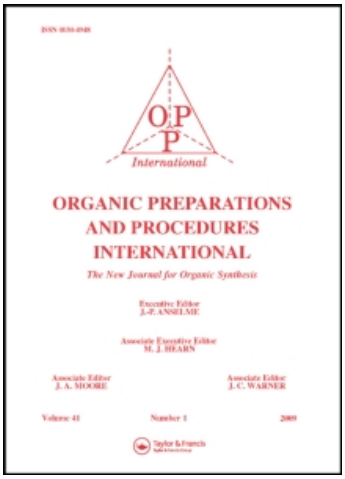

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SYNTHESIS OF 2(N-ALKYLAMINO)ISOBUTYRALDEHYDES

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SYNTHESIS OF 2-(N-ALKYLAMINO)ISOBUTYRALDEHYDES

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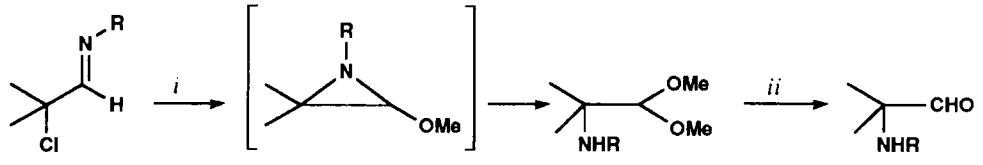
α-Aminoaldehydes are useful bifunctional compounds which can serve as building blocks for elaboration into heterocycles. Sterically hindered α-aminoaldehydes are less accessible because of the difficulties associated with the amination of tertiary centers. We found that the reaction of α-chloroaldimines (**1a-c**)[1] with methanol under reflux overnight gives the rearranged α-aminoacetals (**3**) (78-85%). The free bases **3** are isolated after basic workup of the reaction mixture. However, it is also possible to isolate the hydrochlorides of α-aminoacetals (**3**) in nearly quantitative yields by simple evaporation of methanol from the reaction mixture.[1] The hydrolysis of α-aminoacetals **3** into α-aminoaldehydes (**4**) was performed with ten molar equivalents of aqueous 6N hydrogen chloride in a two-phase system with dichloromethane as co-solvent. After a reflux period of 26 hrs, the α-aminoaldehydes (**4**) (Table 1) were isolated in 68-92% yield after distillation. Lower concentrations of aqueous hydrogen chloride or of oxalic acid hydrolyzed the acetal incompletely or not at all.



1 **2** **3** **4**

i) Δ, MeOH, 18-23 hrs *ii*) 6N HCl, H_2O, CH_2Cl_2, Δ, 26 hrs
a) R = *i*-Pr b) R = Cyclohexyl c) R = *t*-Bu

TABLE 1. Synthesis of α-Aminoacetals (**3**) and α-Aminoaldehydes (**4**)

R	Reaction Time (hrs) 1→3	Yield of Acetal	bp (°C/mmHg)	Reaction Time (hrs) 3→4	Yield of Aldehyde	bp (°C/mmHg)
i-Pr	23	**3a** 85%	64-65/11	26	**4a** 68%	58-64/28
cyclohexyl	18	**3b** 85%	116-119/12	26	**4b** 92%	115-118/12[b]
t-Bu	20	**3c** 78%	75-78/12[a]	26	**4c** 73%	53-55/12[c]

a) Lit.[1] bp 76-80°/15mmHg; b) Lit.[2] bp 84-87°/4mmHg; c) Lit.[3] 75-80°/55mmHg; Lit.[4] bp 112°/130mmHg.

2-(N-Alkylamino)isobutyraldehydes (**4**) have been obtained previously by various methods which often include the use of less common starting materials, and/or of drastic conditions or only

afford low to moderate yields. These routes involve (i) aminolysis of appropriate glycidylic amides and subsequent decarbonylation in sulfuric acid at high temperature,[2] (ii) nitrosation of α-aminooximes,[6] (iii) ozonolysis of N-alkyl 2,2-dimethylallylamines,[3] (iv) reduction of N-alkylaziridinones[7] and (v) reaction of α-bromoisobutyraldehyde with primary amines followed by hydrolysis.[4]

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin Elmer model 1310 spectrophotometer. ^{1}H NMR spectra were measured in $CDCl_3$ on a Varian T-60 (60 MHz), a Jeol JNM-PMX60 NMR spectrometer (60 MHz) and a Jeol JNM-EX270 (270 MHz), while the ^{13}C NMR spectra were recorded on a Varian FT-80 NMR spectrometer (20 MHz). Mass spectra were obtained on a Varian MAT 12 mass spectrometer (70 eV) using a direct inlet or by using a GC-MS coupling (20 m capillary column).

General Procedure for the Synthesis of α-Aminoacetals (3) from α-Chloroaldimines (1).- A solution of 0.1 mole of α-chloroaldimine 1 in 150 mL dry methanol was refluxed for 18-23 hrs (Table 1). The solvent was removed *in vacuo* to about one fourth of the original volume and the residual mixture was poured into 200 mL of 1N sodium hydroxide. The reaction mixture was extracted with dichloromethane, dried (K_2CO_3) and evaporated *in vacuo*. The residual liquid was distilled *in vacuo* to give pure dimethyl acetals of 2-(N-alkylamino)-2-methylpropanal **3** (see Table 1). Compounds **3a**,[8] **3b**[1] and **3c**[1] gave spectroscopic data in complete agreement with data in the literature. Additional ^{13}C NMR data of **3b** and **3c** are given:

Compound 3b, ^{13}C NMR ($CDCl_3$): δ 22.33 (q, Me_2); 25.86 (t, total overlap of 3 CH_2's at the 3-, 4- and 5-position of the cyclohexyl group); 37.19 (t, CH_2's at the 2- and 6-position); 50.39 (d, N<u>C</u>H); 57.64 (s, Me_2<u>C</u>-N); 58.31 (q, $(OMe)_2$); 112.72 (d, CH$(OMe)_2$).

Compound 3c, ^{13}C NMR ($CDCl_3$): δ 24.23 (q, Me_2); 33.19 (q, Me_3); 51.13 (s, N-<u>C</u>Me_3); 58.41 (s, Me_2<u>C</u>-N); 58.10 (q, $(OMe)_2$); 113.57 (d, CH$(OMe)_2$).

Hydrochloride of Compound 3c, mp. 164°, ^{13}C NMR ($CDCl_3$): δ 20.87 (q, Me_2); 29.28 (q, Me_3); 58.78 (q, $(OMe)_2$); 61.57 and 66.25 (each s, Me_2C-N-<u>C</u>Me_3); 107.01 (d, <u>C</u>H$(OMe)_2$).

General Procedure for the Synthesis of 2-(N-Alkylamino)-2-methylpropanal (4).- A solution of 0.05 mol of dimethyl acetal **3** in 80 mL of dichloromethane was triturated with 83 mL of aqueous 6N hydrogen chloride (0.5 mol). The two phases were vigorously stirred under reflux for 26 hrs after which the aqueous phase was cooled in an ice bath and made alkaline with 50% aqueous sodium hydroxide. The organic phase was isolated and the aqueous phase was extracted with dichloromethane. The combined extracts were evaporated *in vacuo* to leave an oil which was distilled to afford pure α-aminoaldehydes **4** (see Table 1).

2-(N-Isopropylamino)-2-methylpropanal (4a): ^{1}H NMR ($CDCl_3$): δ 1.03 (6H, d, J = 6.35Hz, CH<u>Me</u>$_2$); 1.17 (6H, s, CMe_2); 2.87 (1H, septet, J = 6.35Hz, C<u>H</u>Me_2); 9.46 (1H, s, CHO); NH invisible. ^{13}C NMR ($CDCl_3$): 22.35 (q, <u>Me</u>$_2$C); 25.32 (q, CH<u>Me</u>$_2$); 44.22 (d, <u>C</u>HMe_2); 60.95 (s, Me_2<u>C</u>); 205.33 (s, CHO). IR (NaCl); 3330 cm^{-1} (NH); 1727 cm^{-1} (C=O). MS: m/z (%): no M$^+$; 100 (-CHO, 27); 81 (-i-Pr, 2); 84 (2); 72 (MacLafferty, 3); 70 (1); 58 (100-C_3H_6, 100); 44 (10); 43 (10); 42 (16); 41 (15).

Anal. Calcd.: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.88; H, 11.81; N, 10.98

2-(N-Cyclohexylamino)-2-methylpropanal (4b): ^{1}H NMR ($CDCl_3$): δ 1.13 (6H, s, Me_2); 1-2 (10H, m, $(CH_2)_5$); 2.4 (1H, m, NCH); 9.19 (1H, s, CHO); NH invisible. ^{13}C NMR ($CDCl_3$): 22.42 (q, Me_2); 25.84 (t, CH_2 at 4-position of the cyclohexyl group); 25.35 (t, CH_2's at the 3 and 5-position of the cyclohexyl group); 36.25 (t, CH_2's at the 2- and 6-position of the cyclohexyl group); 52.01 (d, NCH); 60.71 (s, $Me_2\underline{C}$-N); 204.26 (d, CHO). IR (NaCl): 3330 cm^{-1} (NH); 1728 cm^{-1} (C=O). MS: m/z (%): 169 (M^+; 0.5); 154 (1); 124 (20); 110 (1); 98 (1); 86 (2); 83 (100); 82 (2); 81 (2); 79 (1); 70 (2); 69 (2); 68 (2); 67 (5); 55 (90); 54 (4); 53 (4); 43 (12); 42 (50); 41 (40).

2-(N-*t*-Butylamino)-2-methylpropanal (4c): ^{1}H NMR (CCl_4): δ 1.11 (9H, s, *t*-Bu); 1.16 (6H, s, Me_2); 1.3 (1H, s, br, N<u>H</u>); 9.36 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): 24.62 (q, Me_2); 32.29 (q, Me_3); 51.50 (s, $\underline{C}Me_3$); 60.92 (s, CMe_2); 205.84 (d, CHO). IR (NaCl): 3360 cm^{-1} (NH); 1730 cm^{-1} (C=O). MS: m/z (%): no M^+; 114 (10); 58 (100); 57 (15); 44 (9); 43 (8); 42 (12); 41 (19). This compound solidified in the refrigerator (-20°).

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