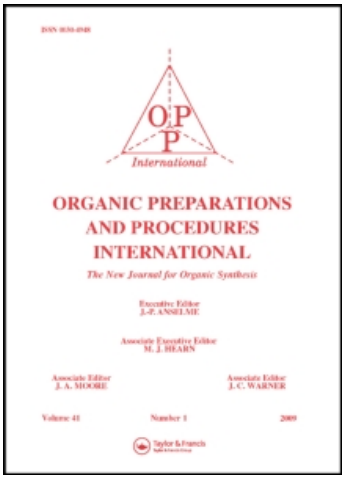

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CONVENIENT SYNTHESIS OF DI(*n*-OCTADECYL)AMINE AND DI(*n*-HEXADECYL)AMINE

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OPPI BRIEFS

CONVENIENT SYNTHESIS OF DI(*n*-OCTADECYL)AMINE AND DI(*n*-HEXADECYL)AMINE

Submitted by Luciano Lattuada* and Fulvio Uberti
(04/09/02)

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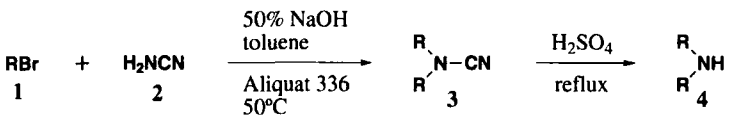
Di(*n*-octadecyl)amine (**4a**) and di(*n*-hexadecyl)amine (**4b**) are important starting materials for the preparation of a wide variety of lipophilic compounds such as synthetic surfactants, lipopeptides,[1,2] glycolipids,[3,4] lipopolyamines,[5,6] lipophilic chelators.[7,8] In the course of our ongoing research on contrast agents for Magnetic Resonance Imaging (MRI)[9,10] we needed large amounts of these two amines for the synthesis of lipophilic gadolinium complexes.[11]

Surprisingly, commercial pure amine **4a** is very expensive[12] while amine **4b** is not available. Typical syntheses of these compounds are based on ammonolysis of fatty alcohols[13] or catalytic hydrogenation of amides or nitriles,[14] but all these procedures require drastic conditions of temperature and pressure and are applied in industrial processes. The very few papers reporting a laboratory scale preparation of amines **4a,b** found in the literature,[3,15-18] all have drawbacks. Alkylation of hexadecyl or octadecylamine with the corresponding bromoalkane,[15] reduction with of *N*-hexadecylhexadecanamide with $LiAlH_4$[16] and $NaBH_4$ reduction of the imines obtained from hexadecyl or octadecylamine and the corresponding aldehydes[3] give only moderate yields (30-40%). The four steps of a new approach for the preparation of secondary amines (including **4b**)[17] make it time consuming, while the reduction of stearonitrile with Rh/Al_2O_3 to give **4a** is far too expensive, due to the large amount of catalyst used.[18] While searching for an easy and economical synthesis of lipophilic secondary amines, we rediscovered the alkylation of cyanamide under phase transfer conditions to give dialkylcyanamides. This procedure has only been applied to benzyl, allyl or small alkyl (up to C_6) halides.[19,20] Although solid cyanamide is commercially available or easily obtainable from calcium cyanamide,[21] we found the use of 50% aqueous cyanamide (commercially available) more convenient in terms of cost and safety.

Treatment of *n*-octadecyl bromide **1a** or *n*-hexadecyl bromide **1b** with a five molar excess of 50% aq. cyanamide **2** in 50% aq. NaOH/toluene at 50° and in the presence of Aliquat® 336 as phase transfer catalyst gave the corresponding alkylcyanamides **3a,b** in 8 h (*Scheme*). Excess of cyanamide was used to achieve the complete conversion of the more expensive alkyl bromide, thus avoiding



a) R = $C_{18}H_{37}$ b) R = $C_{16}H_{33}$

tedious purification in subsequent steps. After the separation and evaporation of the organic phase the crude dialkylcyanamides were directly hydrolyzed to the corresponding amines **4a,b**. Only a small sample of crude **3a** was purified by flash chromatography for characterization. Among the several methods reported in literature for the conversion of dialkylcyanamides into dialkylamines,[22] we found that the acidic hydrolysis is very easy and convenient.[23] In fact, the crude dialkylcyanamide is completely converted after a few hours in refluxing 2 M H_2SO_4. The desired amine is easily isolated by addition of NaOH and extraction with $CHCl_3$ and the crude product was purified by simple trituration in Et_2O. The overall yields of amines **4a,b** are always good (60-70%).

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 spectrometer. Electrospray ionization was performed on a Finnigan TSQ 700 triple quadrupole mass spectrometer fitted with a Finnigan ESI interface. Reactions were monitored by thin layer chromatography (TLC) which was carried out on silica gel plates (Merck KGaA, Silica 60, 0.2 mm) in the following solvent systems (v/v): A = *n*-hexane-Et_2O (9:1), B = CH_2Cl_2-MeOH-25% aq. NH_4OH (9:1:0.1). Spots of intermediates **3a,b** were detected by spraying a solution of 0.2% $Ce(SO_4)_2$ and 3.8% $(NH_4)_6Mo_7O_{24}$ in 10% H_2SO_4 and heating. Spots of products **4a,b** were also detected by spraying 0.5% $KMnO_4$ in 1 M NaOH or 0.2% ninhydrin in EtOH. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. All reagents were obtained from commercial sources and were of analytical grade.

Di(*n*-octadecyl)amine (4a).- A solution of NaOH (200 g, 5 mol) in water (150 mL) was added dropwise to 50% aq. cyanamide (101 g, 1.2 mol) while the temperature was kept below 40°. Aliquat® 336 (5 g, 0.012 mol), *n*-octadecyl bromide (80 g, 0.240 mol) and toluene (200 mL) were added in one portion and the mixture was vigorously stirred at 50° for 8 h. The organic phase was separated and evaporated. The crude dioctadecylcyanamide was suspended in 2 M H_2SO_4 (300 mL) and the mixture refluxed for 8 h. The mixture was cooled to room temperature, diluted with 3.5 M NaOH (310 mL) and extracted with $CHCl_3$ (750 mL). The organic phase was separated, washed with water (250 mL), dried (Na_2SO_4) and filtered. The solution was evaporated to give a crude pale yellow solid which was triturated with Et_2O (400 mL). The solid was collected and washed with Et_2O (100 mL) to give 39.5 g (63%) of the title compound as a white solid, mp. 72.3-73.3°, *lit.*[12] mp. 71-73°, *lit.*[15] mp. 72.0-72.5°.

TLC: R_f: 0.54 (system B).

^{1}H NMR ($CDCl_3$): δ 0.88 (6H, t, J = 6.8 Hz, CH_3); 1.26 (60H, s, CH_2); 1.47 (4H, m, CH_2CH_2N); 2.57 (4H, t, J = 7.1 Hz, CH_2N).

^{13}C NMR ($CDCl_3$): δ 13.86 (CH_3); 22.51, 27.31, 29.20, 29.54, 30.13, 31.78 (CH_2); 50.02 (CH_2N).

Anal. Calcd for $C_{36}H_{75}N$: C, 82.83; H, 14.48; N, 2.68. Found: C, 82.61; H, 14.65, N, 2.69.

Di(*n*-hexadecyl)amine (4b).- *n*-Hexadecyl bromide (67 g, 0.219 mol) was reacted as described above and the title compound 35.8 g (70%) was obtained as a white solid mp. 65.5-66.5°, *lit.*[15] mp. 65.7-65.9°. TLC: R_f: 0.65 (system B).

^{1}H NMR ($CDCl_3$): δ 0.88 (6H, t, J = 6.7 Hz, CH_3); 1.26 (60H, s, CH_2); 1.48 (4H, m, CH_2CH_2N); 2.59 (4H, t, J = 7.4 Hz, CH_2N).

^{13}C NMR ($CDCl_3$): δ 14.46 (CH_3); 23.07, 27.81, 29.75, 29.84, 29.98, 30.01, 30.09, 30.22, 32.32 (CH_2); 50.50 (CH_2N).

Anal. Calcd for $C_{32}H_{67}N$: C, 82.50; H, 14.40; N, 3.01. Found: C, 82.74; H, 14.60, N, 3.12.

Dioctadecylcyanamide (3a) was purified by flash chromatography on silica gel (eluent: *n*-hexane-Et_2O = 9:1) in order to obtain an analytical pure sample of this intermediate, mp. 50-51°. TLC: R_f: 0.40 (system A).

^{1}H NMR ($CDCl_3$): δ 0.86 (6H, t, J = 6.6 Hz, CH_3); 1.24 (60H, s, CH_2); 1.62 (4H, m, CH_2CH_2N); 2.94 (4H, t, J = 7.2 Hz, CH_2N).

^{13}C NMR ($CDCl_3$): δ 13.98 (CH_3); 22.58, 26.40, 27.59, 29.10, 29.26, 29.39, 29.46, 29.59, 31.83 (CH_2); 51.44 (CH_2N); 117.73 (CN).

Anal. Calcd for $C_{37}H_{74}N_2$: C, 81.24; H, 13.64; N, 5.12. Found: C, 80.96; H, 13.91, N, 5.19.

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