion of sulphides to sulphoxides.[1-3] The reaction of *tert*-butyl hypochlorite with alkylthianes or alkylthiolanes can be used for the stereoselective synthesis of *cis*-sulphoxides if carried out in methanol or isopropyl alcohol containing solid sodium carbonate.[1,3,4] On the other hand, the above reaction, when conducted in dichloromethane and followed by basic hydrolysis, results in a mixture of *cis*- and *trans*-sulphoxide stereoisomers.[3] We now report on two stereoselective methods (A and B) suitable to convert 2-alkylthianes **1a–c** into the corresponding *trans*-2-alkylthiane 1-oxides **5a–c** in fairly good (46–64%) yields.



a R = Me; **b** R = Et; **c** R = *i*-Pr

Mechanism. – As it has been suggested[5] earlier, the reaction of *tert*-butyl hypochlorite with cyclic sulphides involves chlorosulphonium and alkoxysulphonium ion intermediates with equatorial chloro and axial alkoxy *S*-substituent, respectively, from which the 1-oxides can be formed by basic hydrolysis (S_N2 at sulphur with inversion) or solvolytic decomposition (S_N1-E1 at the alkoxycarbon with retention).[5,6] Since the conversion of chlorosulphonium ion into alkoxysulphonium ion proceeds very fast, only the latter intermediate can usually be isolated or detected. We have now found that 2-alkylthianes **1a–c** are converted by *tert*-butyl hypochlorite (presumably through the chlorosulphonium salts **2a–c**) into *trans*-1-*tert*-butoxy-2-alkylthianium salts *trans*-**3a–c**. These intermediates with equatorial *S*-*tert*-butoxy group are the ones which are solvolyzed stereoselectively in cold water with retention of the sulphur configuration to yield *trans*-sulphoxides *trans*-**5a–c**. The stereoselective formation of salts *trans*-**3a–c** is assumed to be thermodynamically controlled, so that is can be explained by equatorial preference of the bulky 2-alkyl and 1-*tert*-butoxy groups.

Sulphonium Salts. – 2-Isopropylthiane **(1c)** dissolved in cold (– 30 °C) deuterochloroform was treated with an equimolecular amount of *tert*-butyl hypochlorite. The ^{13}C-NMR spectrum of the mixture showed that only *trans*-1-*tert*-butoxy-2-isopropylthianium chloride (*trans*-**3c**) was present, in almost quantitative yield. The assignment of the *trans*-configuration was based on the β- and γ-effects observed, i.e. on the large downfield and smaller upfield shifts of the signals of C-2, C-6 and C-3, C-5, respectively (cf. the chemical shifts of compound *trans*-*3c* given in the experimental part with those of analogous thiane and thiane-1-oxide derivatives in Lit.[3]).

In another run the reaction was carried out in chloroform/tetrahydrofuran. To the cold (– 50 °C) reaction mixture was added an equimolecular amount of silver perchlorate dissolved in tetrahydrofuran. The perchlorate *trans*-**4c** could be isolated as colourless crystals exhibiting much greater stability than the corresponding chloride *trans*-**3c**. The ^{13}C-NMR spectra of *trans*-**3c** and *trans*-**4c** were almost identical, thus indicating the identity of their sulphonium parts.

Hydrolysis. – In an NMR tube, the solution (37 °C) of *trans*-1-*tert*-butoxy-2-isopropylthianium perchlorate (*trans*-**4c**) in $CDCl_3$ was shaken with D_2O. The ^{1}H-NMR spectrum indicated only the presence of *trans*-2-isopropylthiane 1-oxide (*trans*-**5c**). By HPLC analysis,[7] the ratio *cis: trans* was found to be 3:97. On the other hand, treatment of the perchlorate solution with a solution of NaOD in D_2O resulted in a 65:35 mixture of diastereoisomers *cis*-**5c** and *trans*-**5c**, in accordance with our earlier observations.[3] For these hydrolyses, the coformation of both *tert*-butyl alcohol and isobutylene were detected by ^{1}H-NMR analysis: δ = 1.28 [$(CH_3)_3COH$], 1.75 [$(CH_3)_2C{=}CH_2$].

Preparations. – The sulphoxides *trans*-**5a–c** were prepared either from the isolated *tert*-butoxysulphonium perchlorates *trans*-**4a–c** (Method A) or by direct solvolysis of the *tert*-butoxysulphonium chlorides *trans*-**3a–c** (Method B). The Table shows that both Methods are suitable for the conversion of the sulphides **1a–c** into the sulphoxides *trans*-**5a–c**. Further experiments indicated that the yields and diastereoselectivity were neither sig-

Table. Conversion of 2-Alkylthianes **1a–c** into *trans*-2-Alkylthiane 1-Oxides **5a–c**[a]

Product[b]	Method	Yield (%)	IR (film) ν_{SO} (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ_{CH_3}
5a	A	46	1038	1.42 (d)
	B	37		
5b	A	61	1034	1.05 (t)
	B	57		
	B[c]	38		
5c	A	64	1050	1.06 (d), 1.00 (d)
	B	53		

[a] The ratio of *cis* : *trans* diastereoisomers was determined by HPLC;[7] it varied between 6 : 94 and 2 : 98.

[b] Microanalyses, melting points, and ^{13}C-NMR data of the products were identical with those given in Ref. 3.

[c] The solvent was $CHCl_3$ without THF.

nificantly dependent on the Method used nor on the fact whether or not the *tert*-butyl hypochlorite was distilled before use.

For other sulphides it is advisable to check first the applicability of Method B, because decomposition of the *tert*-butoxysulphonium chlorides may proceed faster, even at 0 °C, than their hydrolysis. Unfortunately, both Methods A and B are unsuitable for converting 2-methylthiolane into the *trans*-1-oxide, as rapid decomposition of the 1-*tert*-butoxythiolanium salt occurs. Finally, it should be noted that the yields of sulphoxides decrease by about 20% when the chloroform used as solvent has not been diluted with tetrahydrofuran.

Solvents of commercial quality were purified before use. Chloroform was boiled with P_2O_5 for 2 h, then submitted to fractional distillation. The absence of $COCl_2$ was checked by the $AgNO_3$ test. Tetrahydrofuran was boiled with $LiAlH_4$ for 24 h, then distilled. Pentane was shaken in a separatory funnel with conc. H_2SO_4 (many times), then with 2 N aqueous NaOH, separated, and distilled from P_2O_5 using a column. The experiments were carried out with *t*-BuOCl[8] purified by distillation at room temperature under reduced pressure (*danger*[9]!); however, the same results were obtained when the undistilled reagent prepared by a safer method[10] was used. In both cases, purity was checked by iodometric titration. Silver perchlorate was dried over P_2O_5 and KOH under reduced pressure at 118 °C (boiling BuOH) for 5 h, then used immediately. IR spectra were obtained on a Zeiss IR-75 instrument. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian A-60D and Varian XL-100 instruments. The details of HPLC analyses are described elsewhere.[7]

***trans*-2-Alkylthiane 1-Oxides 5a–c; General Procedure:**

Method A: In a flask equipped with a $CaCl_2$ tube and a magnetic stirrer, *t*-BuOCl (3.257 g, 30 mmol) is added to a cooled (−50 °C) and stirred solution of a sulphide **1a–c** (30 mmol) in $CHCl_3$ (50 mL)/THF (5 mL), followed after 15 min by a solution of $AgClO_4$ (6.427 g, 31 mmol) in THF (15 mL). The mixture is stirred at −20 °C for 2 h, then cooled below −50 °C and centrifuged immediately. The supernatant solution is poured into cold (0 °C) distilled H_2O (100 mL) and this mixture is stirred without external cooling for 6 h. The two layers are separated in a funnel and the aqueous layer is extracted with CH_2Cl_2 (4 × 20 mL). The organic layers are combined, washed with 1 N aq NaOH (15 mL), and dried ($MgSO_4$). After filtration, the solvent is evaporated under reduced pressure and the residue is distilled under reduced pressure to give the sulphoxide **5** (Table).[3]

Method B: As described in Method A, *t*-BuOCl (3.257 g, 30 mmol) is added to a solution of a sulphide **1a–c** (30 mmol) in cooled (−50 °C) $CHCl_3$ (50 mL)/THF (20 mL). The solution is stirred for 15 min, then poured into cold (0 °C) distilled H_2O (100 mL). The resultant mixture is stirred vigorously without external cooling for 2 h, then separated in a funnel, and worked up as in Method A.

***trans*-1-*tert*-Butoxy-2-isopropylthianium Chloride (*trans*-3c):**

tert-Butyl hypochlorite (54 mg, 0.5 mmol) is added to a cold (−30 °C) solution of 2-isopropylthiane (**1c**; 72 mg, 0.5 mmol) in $CDCl_3$ (0.5 mL); then, the ^{13}C-NMR spectrum is recorded at −30 °C.

^{13}C-NMR ($CDCl_3$/TMS): δ = 65.1 (C-2), 23.0 (C-3), 22.6 (C-4), 22.1 (C-5), 48.1 (C-6), 25.4 [$\underline{C}H(CH_3)_2$], 16.5, 19.6 [$CH(\underline{C}H_3)_2$] 93.1 [$O\underline{C}CH_3)_3$], 28.6 [$OC(\underline{C}H_3)_3$].

As the chloride **3c** cannot be isolated at room temperature, the product was not investigated further.

***trans*-1-*tert*-Butoxy-2-isopropylthianium Perchlorate (*trans*-4c):**

In a flask equipped with a $CaCl_2$-tube and a magnetic stirrer, *t*-BuOCl (435 mg, 4 mmol) is added to a cold (−50 °C) stirred solution of 2-isopropylthiane (**1c**, 577 mg, 4 mmol) in $CHCl_3$ (8 mL)/THF (4 mL), followed by a solution of $AgClO_4$ (830 mg, 4 mmol) in THF (4 mL). After 15 min, more $CHCl_3$ (3 mL) is added to the mixture which is stirred at −20 °C for an additional 2 h, then centrifuged immediately in a stoppered tube (to exclude moisture), and filtered under a stream of dry argon. The filtrate is evaporated to 1/5 of its original volume, then pentane (20 mL) is added to the residue to precipitate the perchlorate *trans*-**4c**. The mother liquor is removed by decantation. The solid product is dissolved in $CHCl_3$ (4 mL), and pentane (25 mL) is added in small portions to the stirred solution. The mother liquor is decanted again and the remaining colourless crystals are washed with pentane (3 × 20 mL). The remaining pentane is removed by an intensive stream of dry argon. Since the product is easily decomposed, the temperature must be kept below 5 °C during the whole procedure. Microanalysis cannot be carried out, as the perchlorate explodes when heated. However, the product proved to be free from chloride ion.

^{13}C-NMR ($CDCl_3$/TMS): δ = 66.1 (C-2), 22.1 (C-3), 22.3 (C-4), 22.2 (C-5), 47.6 (C-6), 26.0 [$\underline{C}H(CH_3)_2$], 16.8, 19.6 [$CH(\underline{C}H_3)_2$], 94.0 [$O\underline{C}(CH_3)_3$], 28.4 [$OC(\underline{C}H_3)_3$].

***trans*-2-Isopropylthiane 1-Oxide (*trans*-5c):**

trans-1-*tert*-Butoxy-2-isopropylthianium perchlorate (*trans*-**4c**; 412 mg, 1.3 mmol) is stirred with distilled H_2O (5 mL) for 1 h; then the solution is extracted with CH_2Cl_2 (3 × 5 mL). The organic layer is washed with 1 N aq. NaOH (3 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure; yield: 180 mg (86%).

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