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Resolution of (1RS, 3RS)-2-N,N′- Dimethyl- aminomethyl-1,3-dithiolane-1,3-dioxide Using Optically Active Acids

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Racemic (1RS,3RS)-2-N,N-dimethylaminomethyl-1,3-dithiolane-1,3-dioxide is resolved by formation of salts with chiral acids [such as (1S)-(+)-10-camphorsulphonic acid, (-)-dibenzoyl-L-tartaric acid, (R)-(-)-mandelic acid]. The best solvent for recrystallization of the diastereomeric mixture is found to be propionitrile and gave 68%ee.

Key Words: Chiral amines, Dithiane, Diastereomeric resolution.

INTRODUCTION

Optically active amines can be obtained in many different ways: by optical resolution, asymmetric synthesis and kinetic resolution. Several methods were used for resolution of amines[1–4]. Pallavicini *et al.*[5] resolved 1-aryl ethylamines with an (S)-isopropylidene glycerol hydrogen phthalate with excellent yield (> 99%) using methanol as a solvent. Toyo'oka *et al.*[6] resolved chiral amines by RP-HPLC using chiral fluorescent derivatization reagents (*i.e.*, DBD-*trans*-4-hydroxy-L-proline, DBD-*cis*-4-hydroxy-L-proline, etc.). These reagents were reacted with chiral amines to produce a couple of diastereomers. Then diastereomers were separated by reversed-phase chromatography.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) and ^{13}C spectra were recorded using a Bruker ACF-250 (^{1}H, 250 and 62.5 MHz) spectrophotometer supported by an Aspect 4000 data system. The chemical shifts were recorded on the d scale and were measured relative to the residual signal of chloroform at d 7.25. All coupling constants are measured in Hertz. Elemental micro analyses were carried out using a Perkin-Elmer 2400 elemental analyzer CHN. Sulfur content was determined by oxygen combustion followed by wet titration. (1S)-(+)-10-Camphorsulphonic acid, (-)-dibenzoyl-L-tartaric acid, (R)-(-)-mandelic acid], propionitrile, (trifluoroanthracenyl)ethanol (TFAE) shift reagent are commercially available.

Resolution of (1RS, 3RS)-2-N,N-dimethylaminomethyl-1,3-dithiolane-1,3-dioxide (3) with (-)-dibenzoyl-L-tartaric acid (5)

(-)-Dibenzoyl-L-tartaric acid (401 mg, 1.06 mmol) in propionitrile (9 mL) and (1RS, 3RS)-2-N,N-dimethylaminomethyl-1,3-dithiolane-1,3-dioxide (3) (208 mg, 1.06 mmol) in propionitrile (8 mL) were combined at room temperature. Since crystallization occurs slowly, the reaction mixture was left for 24 h at room temperature. After 24 h the resulting white crystal was filtered and dried *in vacuo*, gave the salt (7) (0.259 g, 44% yield). δ_H (62.5 MHz, DMSO): 2.25 (6H, s, NMe_2), 2.8 (2H, dd, J= 0.6 and 1.2 Hz, —CHCH$_2$), 3.6–3.7 (4H, m, —CH$_2$—CH$_2$—), 4.3 (1H, t, —CHC*H*$_2$), 5.6 (2H, s, -OCO-C*H*OCOPh), 7.5–8.0 (10 H, m, Ar-H).

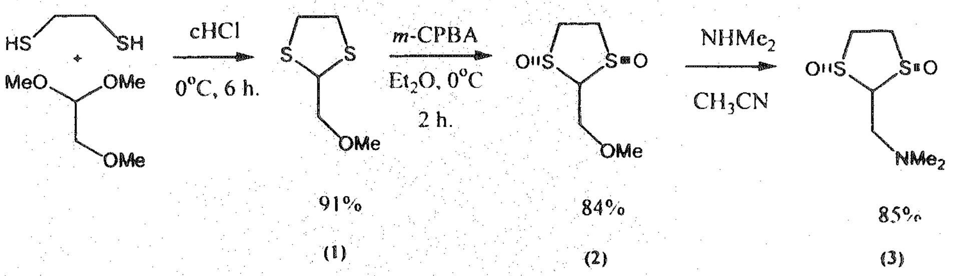
(1RS, 3RS)-2-N,N′-Dimethylaminomethyl-1,3-dithiolane-1,3-dioxide (3)

The salt (7) (0.445 g, 0.8 mmol) was dissolved in acetonitrile (10 mL) at room temperature under nitrogen. To this solution, Na$_2$CO$_3$ (0.339 g, 3.2 mmol) was added. The solution was stirred at rooom temperature for 1 day. After one day the reaction mixture was filtered and washed with cold ethyl acetate then solvents removed *in vacuo*. The title compound was obtained as a white solid (0.106 g, 68% yield). R$_f$ 0.5 [(acetone/methanol (50 : 50)]; m.p. 117–119°C; δ_H (250 MHz, CDCl$_3$) 2.4 (6H, s, NMe$_2$), 2.9 (2H, d, *J* = 8.5, —CHC*H*$_2$), 3.5–3.8 (4H, m, —CH$_2$—CH$_2$), 3.9 (1H, t, —C*H*CH$_2$). δ_C (300 MHz, CDCl$_3$) 45.6 (Me), 50.9 (C-4), 51.4 (C-5), 52.2 (C-6), 90.4 (C-2).

Anal. Calcd. (%) for C$_6$H$_{13}$NO$_2$S: C, 36.9; H, 6,66; N, 7.17; S, 32.8; Found: C, 36.72; H, 6.59; N, 7.07; S, 32.95.

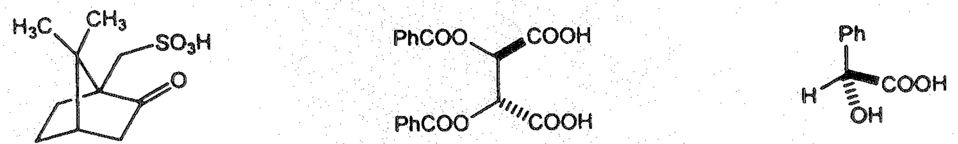
RESULTS AND DISCUSSION

In this paper, the resolution of (1RS, 3RS)-2-N,N-dimethylaminomethyl-1,3-dithiolane-1,3-dioxide using optical resolution method is reported. The racemic amine (3) was prepared using Aggarwal's method[7] in 3 steps and gave 85% of amine (**Scheme-1**).



Scheme-1

The amine (3) was resolved using acidic resolving reagents, Such as (S)-(+)-camphorsulphonic acid (4), (-)-dibenzoyl-L-tartaric acid (5) and (R)-(-)-mandelic acid (6) (**Scheme-2**). (-)-Dibenzoyl-L-tartaric acid was found an efficient acidic reagent for resolution of (1RS,3RS)-2-N,N-dimethylaminomethyl-1,3-dithiolane-1,3-dioxide. The preparation of the salt (7) is shown in **Scheme-3**.

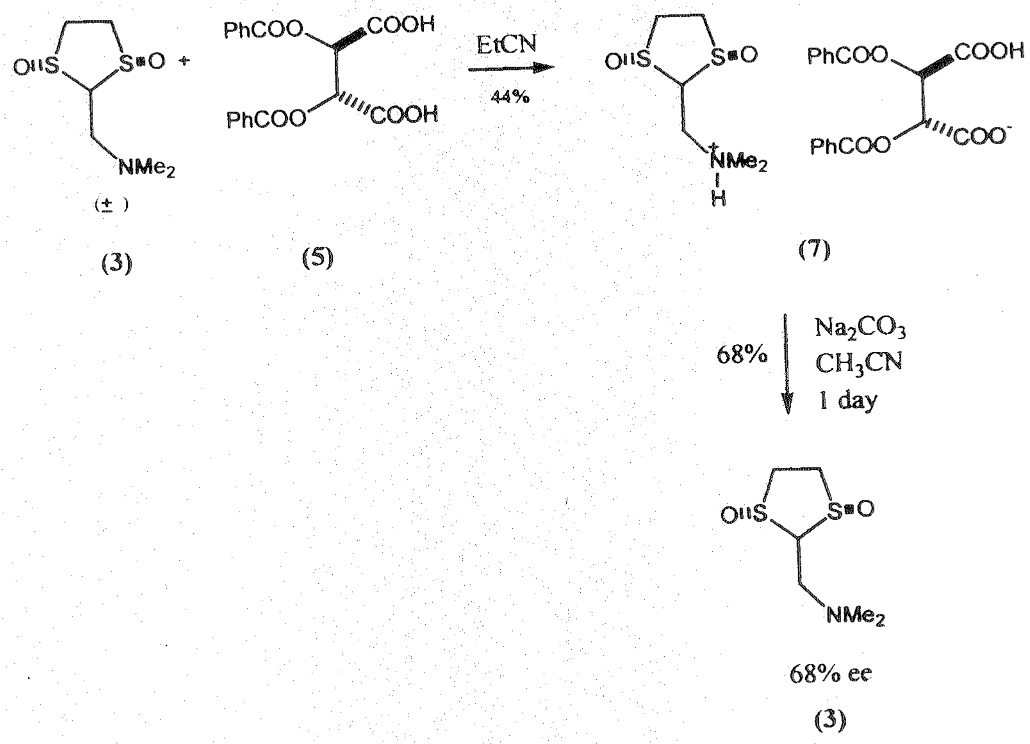


(1S)-(+)-10-Camphorsulphonic acid (4)

(-)-dibenzoyl-L-tartaric acid (5)

(R)-(-)-Mandelic acid (6)

Scheme-2



Scheme-3

TABLE-1
RESOLUTION OF (1RS,3RS)-2-N,N-DIMETHYLAMINOMETHYL-1,3-DITHIOLANE-1,3-DIOXIDE (3)

Entry	Acids	Solvents	Temp (°C) (day)	Yield of salts (%)	$[\alpha]_D$ of salts	Yield of amine (%) (3)	$[\alpha]_D$ of amine (3)	ee (%)[a]
1	5	EtOAc	25 (1 day)	75	—	55	—	0
2	5	$CHCl_3$	0 (7 days)	65	—	54	–23.1 (c 0.1 in $CHCl_3$)	28
3	5	CH_2Cl_2	0 (7 days)	42	–79 (c 0.1 in MeOH)	40	–39 (c 0.1 in $CHCl_3$)	60
4	5	EtCN	25 (1 day)	44	–92 (c 0.1 in MeOH)	—	—	68
5	4	EtOAc	0 (10 days)	84	+2.1 (c 0.1 in MeOH)	86	+3 (c 0.1 in $CHCl_3$)	0
6	4	THF	0 (10 days)	46	+113 (c 0.1 in MeOH)	57	+14 (c 0.1 in acetone)	20
7	6	EtOH	0 (20 days)	26	–76 (c 0.1 in MeOH)	26	–61 (c 0.1 in acetone)	36
8	6	EtOAc	0 (17 days)	77	–99 (c 0.1 in MeOH)	77	–20 (c 0.1 in MeOH)	14

(a) Enantiomeric excess of (3) was determined by integration of the ^{1}H NMR spectrum (from Me) in presence of (trifluoroanthracenyl)ethanol (TFAE) shift reagent.

Recovery of amine (3) from the salts was easy. The salts were dissolved in acetonitrile and Na_2CO_3 added. After one day, the precipitate was filtered and washed with more EtOAc to give required amine (3). The results are summarized in Table-1. The best selectivity was obtained with (-)-dibenzoyl-L-tartaric acid giving 68% ee using EtCN as a solvent (entry 4). Using Pirkle shift reagent, TFAE[8] we determined that enantiomeric excess of (3) was 68%.

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