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Preparative scale synthesis of (*S*)-2-hydroxypropoxyamine hydrochloride

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Abstract

A simple preparation of (*S*)-2-hydroxypropoxyamine hydrochloride by baker's yeast reduction of prochiral *N*-(2-oxopropoxy)phthalimide followed by acid hydrolysis is described.

1. Introduction

Chiral aminoalcohols and their derivatives are widely used in pharmaceuticals, e.g. anesthetics, analgesics etc., and as chiral auxiliaries in asymmetric synthesis.[1,2] They can be produced by reduction of readily available homochiral amino acids whose products are restricted to chiral secondary amines with a primary hydroxy group, or by stereospecific reduction of nitrogen-functionalized ketones which gives chiral secondary alcohols with an α- or β-amino group.[3–6] The last mentioned reaction can be performed by a chemical reduction employing a chiral auxiliary, as well as by enzymatic reduction catalyzed by baker's yeast.[7] Also, lipase catalyzed kinetic resolutions of the racemic mixtures of *N*-substituted secondary aminoalcohols have been reported in the literature.[8]

In spite of a considerable number of papers devoted to the preparation of optically active aminoalcohols, to the best of our knowledge the structurally very close oxyamino alcohols (which are *O*-alkylhydroxylamine derivatives) have not been described until now in optically active form. These compounds, possessing two very reactive functional groups, could be used as synthons in organic synthesis, especially in new drug development. The alkoxyimino group is a common substituent in the third generation of cephalosporine antibiotics[9] (ceftriaxone, cefmenoxime, cefuroxime, ceftazidime and others), as well as in the totally synthetic monobactam antibiotic–

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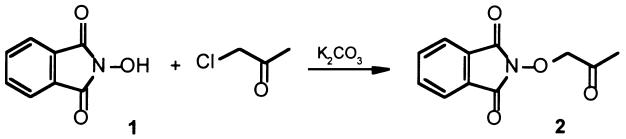
aztreonam. The possibility of inserting another kind of easily derivatized alkoxyimino substituent may be of value in the development of new drugs.

As is well known, baker's yeast mediated reduction of ketones often gives optically active secondary alcohols in high enantiomeric excess. Since oxyamino ketones, similarly to amino ketones, are difficult to isolate in the free state because of Schiff base formation, and we expected the appropriate oxyamino alcohol to be too soluble to extract from water, yeast reduction of masked oxyamino ketone derivative was investigated instead of the oxyamino ketone itself. We chose a phthaloyl moiety as the masking group, because of cheap substrates, and the very simple preparative procedure.

2. Results and discussion

The starting oxyphthalimide-masked ketone was prepared by reaction of chloroacetone with potassium salt of *N*-hydroxyphthalimide. The reaction was carried out in DMSO solution at 20–30°C and gave a good yield of the desired oxyphthalimide derivative **2** (Scheme 1). The *N*-(2-oxopropoxy)-phthalimide **2** was identical to that prepared by Kliegel[10] by oxidation of 2-hydroxypropoxy phthalimide. The structure was confirmed by elemental analysis, ^{1}H NMR and IR spectra.

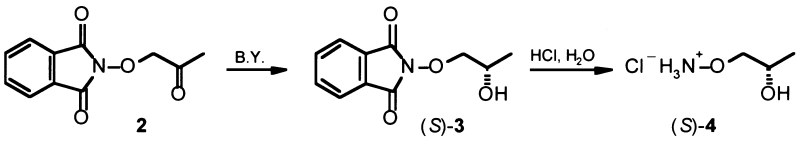


Scheme 1.

As described in the literature[7] baker's yeast reductions of phthalimide masked ketones leading to the corresponding aminoalcohol derivatives were carried out in water:ethanol (8:1 v/v) medium with glucose added to the growing culture. The substrate concentration used was rather low (22 mmol/l) because of its low solubility in the medium, and the reaction times required for complete conversion were long, even up to 10 days. The resulting masked aminoalcohols were obtained in a very high yield (up to 94%) and good enantiomeric excess (ee > 96%).

To avoid the laborious and time consuming extraction procedure, and to increase substrate concentration in the reaction medium, it was decided to carry out baker's yeast reduction of *N*-(2-oxopropoxy)phthalimide **2** in an organic solvent solution. Hexane is the solvent most commonly used for this purpose; however, the oxyphthalimide derivative **2** is insoluble and *t*-butylmethyl ether was chosen instead. It was found that 60 ml of the ether was sufficient to dissolve 0.5 g of the substrate. Usability of instant dry yeast of three brands, 'Fermipan brown' (Gist brocades), 'Saf-instant' (S. T. Lesaffre), and 'Mauripan' (Mauri Foods Ltd), was investigated in the reduction of **2**. In preliminary experiments we found that the reduction of the carbonyl group in *N*-(2-oxo-propoxy)phthalimide (Scheme 2) was very sluggish in *t*-butylmethyl ether solution, and to increase the rate the addition of water was necessary depending on the yeast brand (the original content of water in all of the three brands of yeast was in the range 4–5%).

The required amount of yeast for the reduction to proceed strongly depends on its brand. We found the reduction in *t*-butylmethyl ether solution was much faster than in water and 24 h was



Scheme 2.

sufficient for complete conversion of **2**. This time period was constant in our investigation. Determinations of conversion of **2** were carried out by gas chromatography on HP 50+ middle polar column. The amounts of yeast and water required for 100% conversion of 0.5 g (2.28 mmol) of *N*-(2-oxopropoxy)phthalimide **2** were optimized, and the results of the investigation are summarized in Table 1.

Table 1
Conditions of baker yeast reduction of *N*-(2-oxopropoxy)phthalimide **2** and yields of (*S*)-*N*-(2-hydroxypropoxy)phthalimide **3**

Entry No.	Amount of *t*-butylmethyl ether (ml)	Amount of water (ml)	Yeast brand *)	Amount of the yeast (g)	Conversion (%)	Yield of the isolated product (%)
1	60	3.65	a	4.6	100	60
2	120	3.65	a	4.6	100	61
3	60	3.4	a	4.2	96	60
4	60	2.9	a	3.6	80	--
5	60	3.65	b	4.6	100	61
6	120	3.65	b	4.6	100	60
7	60	3.4	b	4.2	95	59
8	60	4.6	c	3.65	100	63
9	60	2.3	c	1.85	100	73
10	120	2.3	c	1.85	100	73
11	60	2.0	c	1.60	95	--

*) a = Fermipan brown, b = Saf-instant, c = Mauripan

As can be seen from the presented data, the best results were achieved with Mauripan yeast, which appeared almost twice as active as other investigated yeast brands. This is important, because the amount of biomass influences the yield of separated product (the alcohol is adsorbed by yeast more strongly than starting ketone). Also the amount of added water required by Mauripan yeast is much smaller (compare entries 1, 5, and 9 in Table 1). The 73% yield of the isolated enantiomerically pure (ee $>98\%$) (*S*)-*N*-(2-hydroxypropoxy)phthalimide (entry 9) makes the method of preparative value, and increased amount of solvent (entry 10) does not change the yield. The enantiomeric excesses were determined by HPLC on a chiral column with 2-propanol:hexane 1:9 (v/v) as the eluent (flow rate 0.7 ml/s). The chromatogram of the racemic *N*-(2-hydroxypropoxy)phthalimide prepared according to the literature[10] revealed two close peaks of integrated surfaces 42.6 and 57.4% with the retention times of 2410 s and 2261 s, respectively. The chromatograms of the crude products (determined for entries 1, 2, 5, 9, and 10 in Table 1) showed only

one peak with the retention times 2450–2463 s and 96–100% of integrated surface. After recrystallization from ethanol the retention time of **3** was 2457 s and the integrated surface 100%. The (*S*)-*N*-(2-hydroxypropoxy)phthalimide **3** was hydrolyzed with dilute hydrochloric acid at room temperature yielding after work up and crystallization colorless crystals of (*S*)-(+)-2-hydroxypropoxyamine hydrochloride **4** with 70% average yield over five batches.

The absolute configuration of 2-hydroxypropoxyamine hydrochloride **4** was determined by X-ray crystallography on the basis of anomalous dispersion effect; details are given in Section 3.4. As the presence of chloride in the structure gives sufficient anomalous scattering factors a well-shaped single crystal of **4** was chosen for this study. The results showed that (+)-**4** possesses the (*S*)-configuration at the C(2) carbon atom as depicted in Fig. 1. A brief description of the salient features of the X-ray structure is given below.

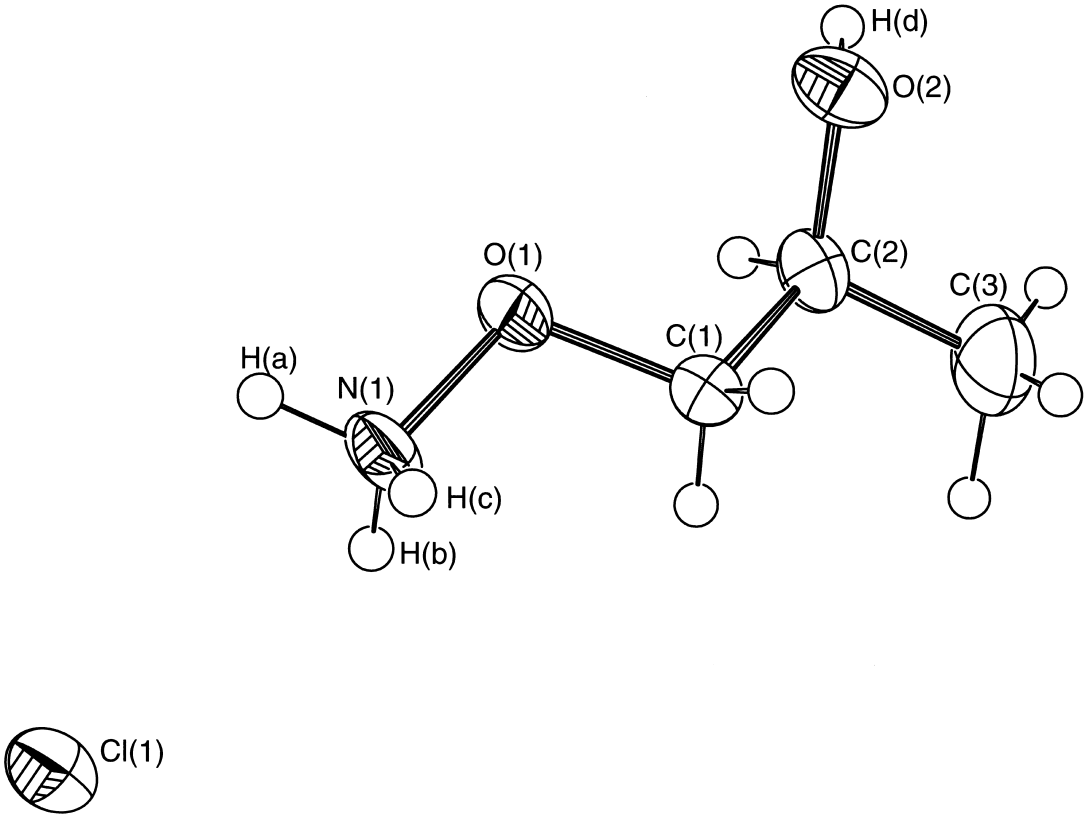


Figure 1. An ORTEP plot[11] of **4** with thermal ellipsoids drawn at 50% probability level. Selected bond lengths [Å]: N(1)–O(1) 1.422(2), O(1)–C(1) 1.440(3), C(1)–C(2) 1.505(2), C(2)–O(2) 1.430(3), C(2)–C(3) 1.515(4). Selected bond angles [°]: N(1)–O(1)–C(1) 109.8(2), O(1)–C(1)–C(2) 107.9(2), C(1)–C(2)–O(2) 107.8(2), O(2)–C(2)–C(3) 111.5(2)

The molecule crystallizes with orthorhombic $P2_12_12_1$ space group symmetry. A search of the Cambridge Structure Database[12] showed that it is the first structurally characterized chiral terminal hydroxylamine compound. Selected bond lengths and bond angles are given in Fig. 1. The most interesting structural feature of this ionic $C_3H_{10}O_2N^+Cl^-$ compound is an infinite cationic zigzag chain along the *b* axis formed by strong intermolecular hydrogen bonds between

N(1)–H(c) and hydroxide O(2) atom. The N···O donor–acceptor distance of 2.814(2) Å and the angle N–H···O value of 168(3)° describe geometry of this interaction. The graph motif descriptor of the chain is $C(6)$.[13] The chloride anions are surrounded by six cationic molecules. The ionic interactions are enforced by the three relatively strong intermolecular hydrogen bonds between O(2)–H(d)···Cl(1), N(1)–H(a)···Cl(1) and N(1)–H(b)···Cl(1) with donor–acceptor distances of 3.109(3) Å, 3.167(3) Å and 3.250(3) Å, and donor–H···Cl angles of 178(3)°, 164(3)° and 154(3)°, respectively. Thus, each chlorine anion is H-bonded to three different cationic $C(6)$ chains and as a result a helix-like structure along the x axis is observed. Taking into account all important intermolecular hydrogen bonds the infinite layers parallel to (100) plane are formed.

3. Experimental

The instant dry *Saccharomyces cerevisiae* yeasts were generously supplied by the producers: Mauri Foods Ltd, Gist brocades and S. T. Lesaffre. Melting points taken on a Franz Kustner apparatus were uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer with TMS as an internal standard. IR spectra were recorded on a Specord M80 Zeiss-Jena spectrometer. GC analyses were performed by using an HP 50+ column on an HP 5890 model, series II. HPLC analyses for the determination of enantiomeric excesses were carried out using a Daicel Chiracel ODH column on a Thermo Separation Products P100 instrument. Optical rotations were measured on a Bellingham–Stanley P20 polarimeter.

3.1. N-(2-Oxypropoxy)phthalimide **2**

To a stirred solution of 10 g (60 mmoles) of *N*-hydroxyphthalimide **1** in 400 ml of anhydrous DMSO 5.3 g (40 mmoles) of anhydrous potassium carbonate was added in a few portions. Next, 9.4 g (100 mmoles) of chloroacetone was added dropwise at 25–30°C. The mixture was stirred for 36 h at room temperature and poured into ice water. The precipitate of *N*-(2-oxopropoxy)-phthalimide was filtered off and dried. The crude product was recrystallized from 96% ethanol. Yield 8.6 g (65%) of colorless crystals, mp 120–122°C. Lit.[10] gives mp 115–117°C. Anal. calcd for $C_{11}H_9NO_4$: C, 60.27%; H, 4.14%; N, 6.39%. Found: C, 60.16%; H, 4.14%; N, 6.38%. ^{1}H NMR in $CDCl_3$ (δ ppm): 2.35 (s, 3H); 4.69 (s, 2H); 7.75–7.89 (m, 4H). IR in Nujol suspension: 1700 cm^{-1} (ν C=O).

3.2. (S)-N-(2-Hydroxypropoxy)phthalimide **3**

To a solution of 2 g (9.12 mmoles) of *N*-(2-oxopropoxy)phthalimide **2** in 240 ml of *t*-butyl methyl ether in a 1 l Erlenmayer flask, 7.5 ml of tap water was added, followed by 11.0 g of Mauripan yeast (*Saccharomyces cerevisiae*). The flask was shaken at room temperature for 24 h (with free access of air). The biomass was filtered off and extracted with 150 ml of ethyl acetate. The resulting solutions were evaporated to dryness and obtained (*S*)-*N*-(2-hydroxypropoxy)-phthalimide was purified by recrystallization from ethyl acetate:hexane 6:1 mixture yielding 1.45 g (73%) of colorless crystals, mp 94–96°C. Optical rotation was measured in chloroform solution: $[\alpha]_D^{22} = +41$. Enantiomeric excess was measured by HPLC on a Chiralcel ODH column in hexane:2-propanol (9:1 v/v) solution, ee > 98%. Anal. calcd for $C_{11}H_{11}NO_4$: C, 59.73%; H, 5.01%; N, 6.33%. Found: C, 59.72%; H, 4.99%; N, 6.51%. ^{1}H NMR in $CDCl_3$ (δ ppm): 1.17 (d, 3H,

J = 6.2 Hz); 3.83–3.90 (m, 2H); 3.91–4.10 (m, 1H); 4.19–4.25 (m, 1H); 7.75–7.89 (m, 4H). IR in Nujol suspension: 3210 cm^{-1} (ν OH), 1710 cm^{-1} (ν C=O).

3.3. (S)-2-Hydroxypropoxyamine hydrochloride **4**

A solution of 1.1 g (5 mmoles) of (*S*)-*N*-(2-hydroxypropoxy)phthalimide **3** in 12 ml of 18% aqueous HCl solution was stirred at room temperature for 8 h. After evaporation of the acid under reduced pressure the resulting oily 2-hydroxypropoxyamine hydrochloride was crystallized from 2-propanol:ethyl ether 1:6 mixture. Yield 0.46 g (72%) of colorless crystals, mp 114–116°C.

Optical rotation was measured in H_2O solution: $[\alpha]_D^{22} = +19$. Enantiomeric excess was measured by HPLC on a Chiralcel ODH column in hexane:2-propanol (9:1 v/v) solution, ee > 98%. Anal. calcd for $C_3H_{10}NO_2Cl$: C, 28.25%; H, 7.90%; N, 10.98%. Found: C, 28.45%; H, 7.65%; N, 10.90%. ^1H NMR in DMSO-d_6 (δ ppm): 1.00–1.03 (m, 3H); 3.61 (bs, 2H); 3.79–3.89 (m, 4H).

Table 2
Crystal and structure refinement data for (*S*)-2-hydroxypropoxyamine hydrochloride **4**

Empirical formula	$C_3H_{10}O_2N^+Cl^-$
Formula weight	127.57
Temperature, K	293(2)
Wavelength, Å	1.54056
Crystal system	Orthorhombic
Space group	$P\,2_12_12_1$
Unit cell dimensions a, Å	5.6666(8)
b, Å	9.6049(9)
c, Å	11.7912(7)
Volume, $Å^3$	641.76(12)
Z	4
Calculated density, Mg/m^3	1.320
Absorption coefficient, mm^{-1}	4.548
F(000)	272
Crystal size, mm	0.840 x 0.385 x 0.280
2θ range for data collection, °	5.94 to 73.83
Reflections collected / unique	1211 / 1211
Absorption correction	Semi-empirical (ψ-scan)
Max. and min. transmission	0.995 and 0.789
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1211 / 0 / 105
Goodness-of-fit on F^2	1.213
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0357, wR_2 = 0.0843
Absolute structure parameter	0.01(2)
Extinction coefficient	0.116(5)
Largest diffraction. peak and hole, e $Å^{-3}$	0.315 and –0.354

3.4. Crystal structure determination of **4**

Single crystals of (*S*)-2-hydroxypropoxyamine hydrochloride **4**, suitable for X-ray diffraction studies, were crystallized by slow evaporation from dilute hydrochloric acid. A well-shaped single crystal of approximately 0.3×0.4×0.8 mm was placed in a thin walled capillary tube (Lindemann glass 0.5 mm) to avoid long contact with atmospheric moisture. The tube was plugged with grease, then flame-sealed and mounted on a goniometer head of a four-circle MACH 3 (Nonius B.V.) diffractometer. The crystal class and the orientation matrix were obtained from the least-square refinement of 25 reflections using graphite-monochromated Cu–Kα radiation ($\lambda = 1.54056$ Å). The intensities were corrected for Lorentz and polarization factors. A semi-empirical absorption correction was applied on the basis of intensities of 7 reflections measured at different azimuthal angles (ψ-scan).[14] The structure was solved by direct methods using the SHELXS-86 program[15] which revealed the positions of all non-hydrogen atoms. Full-matrix least-squares refinement method against F^2 values was carried out by using the SHELXL-97 program.[16] All non-hydrogen atoms were refined with anisotropic displacement parameters. The H atoms were located by successive difference Fourier maps and refined with isotropic temperature factors. A final electron density map showed no significant residual density. Final results give $R_1 = 0.0357$ and $wR_2 = 0.0843$ for 1211 reflections with $I > 2\sigma(I)$. The absolute structure was established based on anomalous dispersion using the Flack parameter x.[17] The x refined during the final structure factor evaluation of the model with the molecule of the *S* absolute configuration amounted to a value of 0.01(2). Refinement of a racemic twin resulted in a twin ratio *S*:*R* of 0.99:0.01(2), which allowed us to abandon the twin model and confirmed the *S* absolute configuration assumed. Refinement of the *R* configuration resulted in a wR_2 of 0.132, $R_1 = 0.051$ and $S = 1.89$, while the x parameter was calculated to be 0.95(4). Neutral atom scattering factors and anomalous dispersion corrections were taken from the International Tables for Crystallography.[18] The selected crystallographic data, the parameters of data collections and refinement procedures are presented in Table 2. All crystallographic data (excluding structure factors) for the structure of **4** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 141851. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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