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Note

High-performance liquid chromatography of cyclic sulphilimine and sulphoxide diastereoisomers

ISTVÁN JALSOVSZKY*, GYULA SZÓKÁN, FERENC RUFF and ÁRPÁD KUCSMAN
Institute of Organic Chemistry, Eötvös University, P.O. Box 325, H-1445 Budapest (Hungary)
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Sulphilimines together with sulphoxides, accompanied by an equimolecular amount of *p*-toluenesulphonamide, are formed from sulphides and chloramine-T in solvents containing water (Mann–Pope reaction). As reported earlier[1], the conversion of alkyl aryl sulphides with a chiral alkyl group led to mixtures of diastereoisomers; product distributions were measured by high-performance liquid chromatography (HPLC), using silica as the column packing material[2]. The major diastereoisomers proved to be heterochiral analogues, suggesting different stereochemistry for sulphilimine and sulphoxide formations.

This paper is concerned with the conversion of cyclic sulphides (Fig. 1), more closely with that of 2- or 4-substituted thianes (1a–d and 1e–f) and 2-alkylthiolanes (4a–d). An HPLC procedure has been developed and applied to the separation and determination of the *cis*- and *trans*-isomers of cyclic sulphilimines (2a–f and 5a–d) and sulphoxides (3a–f and 6a–d) formed from the corresponding sulphides. The results make a contribution to the HPLC analysis of organic sulphur compounds and diastereoisomers[2–6]. The comparison of product distributions obtained for the conversion of cyclic and acylic sulphides may also provide a means of establishing the stereochemistry of the Mann–Pope reaction[7,8].

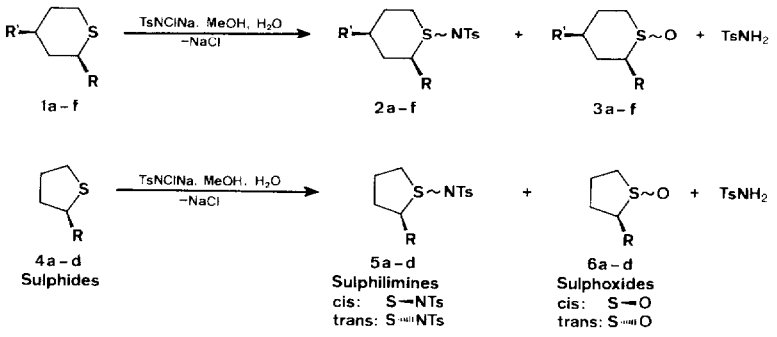

Fig. 1. Conversion of cyclic sulphides to sulphilimines and sulphoxides. R′ = H (a–d), R = CH_3 (a), C_2H_5 (b), iso-C_3H_7 (c) and *tert.*-C_4H_9 (d); R = H (e–f), R′ = *tert.*-C_4H_9 (e), Ph (f).

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TABLE I

SEPARATION OF *CIS- AND TRANS*-ISOMERS OF CYCLIC SULPHILIMINES (2a–f, 5a–d) AND SULPHOXIDES (3a–f, 6a–d)

Relative standard deviation of k' values, 1%.

Sulphide (I)	*p-Toluenesulphonamide*			*Sulphilimines and sulphoxides*					*Eluent** *(v/v)*
	II:k'	*III*:k'	α (R_s)	*IV*:k'	α (R_s)	*V*:k'	α (R_s)	*VI*:k'	
1a	0.35	*cis*-3a	1.31	*trans*-3a	1.33	*cis*-2a	1.20	*trans*-2a	E–P–M (55:36:9)
		1.38	(1.44)	1.81	(1.78)	2.40	(1.36)	2.88	
1b	0.28	*cis*-3b	1.41	*cis*-2b	1.17	*trans*-3b	1.32	*trans*-2b	E–P–M (70:24:6)
		1.70	(2.75)	2.40	(1.24)	2.80	(3.10)	3.70	
1b	0.25	*cis*-3b	1.36	*trans*-3b	1.26	*cis*-2b	1.29	*trans*-2b	E–P–M (55:36:9)
		1.02	(1.41)	1.39	(1.20)	1.75	(1.74)	2.26	
1c	0.25	*cis*-3c	1.29	*cis*-2c	1.33	*trans*-3c	1.13	*trans*-2c	E–P–M (70:24:6)
		1.40	(2.09)	1.80	(2.36)	2.40	(1.66)	2.70	
1d	0.22	*cis*-3d	1.40	*cis*-2d	1.24	*trans*-3d	1.24	*trans*-2d	E–P–M (70:24:6)
		1.03	(1.74)	1.44	(1.39)	1.79	(1.54)	2.22	
1e	0.12	*trans*-2e	1.12	*cis*-2e	2.69	*cis*-3e	1.26	*trans*-3e	E–A (96:4)
		1.30	(0.72)	1.45	(6.51)	3.90	(1.68)	4.90	
1f	0.14	*trans*-2f	1.29	*cis*-2f	2.32	*cis*-3f	1.22	*trans*-3f	E–A (96:4)
		1.70	(1.38)	2.20	(6.00)	5.10	(1.24)	6.20	
4a	0.24	*cis*-6a	1.16	*trans*-6a	1.33	5a**			
		3.70	(1.24)	4.30	(3.30)	5.70			
4a	0.00					*cis*-5a	1.15	*trans*-5a	E–O (90:10)
						12.00	(0.60)	13.80	
4b	0.28	*cis*-6b	1.18	*trans*-6b	1.36	*cis*-5b	1.16	*trans*-5b	E–P–M (70:24:6)
		2.80	(1.44)	3.30	(2.91)	4.50	(1.35)	5.20	
4c	0.17	*cis*-5c	1.21	*cis*-6c	1.20	*trans*-5c	1.27	*trans*-6c	E–A (96:4)
		3.40	(1.64)	4.10	(1.50)	4.90	(2.38)	6.20	
4d	0.53	*cis*-6d	1.52	*trans*-6d	1.65	*cis*-5d	1.11	*trans*-5d	E–P–M (53:43:4)
		2.40	(3.00)	3.64	(3.93)	5.99	(1.48)	6.65	

* Solvents used for elution: A = ethanol (96%); E = diethyl ether; M = methanol; O = 2-octanol; P = pentane.

** The peaks of *cis*- and *trans*-5a are fused.

EXPERIMENTAL

Equipment, packing materials and other conditions

Chromatographic separations were performed using a laboratory-assembled instrument described previously[2]. Hypersil silicas with spherical particles (4.5 and 5 μm) were used as packing materials[2]. Various mixtures of diethyl ether, pentane, methanol, ethanol (96%) and 2-octanol were used as mobile phases. All solvents used were of analytical-reagent grade and were redistilled.

Materials

Authentic samples of the *cis*- and *trans*-isomers of some thiane-1-tosylimides (2a–f)[7–10], thiolane-1-tosylimides (5a–d)[7,8], thiane-1-oxides (3a–f)[7,8,11,12] and thiolane-1-oxides (6a–d)[7,8] were prepared from the corresponding cyclic sulphides (1a–f and 4a–d). Relative configurations were determined by ^{13}C NMR spectroscopic methods[7,8] and X-ray analysis[10,13].

Product distributions, including *cis:trans* ratios, were measured for the crude products obtained by the conversion of cyclic sulphides with chloramine-T[7,8]. To a cooled solution of a sulphide (0.1 mmol) in methanol (80 ml) was added a solution of chloramine-T (0.1 mmol) in water (20 ml) with stirring. The mixture was allowed to stand overnight then the methanol was evaporated *in vacuo* at room temperature. The residue was dissolved in water and the mixture (50 ml) was extracted three times with 10 ml of dichloromethane, dried (magnesium sulphate) and then the solvent was removed by distillation under reduced pressure. As the UV absorbance of cyclic sulphoxides at 220 nm was found to be much smaller than that of sulphilimines, the mixtures of the two compounds obtained were separated using the following procedure. Crude products were carefully dried (20°C, 133 Pa, 20 min), then triturated three times with 5 ml of dry pentane and filtered. The filtrate was evaporated to give the sulphoxide (together with small amounts of *p*-toluenesulphonamide, sulphilimine and sulphide; sample A), while the residue was sulphilimine together with *p*-toluenesulphonamide (sample B). Samples A and B were dissolved in methanol (0.3 and 50 ml, respectively), then 10 μl of each of the solutions were injected.

RESULTS AND DISCUSSION

Experimental data on the chromatographic separations, including capacity factors (k'), separation factors (α) and resolutions (R_s), observed for the *cis–trans* diastereoisomers of some cyclic sulphilimines and sulphoxides are summarized in Table I.

With an increase in polarity, unchanged sulphides (peak I), *p*-toluenesulphonamide (peak II) and diastereoisomeric sulphoxide and sulphilimine products (peaks III–VI) showed selective sorption on the silica adsorbent. Sulphides were usually not retained on the silica adsorbent, and appeared, together with the solvent, as the first peak in the chromatogram.

Under isocratic conditions optimum analysis times (15–30 min; 1 h for 5a) and resolutions were achieved with the instrumentation described previously[2] and with the eluents listed in Table I, Baseline separations required for quantitative analysis were obtained without difficulty (α = 1.1–1.5; R_s = 1.2–3.1).

The optimization of the eluent composition is shown in Table I. The concentration of diethyl ether in the solvent was varied by the addition of different amounts of an alcohol (methanol, ethanol or 2-octanol) and pentane. As found previously for acyclic substrates[2], k' increased with increasing concentration of pentane in the mobile phase, and the k' and α values decreased when a small amount of methanol was added to the eluent. In general, the sulphoxide diastereoisomers were well separated from the sulphilimine analogues, and a separation of the *cis–trans* isomers was also achieved.

As shown in Table I, compounds obtained from 2-alkyl-substituted sulphides (except 4c) were eluted by methanol–diethyl ether–pentane mixtures in the following order: sulphide, sulphonamide, *cis–trans*-sulphoxides and *cis–trans*-sulphilimines; both *cis*-sulphoxides and *cis*-sulphilimines were eluted faster than the *trans*-isomers. The sulphilimine derivative of 2-methylthiolane (*cis–trans*-5a) was separated only if 2-octanol (instead of methanol) was added to the diethyl ether eluent.

For the derivatives of 2-isopropylthiolane (5c and 6c), 4-*tert*.-butylthiane (2e and 3e) and 4-phenylthiane (2f and 3f), the efficiency of the separation was increased by using 96% ethanol instead of pure ethanol. Owing to the increased polarity of the eluent (containing 4% of water), the elution followed a reversed order: the more polar sulphilimines and the *trans*-isomers exhibited lower retentions; with 2-isopropylthiolane derivatives an unusual order of elution, *cis*-5c, *cis*-6c, *trans*-5c and *trans*-6c, was observed.

Using the same eluent and substrates with an identical 2-alkyl group, larger k' values were found for 1-substituted thiolanes than for thiane analogues (see, *e.g.*, 2-ethyl derivatives in Table I). With increasing bulkiness of the 2-alkyl group a decrease in retention occurred.

Quantitative data for diastereoisomeric product distributions[7,8] were obtained by evaluating the chromatograms, which were similar to those shown in ref. 2, Figs. 1–4. For the reaction of 2-ethylthiane (1b) with chloramine-T in methanol–water (80:20), the evaluated product distributions were 2b:3b = 89:11, *cis*-3b:*trans*-3b = 36:64 and *cis*-2b:*trans*-2b = 5:95; the ratio of molar absorptivities at 220 nm was $TsNH_2$:2b:3b = 25.3:28.3:1. Similar product distributions were found in the other reactions investigated. However, the diastereoselectivity was poorer in the conversion of 2-alkylthiolanes. With 2-ethylthiolane (4b), the product distributions 5b:6b = 57:43, *cis*-6b:*trans*-6b = 45:55 and *cis*-5b:*trans*-5b = 37:63 were measured; the ratio of molar absorptivities at 220 nm was $TsNH_2$:5b:6b = 19.9:22.7:1. The standard deviation was 2% "absolute". The diastereoisomeric distributions indicate that cyclic sulphoxide and sulphilimine products are homochiral analogues, suggesting a similar mechanism for their formation. On the other hand, the different stereoselectivities may be accounted for by the participation of the solvent molecules in the reaction yielding sulphoxide.

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