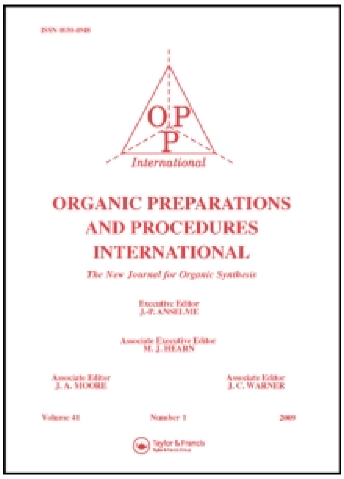

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A PRACTICAL SYNTHESIS OF (3aα, 6aα)-1,3-DIBENZYL HEXAHYDRO-1*H*-THIENO[3,4-*d*]IMIDAZOL-2(3*H*)-ONE

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A PRACTICAL SYNTHESIS OF (3aα, 6aα)-1,3-DIBENZYL HEXAHYDRO-1*H*-THIENO[3,4-*d*]IMIDAZOL-2(3*H*)-ONE

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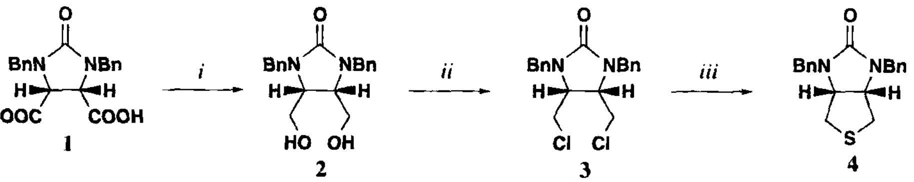
During the course of our investigation on the synthesis of *d*-biotin, which is utilized as a nutritional supplement for humans and animals,[1,2] (3aα, 6aα)-1,3-dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (**4**) was required as a key intermediate, which had previously been prepared by Lavielle *et al.*[3] In our hand, however, this procedure resulted in little product (ca. 5% overall yield). Herein we present a modified, simple method for the synthesis of **4** with an overall yield of 77% from the known 1,3-dibenzyl-2-imidazolidone-4,5-*cis*-dicarboxylic acid (**1**)[4] as shown in the scheme.

Selective reduction of **1** with $Zn(BH_4)_2$ generated *in situ* by reaction of KBH_4 with $ZnCl_2$, in anhydrous THF at reflux for 10 h afforded cleanly the corresponding diol **2** in 92% yield. Since the mesylate of **2** used in Lavielle's procedure was poorly soluble in EtOH, it was decided to use the dichloride **3**. However, attempted chlorination of the hydroxyl groups in **3** with $SOCl_2$, PCl_3, $POCl_3$ was unsuccessful. The corresponding dichloride **3** was ultimately obtained in 91% yield using Vilsmeier reagent (chloromethylenedimethylammonium chloride), which was conveniently prepared by reaction of PCl_5 with anhydrous DMF.[5] Treatment of **3** with $Na_2S•9H_2O$ in a diphase system ($CHCl_3$-H_2O) with a catalytic amount of triethylbenzylammonium chloride (TEBAC) as a phase-transfer catalyst at reflux for 6h afforded the desired **4** as white crystals in 92% yield. It is worth mentioning that the reaction time was longer (14 h) and the yield of **4** decreased to 64% when no phase-transfer catalyst was employed.



i) KBH_4, $ZnCl_2$, THF; *ii*) $[(CH_3)_2N{=}CHCl]\ Cl^-$, DMF; *iii*) $Na_2S•9H_2O$, TEBAC, $CHCl_3$, H_2O

In summary, an improved method has been developed for large scale preparation of **4** in 77% yield from **1**. Compared to the previously reported method, this procedure gave higher overall yields and involved more convenient manipulations.

EXPERIMENTAL SECTION

Melting points were taken on a WRS-1 digital melting point apparatus and were uncorrected. Elemental analyses were performed on a Carlo-Erba 1106 elemental analyzer. IR spectra were recorded on a Nicolet FI-IR 360 Spectrophotometer. ^1H NMR spectra were run on a Bruker AM-300 (300MHz) spectrometer with TMS as an internal standard. Chemical shifts were reported in ppm downfield (δ). Mass spectra were measured on a HP5988A instrument by direct inlet at 70 ev. THF was distilled from sodium benzophenone ketyl. All other materials were obtained from commercial suppliers and used as received. 1,3-Dibenzyl-2-imidazolidone-4,5-*cis*-dicarboxylic acid (**2**) was synthesized according to the procedure described by Goldberg and Sternbach.[4]

1,3-Dibenzyl-4,5-*cis*-bis(hydroxymethyl)-2-imidazolidone (2).- To a suspension of $ZnCl_2$ (108 g, 0.794 mol) in THF (1.1 L) under N_2 was added KBH_4 (84.6 g, 1.57 mol) and the mixture was stirred at room temperature for 2 h. Then 1,3-dibenzyl-2-imidazolidone-4,5-*cis*-dicarboxylic acid (**1**, 127.4 g, 0.36 mol) was added in three portions. The reaction mixture was stirred vigorously at reflux for 10 h. The contents were cooled to10° and the excess hydride was carefully destroyed with 3N HCl (450 mL). After gas evolution had ceased, the mixture was extracted with $CHCl_3$ (3 x 250 mL). The combined organic extracts were washed with 10% aq. Na_2CO_3 (100 mL), and water (250 mL), then dried over Na_2SO_4 .The solvent was removed on a rotary evaporator to give the crude product. Recrystallization from CH_2Cl_2-Et_2O gave pure **2** (108 g, 92%) as a white solid, mp. 131-132°, *lit.*[3] mp. 131°. IR (KBr): 3217, 1673, 1035 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.21-7.34 (m, 10 H, ArH), 4.90 (t, 2 H, J = 3.9 Hz, 2 x OH, exchangeable with D_2O), 4.70, 4.08 (2d, 4 H, J = 15.6 Hz, 2 x CH_2Ph), 3.59 (m, 2 H, 2 x HCN), 3.36 (t, 4 H, CH_2OH). MS (m/z, %): 326 (M^+, 5), 295 (30), 265 (12), 91 (100), 65 (10).

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.94; H, 6.75; N, 8.59. Found: C, 69.68; H, 6.99; N, 8.67

1,3-Dibenzyl-4,5-*cis*-bis(chloromethyl)-2-imidazolidone (3).- To a well-stirred mixture of chloromethylenedimethyl-ammonium chloride (30.8 g, 0.24 mol) and anhydrous DMF (175 mL) was added dropwise a solution of **2** (70 g, 0.215 mol) in anhydrous DMF (250 mL) at 0° over a period of 1.5 h. The reaction mixture was stirred at 100° for 5 h, then cooled to room temperature. After removal of the DMF under vacuum, CH_2Cl_2 (300 mL) and water (250 mL) were added to the reaction mixture. The organic layer was washed with saturated aq. $NaHCO_3$ (3 x 100 mL) and water (2 x 75 mL), then dried over Na_2SO_4. The solvent was removed on rotary evaporator to give the crude product. Recrystallization from $CHCl_3$-petroleum ether (60-90°) gave pure **3** (70.8 g, 91%) as a white crystalline powder, mp.95-97°. IR (KBr): 1686, 1453, 1257, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37-7.25 (m,10 H, ArH), 4.85, 4.24 (2d, 4 H, J = 15.6 Hz, 2 x CH_2Ph), 3.78 (t, 2 H, J = 2.6 Hz, HCN), 3.72 (t, 4 H, J = 6.3 Hz, CH_2Cl_2). MS (m/z, %): 363 (M^+, 4), 312 (23), 271 (2), 91 (100), 65 (9). HRMS (m/z): Calcd for $C_{19}H_{20}Cl_2N_2O$: 363.2847. Found: 363.2835.

Anal. Calcd for $C_{19}H_{20}Cl_2N_2O$: C, 62.81; H, 5.51; N, 7.71. Found: C, 62.65; H, 5.48; N, 7.59

(3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (4).- A mixture of **3** (71 g, 0.196 mol), $Na_2S{\cdot}9H_2O$ (46 g, 0.59 mol), triethylbenzylammonium chloride (1.1 g, 0.048 mol), $CHCl_3$ (150 mL) and water (150 mL) was vigorously stirred at reflux for 6 h, and cooled to room temperature.[6] Water (120 mL) was added to the reaction mixture. The organic layer was separated and the aqueous phase extracted with $CHCl_3$ (3 x 150 ml). The combined organic extracts were washed with water (3 x 100 mL) and dried over Na_2SO_4. The solvent was removed on rotary evaporator to give the crude product. Recrystallization from CH_2Cl_2-Et_2O afforded pure **4** (58.4 g, 92%) as white crystals, 125-127°, *lit.*[3] mp. 125°. IR (KBr): 1688, 1482, 1248, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.26-7.37 (m, 10 H, ArH), 4.76, 4.18 (2d, 4 H, *J* = 15 Hz, 2 x CH_2Ph), 3.98 (m, 2 H, 2 x HCN), 2.75 (dd, 2 H, *J* = 12.5, 2.5 Hz, $CH_{endo}S$), 2.69 (dd, 2 H, *J* = 12.5, 4.5 Hz, $CH_{exo}S$). MS (m/z; %): 324 (M^+, 23), 277 (9), 233 (22), 187 (8), 91(100), 65(18).

Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.37; H, 6.17; N, 8.64. Found: C, 70.18; H, 6.39; N, 8.91

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