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Enantioselective Synthesis of Thiols by Thione-Thiol Rearrangement Catalyzed by Optically Active Pyridine *N*-Oxides

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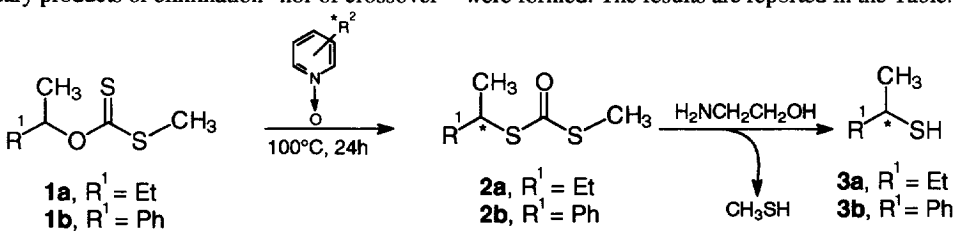
Abstract: Enantiomerically enriched thiols were prepared by rearrangement under mild conditions of racemic carbonodithioic *O,S*-dialkyl esters catalyzed by optically active pyridine *N*-oxides, followed by reaction with 2-aminoethanol of the carbonodithioic *S,S*-dialkyl esters thus formed. Enantioselectivities up to 37.7% was obtained.

The synthesis of non-racemic chiral thiols has not been widely studied. The most significant methods reported in the literature consist of (i) resolution of racemates,[1] (ii) utilization of optically active substrates of both natural[2-5] and non-natural[5-7] origin, and (iii) asymmetric syntheses; examples of the last methods are reported in a recent paper, which describes the use of a chiral synthetic equivalent of hydrogen sulfide.[8] To the best of our knowledge, there are no reports on the synthesis of optically active thiols from racemic sources by asymmetric catalysis. A few years ago, an efficient synthesis of thiols was reported,[9-11] based on a Newman-Kwart-type thione-thiol rearrangement catalyzed by pyridine *N*-oxide and occurring under mild conditions. This prompted us to exploit our experience in the synthesis of optically active substituted pyridines to attempt an enantioselective synthesis of thiols by rearrangement of carbonodithioic *O,S*-dialkyl esters to carbonodithioic *S,S*-dialkyl esters catalyzed by optically active pyridine *N*-oxides.

The racemic starting materials **1a** and **1b** (Scheme 1) were prepared from 2-butanol and 1-phenylethanol, respectively, as described in the literature.[12] The optically active *N*-oxides (Table) were prepared by oxidation with m-chloroperbenzoic acid[13] of the corresponding substituted pyridines. In the case of (*S*)-(–)-3-(1-methyl-2-pyrrolidinyl)pyridine (nicotine) the oxidation afforded a mixture of the two diastereomeric (1'*R*,2'*S*)- and (1'*S*,2'*S*)-3-(1-methyl-2-pyrrolidinyl)pyridine *N,N'*-dioxides (nicotine *N,N'*-dioxide) in the ratio of 0.8:1;[14] this mixture was used as such as a catalyst. The rearrangement reactions of **1a-b** were carried out under argon at 100°C using 50% moles of catalyst; for comparison purposes all the reactions were carried out for 24 h. Products **2a-b** were obtained in fair to good yields; they were subsequently transformed in the corresponding thiols by reaction with 2-aminoethanol.[9,15] In the rearrangement reactions no secondary products of elimination[7] nor of crossover[11] were formed. The results are reported in the Table.



1a, R^1 = Et
1b, R^1 = Ph

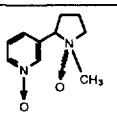
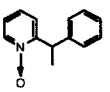
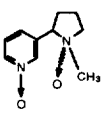
2a, R^1 = Et
2b, R^1 = Ph

3a, R^1 = Et
3b, R^1 = Ph

R^2 = 3-(*N*-Methylpyrrolidinyl *N*-oxide), 2-(1-phenylethyl), 2-myrthanyl

Scheme 1

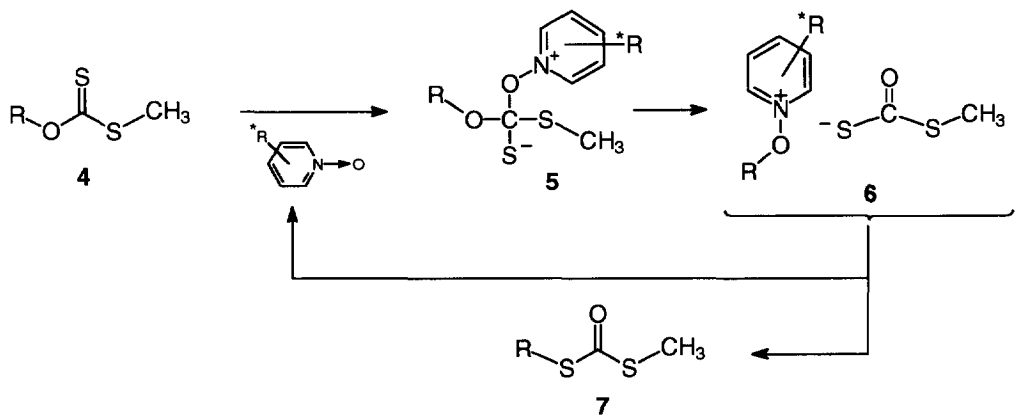
Table: Synthesis of optically active thiols by rearrangement of **1a-b** to **2a-b** catalyzed by pyridine *N*-oxides

Substrate	Catalyst	Conv./%	Carbonodithioic *S,S*-Dialkyl esters		Thiols		
			Product (Yield/%)[a]	$[\alpha]_D^{25}$	Product (Yield/%)[b]	$[\alpha]_D^{25}$	O.p./% (Conf.)
1a		65	**2a** (60)	-26.5	**3a** (55)	-13.2	37.7[c] (*S*)
1a		88	**2a** (80)	<0.1	**3a** (70)	<0.1	<1[c] (*S*)
1a		58	**2a** (50)	-0.1	**3a** (48)	<0.1	<1[c] (*S*)
1b		52	**2b** (49)	-24.8	**3b** (35)	-9.8[d]	11.4[e] (*S*)

[a]Determined by GLC. [b]Determined on the distilled product. [c]$[\alpha]_{Dmax}^{25}$ = -35.0 (Ref. 16). [d]At 20°C. [e]$[\alpha]_{Dmax}^{20}$ = -89.0 (ref. 1, 17).

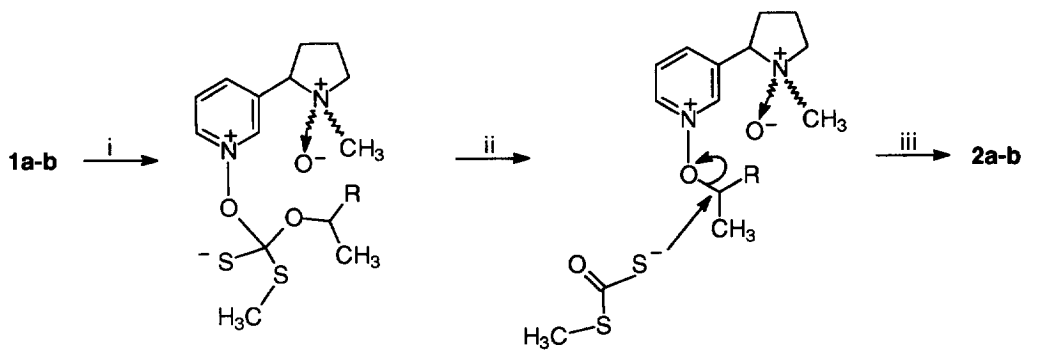
As shown in the Table all the catalysts tested gave asymmetric induction; however, only nicotine *N,N*-dioxide proved to be fairly efficient, affording optical yields up to 37.7%.

K. Harano *et al.* discussed in detail the possible mechanisms of the thione-thiol rearrangement catalyzed by pyridine *N*-oxide;[9,11] among the various hypotheses advanced, the mechanism that best suits our results is that reported in Scheme 2. It involves the nucleophilic attack of pyridine *N*-oxide on the thiocarbonyl carbon of the carbonodithioic *O,S*-dialkyl ester **4** leading to the formation of the zwitterionic intermediate **5**, which subsequently undergoes rearrangement and fragmentation to the alkoxyammonium cation-dithiocarbonate anion pair **6**; internal nucleophilic attack by the dithiocarbonate anion gives the final product **7**.



Scheme 2

According to this scheme, in the case of the reactions catalyzed by nicotine *N,N*-dioxide, which gave the most significant results, the two key intermediates of reaction possess structures **8** and **9** (Scheme 3). Examination of both Scheme 2 and 3 shows that there are three steps which could determine the enantioselectivity: i) formation of **8**; ii) rearrangement-fragmentation of **8** to **9**; iii) transformation of **9** to products. At the present stage of the research we cannot decide which step plays the major role. However, the fact that the best results were obtained under the catalysis of the nicotine *N,N'*-dioxide, *i.e.*, with a pyridine *N*-oxide having the stereogenic center in a more remote position in respect to the reaction center(s) compared to the other catalysts taken into consideration, suggests the intervention of the tertiary *N*-oxide moiety in the enantiodiscriminating step. Such an intervention, however, does not exert catalytic activity, as shown by the results of an independent experiment carried out with *N*-methylpyrrolidine *N*-oxide, in which no rearrangement occurred under our reaction conditions.



Scheme 3

Experimental

General. - Boiling points are uncorrected. GLG analyses were performed on a Perkin Elmer model 8500 instrument equipped with a 30 m silica wide bore column filled with SE-54 (Supelco). Mass spectra were recorded on a Perkin Elmer Ion Trap Detector (ITD) connected to a Perkin Elmer model 8310 gas chromatograph. ^{1}H NMR (300 MHz) spectra of $CDCl_3$ solutions were recorded using a Varian VXR 300s spectrometer. Chemical shifts are reported in ppm downfield from internal Me_4Si; *J* values are given in Hz. Optical rotations were measured on a Perkin Elmer model 241 Polarimeter. HPLC analyses were performed on a Perkin Elmer Series 4 instrument equipped with an UV-VIS variable wavelength detector, using column and conditions described in the literature.[15]

(*S*)-(–)-Nicotine (Aldrich) was used as received. (–)-2-[(1*R*,2*S*)-6,6-dimethylbicyclo[3.1.1.] hept-2-yl]pyridine and (*S*)-(+)-1-phenyl-1-(2-pyridyl)ethane were prepared as previously described.[18] The oxidation of substituted pyridines to the corresponding pyridine *N*-oxides was carried out following a procedure reported in the literature.[14] Physical constants and spectroscopic data for the following three pyridine *N*-oxides used were in agreement with literature data: nicotine *N,N'*-dioxide;[14,15] (–)-2-[(1*R*,2*S*)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl]pyridine *N*-oxide;[19] (*S*)-(+)-1-phenyl-1-(2-pyridyl)ethane *N*-oxide.[20]

Carbonodithioic *O*-(2-Butyl) *S*-Methyl Ester (1a). – Anhydrous dimethylsulfoxide (DMSO) (150 mL) was added under argon to sodium hydride (3.6 g, 0.15 mol) and the mixture was heated at 70-75 °C under stirring for 45 min. After cooling, 2-butanol (7.4 g, 0.10 mol) was added dropwise and the mixture was stirred

at room temperature for 1 h. A solution of carbon disulfide (9.2 g, 0.12 mol) in anhydrous DMSO (25 mL) was then slowly added, keeping the temperature of the reaction vessel under 45 °C with an external ice-water bath. After 1 h stirring at room temperature, a solution of methyl iodide (17 g, 0.12 mol) in anhydrous DMSO (25 mL) was added. The reaction mixture was stirred 1 h at room temperature and then quenched with ice-water. The aqueous phase was extracted three times with hexane (3x50 mL). The combined organic fractions were washed several times with water to remove DMSO, dried (Na_2SO_4) and evaporated. The residue was distilled under reduced pressure, affording **1a** (12 g, 73%), b.p. 70-72 °C at 10 Torr (lit.,[21] b.p. 78 °C at 11 Torr); (Found: C, 43.7; H, 7.1. $C_6H_{12}OS_2$ requires C, 43.85; H, 7.35); ^{1}H NMR δ 0.95 (3H, t, *J* 6.4), 1.38 (3H, d, *J* 5.1), 1.60 - 1.90 (2H, m), 2.55 (3H, s), 5.65 (1H, s, *J* 6.2); MS: *m/z* 164 (M^+).

Carbonodithioic *O*-(1-Phenylethyl) *S*-Methyl Ester (1b). – The above procedure was followed, using 1-phenylethanol (12.2 g, 0.10 mol), to prepare **1b** (16.5 g, 78%), b.p. 73-75 °C at 15 Torr (Found: C, 56.15; H, 5.35. $C_{10}H_{12}OS_2$ requires C, 56.55; H, 5.7); ^{1}H NMR δ 1.52 (3H, d, *J* 6.2), 2.89 (3H, s), 4.92 (1H, q, *J* 6.2), 7.20 - 7.40 (5H, m, Ph); MS: *m/z* 212 (M^+).

Rearrangement of 1a to 2a. – A mixture of **1a** (3 g, 18.2 mmol) and the appropriate pyridine *N*-oxide (9.1 mmol) was heated under stirring at 100°C for 24 h under argon. After cooling, the mixture was diluted with hexane and eluted through a short column of silica gel in order to remove the catalyst. Evaporation of the solvent and distillation under reduced pressure afforded carbonodithioic *S*-(2-butyl) *S*-methyl ester (**2a**) in different yields depending on the catalyst (Table), b.p. 74-76 °C at 10 Torr (lit.,[7] b.p. 86 °C at 14 Torr); ^{1}H NMR δ 0.92 (3H, t, *J* 6.8), 1.34 (3H, d, *J* 5.2), 1.64 - 1.81 (2H, m), 2.52 (3H, s), 3.68 - 3.78 (1H, m,); MS: *m/z* 164 (M^+).

Rearrangement of 1b to 2b. – The above procedure was followed. Distillation under reduced pressure afforded carbonodithioic *S*-(1-phenylethyl) *S*-methyl ester (**2b**), b.p. 70-72 °C at 10 Torr (Found: C, 56.2; H, 5.55. $C_{10}H_{12}OS_2$ requires C, 56.55; H, 5.7); ^{1}H NMR δ 1.52 (3H, d, *J* 6.7), 2.95 (3H, s), 4.91 (1H, q, *J* 6.7), 7.20-7.40 (5H, m, Ph); MS: *m/z* 212 (M^+).

(*S*)-(–)-2-Butanethiol (3a). – A mixture of **2a** (3 g, 18.3 mmol) and 2-aminoethanol (1.5 g, 24.6 mmol) was heated at 70 °C for 10 min. Fractional distillation of the mixture at ambient pressure afforded **3a** (1.39 g, 95%), b.p. 83-84 °C (lit.,[22] b.p. 83 °C at 735 Torr); ^{1}H NMR δ 0.90 (3H, t, *J* 6.8), 1.42 (3H, d, *J* 5.7), 1.44-1.63 (2H, m), 2.92 (1H, s, *J* 5.7). Optical data are reported in the Table.

(*S*)-(–)-1-Phenylethanethiol (3b). – The above procedure was followed, using **2b** (2.8 g, 13.2 mmol). Fractional distillation under reduced pressure afforded **3b** (1.57 g, 93%), b.p. 98-100 °C at 20 Torr (lit.,[23], b.p. 87-88 °C at 15 Torr); ^{1}H NMR δ 1.45 (3H, d, *J* 6.7); 4.85 (1H, q, *J* 6.7); 7.20-7.40 (5H, m, Ph). Optical data are reported in the Table.

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