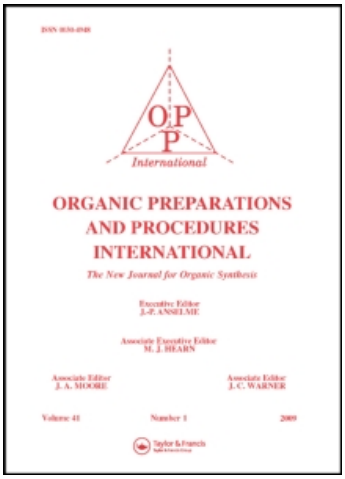

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A NEW APPROACH TO THE SYNTHESIS OF 1,3-AMINOALCOHOLS FROM *MESO* CYCLIC ACID ANHYDRIDE

Jia-Hai Ye[a]; You Huang[a]; Ru-Yu Chen[a]
[a] Institute of Elemento-Organic Chemistry, Nankai University, State Key Laboratory of Elemento-Organic Chemistry, Tianjin, P. R., CHINA

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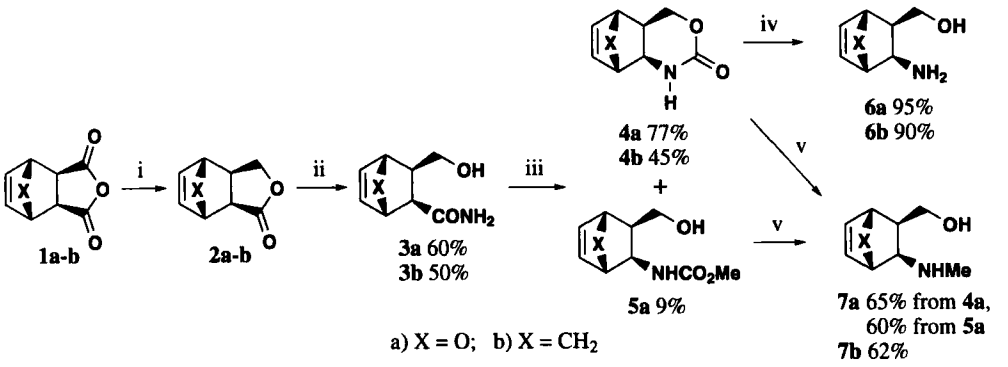
A NEW APPROACH TO THE SYNTHESIS OF 1,3-AMINOALCOHOLS FROM *MESO* CYCLIC ACID ANHYDRIDE

Submitted by Jia-Hai Ye, You Huang and Ru-Yu Chen*
(07/29/02)

Institute of Elemento-Organic Chemistry
State Key Laboratory of Elemento-Organic Chemistry
Nankai University, Tianjin 300071, P. R. CHINA

1,3-Aminoalcohols and their derivatives play important roles in the synthesis of various compounds with biological activity.[1] For example, the naturally occurring amino sugars are important components of several antibiotics.[2] Carbocyclic nucleosides containing an amino cyclanol moiety exhibit potent antiviral activity.[3] Chiral 1,3-aminoalcohols can be obtained from their racemic mixtures through enzymatic resolution and have been used as chiral auxiliaries in asymmetric syntheses.[4] Although several synthetic methods of 1,3-aminoalcohols have been described,[5] to our knowledge only Fülöp and coworkers have reported a route to 1,3-aminoalcohols from *meso* cyclic acid anhydrides. In Fülöp's method, the β-amino acid was prepared by a Hofmann rearrangement of the carboxamide, obtained by ammonolysis of cyclic anhydride. Lithium aluminium hydride (LAH) reduction of the amino acid gave 1,3-aminoalcohols.[6, 7] We now report a new route to 1,3-aminoalcohols from *meso* cyclic acid anhydrides.

Treatment of lactones **2a,b** prepared from the readily available Diels-Alder adducts **1a,b**, with ammonia gave amido alcohols **3a,b**. While the Hofmann rearrangement of the amidoalcohols **3** with sodium hypochlorite did not occur, the reaction of alcohol **3a** with bis(acetoxy)iodobenzene under mild conditions led to the **4a** and **5a** (9:1 ratio); only cyclic carbamate **4b** was obtained from **3b** under the same conditions. Hydrolysis of carbamates **4a,b** in the presence of $Ba(OH)_2 \cdot 8H_2O$ in a mixture of dioxane and water afforded 1,3-aminoalcohols **6a,b**. The reduction of **4a,b** and of **5a** with LAH led to the N-methyl-1,3-aminoalcohols **7a,b**. This method may be useful for the synthesis of chiral 1,3-aminoalcohols from *meso* cyclic acid anhydrides without resolution of the racemic mixtures.[8]



EXPERIMENTAL SECTION

All melting points were determined on a Yanaco apparatus and are uncorrected. IR were recorded on a Shimadzu-IR4335 spectrometer(KBr). ^{1}H NMR spectra were measured on a Brucker AC-P200 NMR(200MHz) instrument in $CDCl_3$ or DMSO-d_6; chemical shifts are expressed as δ units and TMS was used as an internal standard. Elemental analyses were carried out on a Yanaco CHN CORDER MT-3 apparatus. Compounds **1a,b** and **2a,b** were prepared according to literature procedures.[9,10]

General Procedure for Compounds 3.- Ammonia dried over KOH was bubbled for 2 h through a solution of lactones **2a,b** (0.033 mol) in MeOH (20 mL) cooled to 0°C. The reaction mixture was then stirred for 2 days at room temperature. Evaporation led to the crude products which were recrystallized, from a 2:1 mixture of MeOH-acetone to provide **3a,b** as white crystals.

Compound 3a, mp. 176-178°C, 60% yield. ^{1}H NMR(DMSO-d_6): δ 1.81 (1H, m), 2.15 (1H, d, J = 5.3 Hz). 3.16 (1H, t, J = 5.3 Hz), 3.33 (1H, br, OH), 3.55 (1H, dd, J = 2.2 Hz, 5.2 Hz), 4.72 (2H, d, J = 1.6 Hz), 6.4 (2H, s), 6.85 (1H, s), 7.12 (1H, s). IR: 3376, 3190, 3014, 2998, 2972, 2890, 1649, 1429, 1033, 1317, 1294 cm^{-1}.

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.75; H, 6.62; N, 8.29

Compound 3b, mp. 148-150°C, 50% yield. ^{1}H NMR(DMSO-d_6): δ 1.15 (1H, m), 1.62 (1H, m). 1.87 (1H, d, J = 4.0 Hz), 2.06 (1H, d, J = 5.0 Hz), 2.48 (1H, s), 2.78 (1H, s), 3.12 (1H, t, J = 5.3 Hz), 3.34 (1H, br, OH), 3.53 (1H, dd, J = 2.2 Hz, 5.3 Hz), 6.14 (2H, dd, J = 1.5 Hz, 4.5 Hz), 6.80 (1H, s), 7.16 (1H, s). IR: 3421, 3358, 3183, 3062, 2995, 2966, 2886, 1653, 1621, 1412, 1300, 1029 cm^{-1}.

Anal. Calcd for $C_9H_{13}NO_2$; C, 64.65; H, 7.74; N, 8.38. Found: C, 64.73; H, 7.86; N, 8.29

General Procedure for Compounds 4 and 5.- Alcohols **3a,b** (0.01 mol) and bis(acetoxy)iodobenzene (3.20 g, 0.01 mol) were added together as solids to a stirred solution of KOH (1.12 g, 0.02 mol) in MeOH (60 mL), cooled in ice-water bath. The reaction mixture was

allowed to warm up to room temperature. After 1 h, MeOH was evaporated and then $CHCl_3$ and water 100 ml (v:v = 1:1) were successively added to the residue with stirring. Separation of the layers, followed by extraction of the aqueous layer with $CHCl_3$ (3 x 60 mL) and drying of the organic extract ($MgSO_4$), gave **4** and **5**, after evaporation and column chromatography on silica gel (AcOEt:light petroleum ether:MeOH = 3:2:1 to 3:1:2).

Compound 4a, white solid, mp. 129-134°C, 77% yield. ^1H NMR($CDCl_3$): δ 2.20 (1H, m), 3.45 (1H, d, J = 3.5 Hz). 4.13 (1H, q, J = 3.2 Hz), 4.38 (1H, q, J = 2.7 Hz), 4.77 (2H, d, J = 3.8 Hz), 6.35 (2H, J = 3.2 Hz, 12 Hz), 6.88 (1H, br, NH). IR: 3400-3307 (br), 3084, 2953, 2852, 1735, 1674, 1612, 1437, 1219, 1193, 1111, 707 cm^{-1}.

Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.53; H, 5.34; N, 8.42

Compound 4b, white solid, mp. 92-94°C, 45% yield. ^1H NMR($CDCl_3$): δ 1.52 (1H, dd, J = 1.1 Hz, 4.7 Hz), 1.87 (1H, d, J = 5.7 Hz), 2.09 (2H, m), 2.66 (1H, s), 2.80 (1H, s), 3.32 (1H, d, J = 3.9 Hz), 3.92 (1H, dd, J = 3.9 Hz, 5.7 Hz), 4.37 (1H, dd, J = 3.7 Hz, 5.7 Hz), 5.74 (1H, br, NH), 6.05 (1H, q, J = 1.6 Hz), 6.25 (1H, q, J = 1.6 Hz). IR: 3325, 3287, 3.71, 2975, 2915, 1723, 1707, 1365, 1285, 1241, 1035, 708 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.53; H, 6.66; N, 8.49

Compound 5a, white solid, mp. 91-93°C, 9% yield. ^1H NMR($CDCl_3$): δ 1.76 (2H, m), 1.96 (1H, m), 3.65 (3H, s, CH_3), 3.89 (2H, m), 4.67 (1H, s), 4.85 (1H, s), 5.60 (1H, br, NH), 6.42 (2H, m). IR: 3647, 3544, 3460, 3031, 2951, 1893, 1744, 1456, 1435, 1306, 1270, 1193, 1011, 918 cm^{-1}.

Anal. Calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.58; N, 7.03. Found: C, 54.25; H, 6.62; N, 7.09

General Procedure for Compounds 6.- To a solution of **4a,b** (0.005 mol) in dioxane and water 30 mL (v:v = 1:1) was added $Ba(OH)_2 \cdot 8H_2O$ (10 g, 0.030 mol) and the mixture was heated at reflux (60-90°C) for 10 h. The resulting mixture was cooled to room temperature and filtered, the solids were washed three times with AcOEt. Evaporation of the Combined organic phases followed by recrystallization of the solid residue from $CHCl_3$ led to 1,3-aminoalcohols **6a,b**.

Compound 6a, white solid, mp. 136-138°C, 95% yield. ^1H NMR ($CDCl_3$): δ 1.94-1.99 (2H, m), 2.74 (3H, br, 2NH+OH), 3.10 (1H, d, J = 3.7 Hz), 3.79-3.62 (1H, m), 4.48 (1H, s), 4.52 (1H, s), 6.32 (2H, dd, J = 2.1 Hz, 3.0 Hz). IR: 3316, 3144, 3064, 2999, 2946, 2854, 1485, 1456, 1317, 1116, 1037 cm^{-1}.

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 65.63; H, 7.86; N, 9.89

Compound 6b, white solid, mp. 92-94°C, 90% yield. ^1H NMR ($CDCl_3$): δ 1.52 (1H, m), 1.90-2.12 (4H, m), 2.46 (1H, s), 2.69 (1H, s), 3.58 (3H, br, 2NH+OH), 4.24 (2H, m), 6.11 (2H, dd, J = 1.3 Hz, 5.6 Hz). IR: 3435, 3315, 3225, 3008, 2964, 2879, 1634, 1548, 1470, 1376, 1038 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.11; H, 9.36; N, 9.99

General Procedure for Compounds 7.- To a solution of **4a,b** (or **5a**) (0.005 mol) in dry THF (60 mL) was added a solution of $LiAlH_4$ (0.80 g, 0.02 mol) in dry THF (10 mL) at 0°C. The mixture was heated at reflux for 5 h. The mixture was carefully hydrolyzed with cold water and the precipitated solid was washed three times with AcOEt (3 x 20 mL). The filtrate was separated

and the aqueous layer was extracted with AcOEt (3 x 30 mL). The combined AcOEt extracts were evaporated and chromatographed on silica gel (AcOEt:light petroleum ether: MeOH=3:1:3) to afford 0.507 g (65%) of **7a**. and 0.478g (62%) of **7b**.

Compound 7a, colorless oil, 65% yield from **4a** and 60% from **5a**. ^{1}H NMR ($CDCl_3$): δ 2.06 (1H, m), 2.48 (3H, s, CH_3), 2.73 (1H, m), 3.28 (2H, br, NH+OH), 3.60 (1H, t, J = 5.6 Hz), 3.75 (1H, s), 4.45 (1H, s), 4.81 (1H, s), 6.23-6.41 (2H, m). IR: 3411, 3361, 3022, 2957, 1720, 1699, 1620, 1525, 1434, 1362, 1153, 914 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.83; H, 8.49; N, 8.99

Compound 7b, colorless oil, 62% yield. ^{1}H NMR ($CDCl_3$): δ 1.48 (2H, dd, J = 4.5Hz, 8.9Hz), 1.83 (1H, m), 2.35 (1H, s), 2.45 (3H, s, CH_3), 2.58 (1H, d, J = 4.0 Hz), 2.79 (1H, s), 3.45 (1H, s), 3.71 (1H, dd, J = 2.5 Hz, 5.0 Hz), 6.13 (2H, dd, J = 1.4 Hz, 14 Hz). IR: 3300, 3060, 2968, 2876, 1476, 1454, 1328, 1084, 1028 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.63; H, 9.86; N, 9.19

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