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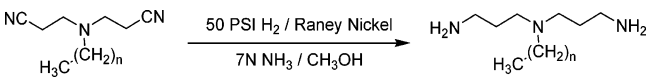
Preparation of *N*-Alkylbis(3-aminopropyl)amines by the Catalytic Hydrogenation of *N*-Alkylbis(cyanoethyl)amines

Travis T. Denton, Abigail S. Joyce, and Donald E. Kiely*

Shafizadeh Rocky Mountain Center for Wood and Carbohydrate Chemistry, University of Montana, Missoula, Montana 59812

donald.kiely@umontana.edu

Received February 5, 2007



An improved process for the preparation of *N*-alkylbis(3-aminopropyl)amines is described. These triamines are of interest as monomers for the condensation polymerization with esterified carbohydrate diacids (aldaric acids) to generate the corresponding poly(4-alkyl-4-azaheptamethylene aldaramides). The triamine synthesis is comprised of two efficient steps and requires no chromatographic purification. Bisconjugate addition of alkylamines to acrylonitrile followed by catalytic hydrogenation of the *N*-alkylbis(cyanoethyl)amines over Raney nickel yields the target *N*-alkylbis(3-aminopropyl)amines. Much less solvent was used in the bisconjugate addition step then previously reported, and in the second step, a relatively low-pressure catalytic hydrogenation (50 psi of hydrogen) was employed using Raney nickel as the catalyst in a 7 N methanolic ammonia solvent system to afford the *N*-alkylbis(3-aminopropyl)amines of high purity in nearly quantitative yield.

The reduction of nitriles is a fundamental synthetic organic transformation for the preparation of primary amines and is commonly carried out with varying degrees of success using lithium aluminum hydride[1−6] or by catalytic hydrogenation procedures.[7−15] The target triamines in this report were previously prepared by reduction of the precursor *N*-alkylbis(cyanoethyl)amines using a very large molar excess of lithium aluminum hydride in order to minimize secondary and tertiary amine byproduct formation.[6] The principal objective of the work described here was to establish a more efficient preparation of the triamines by use of a relatively low-pressure catalytic hydrogenation procedure that would avoid formation of unwanted secondary and tertiary amine byproducts. Catalytic hydrogenation of nitriles has been successfully employed under high-pressure conditions to make dendrimers,[16,17] but success is not normally achieved under much lower pressures wherein byproduct contamination is significant.[17]

A number of experimental procedures to decrease byproduct formation during the hydrogenation have been reported. These procedures include addition of ammonia[7] and inorganic bases, such as sodium hydroxide[18,19] or lithium hydroxide,[20] to the solutions containing the nitriles to be reduced. Side reactions may also be eliminated during hydrogenation by the direct acylation of the product primary amine with acetic anhydride[8] or by protonation with acid.[21−24] Ammonia in the reaction mixture is thought to reduce secondary and tertiary amine formation by competing with the newly formed primary or secondary amines, respectively, for conjugate addition to the intermediate imine (**B**, Scheme 1) formed from the nitrile (**A**).[25] In contrast, inorganic base is thought to selectively poison the catalyst toward hydrogenolysis reactions and/or inhibit the deposition of oligomeric secondary amines that block the active sites on the catalyst.[18] When a single nitrile is to be reduced, catalytic hydrogenation can be accomplished in the presence of variable concentrations of methanolic ammonia with minimum byproduct formation.[26−29] However, it has been reported

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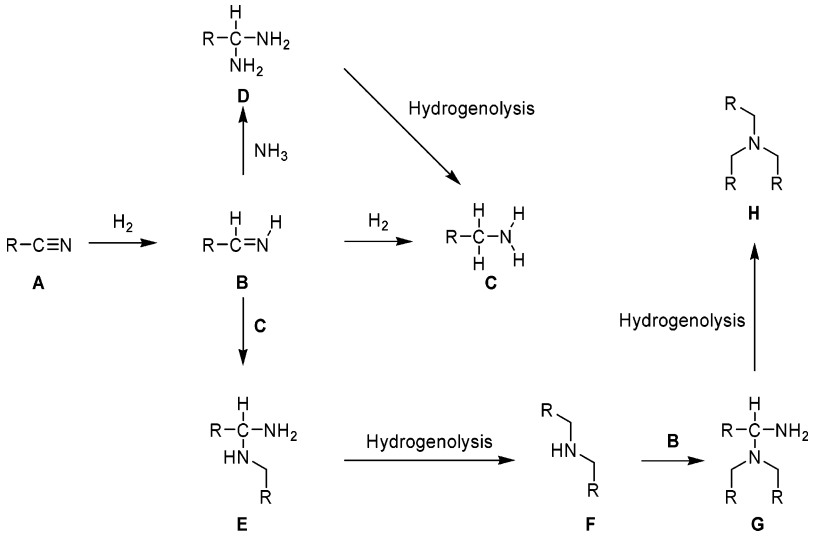
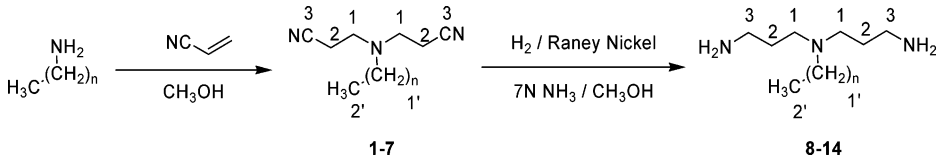
10.1021/jo070245v CCC: $37.00
Published on Web 05/31/2007

SCHEME 1. Byproduct Forming Reaction Pathways in the Hydrogenation of Nitriles



SCHEME 2. Synthesis of *N*-Alkylbis(cyanoethyl)amines and *N*-Alkylbis(3-aminopropyl)amines



that, when multiple nitriles are to be reduced, inclusion of ammonia and very high pressures of hydrogen are required.[16,17]

In the present note, we present an efficient and facile, two-step procedure for the synthesis of *N*-alkylbis(3-aminopropyl)-amines (**8**−**14**) that includes the low-pressure, catalytic hydrogenation of *N*-alkylbis(cyanoethyl)amines (**1**−**7**) in 7 N methanolic ammonia, using Raney nickel as the catalyst, in a commercially available, all stainless steel, Parr shaker type hydrogenation apparatus (Scheme 2).

An optimized procedure for the synthesis of the intermediate dinitriles (**1**−**7**) was developed employing the bisconjugate addition of primary amines that typically employed a 3.5:1 molar ratio of acrylonitrile/alkylamine in methanol (**1**−**6**) at 45 °C or 1-butanol (**7**) at 70 °C and reaction times that were typically 16−24 h. The previously reported procedure for the preparation of *N*-alkylbis(cyanoethyl)amines used approximately 18 times the volume of methanol and was carried out in the dark at room temperature for 3 days.[6] All of the *N*-alkylbis(cyanoethyl)amines (**1**−**7**) were comprehensively characterized by melting point (where applicable), ^{1}H NMR, ^{13}C NMR, gas chromatography, low-resolution mass spectrometry, and elemental analysis. Attempts to further improve the bisconjugate addition by the use of various combinations of reaction solvents (ethanol, methanol, chloroform, and tetrahydrofuran) were unsatisfactory.

The primary objective of this work was to develop a convenient, low-pressure method for the catalytic hydrogenation of *N*-alkylbis(cyanoethyl)amines using a conventional Parr shaker type hydrogenation apparatus. The previously published procedure for the reduction of the *N*-alkylbis(cyanoethyl)amines used an 800 mol % excess of lithium aluminum hydride in diethyl ether.[6] To avoid the use of ether as solvent and large amounts of hydride, a low-pressure catalytic hydrogenation conversion of the dinitriles **1**−**7** had to be established. As noted (Scheme 1), catalytic reductions of nitriles are generally complicated by the formation of side-product secondary (**F**) and tertiary amines (**H**). The former product results from the addition of the primary amine product (**C**, Scheme 1) to the intermediate imine (**B**) and the latter product from the addition of secondary amine (**F**) to more of the imine (**B**). This problem can potentially be avoided by addition of ammonia to the reduction solution. The ammonia reacts with the intermediate imine (**B**, Scheme 1) to form a 1,1-diamine (**D**), which is subsequently cleaved by hydrogenolysis to afford the product primary amine (**C**), thus protecting the imine (**B**) from the 1,2 addition of the product primary amine. The *N*-alkylbis(cyanoethyl)amines (**1**−**7**) were successfully reduced to *N*-alkylbis(3-aminopropyl)amines (**8**−**14**) on a 5 g scale by catalytic hydrogenation using Raney nickel as the catalyst (2 mL) in a 7 N methanolic ammonia solution (Table 1). The high (7 N) ammonia concentration worked well in the hydrogenations, but at decreased concentrations (1, 2.5, or 5 N), secondary and tertiary amine byproducts were formed, as detected by electrospray mass spectrometry. The use of 2 mL of Raney nickel in a typical reaction mixture normally resulted in the complete reduction of both nitrile functionalities in less than 24 h, whereas the use of less Raney nickel catalyst considerably slowed down the reduction rate. A major setback

TABLE 1. Catalytic Hydrogenation of *N*-Alkylbis(cyanoethyl)-amines (1−7) to *N*-Alkylbis(3-aminopropyl)amines (8−14)[a]

dinitrile	alkyl group	product	yield (%)	purity[b] (%)
1	hexyl	**8**	98	>99
2	octyl	**9**	98	>99
3	decyl	**10**	98	>99
4	dodecyl	**11**	98	>97
5	tetradecyl	**12**	98	>99
6	hexadecyl	**13**	99	>99
7	octadecyl	**14**	98	>99

[a] The dinitriles were hydrogenated under 50 psi of hydrogen using Raney nickel as the catalyst. [b] Percent purity was determined by gas chromatography.

in the procedure was encountered using a conventional Parr shaker type hydrogenation apparatus fitted with a brass gas reservoir and brass fittings. Ammonia in the reaction flask diffused into the gas reservoir, causing it to corrode and fracture. In addition, a significant amount of a blue colored, dissolved copper complex was generated in the filtered diamine solution. **For this reason, it was necessary to use an all stainless steel apparatus to carry out the desired hydrogenations.**

A second problem that developed came from the use of different Raney nickel catalysts from different vendors. While they all performed adequately as catalysts, some of them produced a green-blue colored nickel complex residue in the final product after solvent removal. The nickel complex was also produced by shaking a methanolic ammonia solution with the catalyst, but in the absence of nitrile starting material, under 50 psi of hydrogen, confirming that the origin of the green-blue complex was the Raney nickel catalyst. A number of methods were attempted to remove this green-blue material from the product mixture. In all instances, immediately after completion of the reaction, the catalyst was removed by filtration through a pad of Celite, and the solution was concentrated to minimize formation of the nickel complex. Allowing the unfiltered reaction mixture to stand for extended periods of time resulted in formation of additional nickel complex. Removal of the nickel complex from product amines chromatographically (short column of basic alumina) was unsuccessful as the amines were only soluble in alcohols which did not effect separation of the complex from amines.

In a second attempt, the product mixture was dissolved in methanol, the pH adjusted to 1 with concentrated HCl, and the solution was passed through a silica-polyamine-EDTA composite material.[30] This composite successfully removed the nickel, although a number of additional steps were required to obtain the free base amines. The methanolic solution was made basic by the addition of 2 N sodium carbonate$_{(aq)}$, and the precipitated sodium chloride and excess sodium carbonate were removed by filtration. The solution was concentrated, and the residue was suspended in dichloromethane to dissolve the product and further precipitate any inorganic salts. The slurry was filtered and concentrated, and this process was repeated until no more precipitate was observed. Ultimately, this method proved to be too complicated to be used routinely.

In another attempt to remove the nickel complex, advantage was taken of the insolubility of nickel hydroxide in water and methanol. Aqueous solutions of water-soluble product amines were taken to pH 10 with aqueous sodium hydroxide. The nickel hydroxide rapidly precipitated from solution at room temperature and was removed by filtration and the filtrate concentrated. The problem with this procedure came with the subsequent removal of the residual aqueous sodium hydroxide. Azeotropic distillation of the water with toluene, at the same time precipitating the sodium hydroxide, proved cumbersome due to the low solubility of some of the amines in toluene. When the contaminated amine product mixture was dissolved in methanol and the solution heated to ca. 60 °C for 10 min, nickel hydroxide precipitated and could be removed by filtration. However, removal of the sodium hydroxide, as above, was judged to be too complicated for practical application. Ultimately, to remove the nickel complex, the reduction product mixture was dissolved in 95% ethanol to which Dowex Monosphere 550A ($^-$OH) anion exchange resin was added. The slurry was refluxed for 30 min and cooled to room temperature; the resin and insoluble nickel hydroxide were removed by filtration, and the filtrate was concentrated to afford the pure product. Fortuitously, the first batch of older Raney nickel used in the Experimental Section afforded clear product amine solutions, and removal of the contaminant nickel was not necessary. However, one hydrogenation example is given in the Experimental Section describing the use of a batch of Raney nickel that generated a green-blue nickel complex which was subsequently removed using $^-$OH form ion-exchange resin, as described.

In conclusion, we have developed an efficient, high yielding preparation of *N*-alkylbis(cyanoethyl)amines and a subsequent reduction procedure to afford *N*-alkylbis(3-aminopropyl)amines in nearly quantitative yields by the Raney nickel catalyzed hydrogenation in a commercially available, all stainless steel Parr shaker type hydrogenation apparatus. The production of secondary and tertiary amine byproducts was eliminated by the use of a 7 N methanolic ammonia solvent, and a simple method was developed for the successful removal of a nickel complex contaminant by the precipitation of nickel hydroxide using an $^-$OH form anion exchange resin.

Experimental Section

Preparation of *N*-Hexylbis(cyanoethyl)amine (1). Representative Procedure for the Bisconjugate Addition of Primary Alkylamines to Acrylonitrile. To acrylonitrile (43.4 mL, 661.5 mmol) in methanol (40 mL) at 0 °C was added hexylamine (25 mL, 189 mmol) in methanol (25 mL) dropwise over 30 min. The ice bath was removed, and the solution was warmed to 45 °C and stirred for 16 h. The solvent and excess acrylonitrile were removed in vacuo to afford the title compound **1** (38.2 g, 98% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.86−2.82 (m, 4H), 2.51 (t, J = 7.3 Hz, 2H), 2.47−2.43 (m, 4H), 1.43 (br m, 2H), 1.27−1.17 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H); LRMS (ESI) *m*/*z* calcd for $C_{12}H_{22}N_3$ $[M + H]^+$ 208.2, found 208.2; *m*/*z* calcd for $C_{14}H_{25}N_4$ $[M + H + CH_3CN]^+$ 249.2, found 249.2; *m*/*z* calcd for $C_{24}H_{43}N_6$ $[M + H + M]^+$ 415.4, found 415.4; GC (FID) >99% (t_R = 9.17 min, Program 1). Anal. Calcd for $C_{12}H_{21}N_3$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.49; H, 10.31; N, 20.47.

Preparation of *N*-Hexylbis(aminopropyl)amine (8). Representative Procedure for the Hydrogenation of *N*-Alkylbis(cyanoethyl)amines. To a 500 mL hydrogenation flask were added *N*-hexylbis(cyanoethyl)amine (5 g, 24.1 mmol), methanolic ammonia (7 N, 100 mL), and Raney nickel (2 mL, washed three times with methanol). The flask was transferred to an all stainless steel Parr shaker type hydrogenation apparatus, charged with hydrogen (50 psi), and shaken (1 min). **(Caution: An all stainless steel hydrogenator is necessary for this step to avoid corrosion and possible explosion.)** The flask was evacuated under aspirator vacuum (1 min) and subsequently charged with hydrogen (50 psi, 1 min) three times, and the resultant slurry/solution was shaken under hydrogen at 50 psi for 24 h. The catalyst was removed by filtration through a pad of Celite (washing with methanol), and the solution was concentrated in vacuo to afford the title compound **8** (5.1 g, 98% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.72 (t, J = 7.3 Hz, 4H), 2.44 (t, J = 7.3 Hz, 4H), 2.38 (t, J = 7.3 Hz, 2H), 1.92 (br s, 4H), 1.59 (m, 4H), 1.41 (m, 2H), 1.35−1.2 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H); LRMS (ESI) *m*/*z* calcd for $C_{12}H_{30}N_3$ $[M + H]^+$ 216.2, found 216.2; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{30}N_3$ $[M + H]^+$ 216.2440, found 216.2449; GC (FID) >99% (t_R = 8.41 min, Program 1; t_R = 7.11 min, Program 2).

Preparation of *N*-Dodecylbis(3-aminopropyl)amine (11). Representative Procedure for the Hydrogenation of *N*-Alkylbis(cyanoethyl)amines and Subsequent Removal of the Green-Blue

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Nickel Complex using $^{-}$OH Form Ion-Exchange Resin. *N*-Dodecylbis(cyanoethyl)amine (5 g, 17.2 mmol) was hydrogenated according to the procedure for **8** to afford the title compound **11** containing a green-blue nickel complex. The resultant material was dissolved in 95% EtOH (100 mL), and to the resultant solution was added Dowex monosphere 550A ($^{-}$OH) anion exchange resin (21.5 mL, 25.8 mmol $^{-}$OH). The slurry was refluxed for 30 min, cooled to rt, and the resin was removed by gravity filtration. The resin was subsequently washed with 95% EtOH (2 × 20 mL), and the combined filtrate was concentrated in vacuo to afford the nickel-free title compound **11** (4.89 g, 96% yield) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.70 (t, J = 7.3 Hz, 4H), 2.43 (t, J = 7.3 Hz, 4H), 2.35 (t, J = 7.3 Hz, 2H), 1.56 (m, 4H), 1.45−1.31 (m, 6H), 1.30−1.21 (m, 18H), 0.86 (t, J = 6.6 Hz, 3H); LRMS (ESI) m/z calcd for $C_{18}H_{39}N_2$ $[M - NH_2]^+$ 283.3, found 283.3; LRMS (ESI) m/z calcd for $C_{18}H_{42}N_3$ $[M + H]^+$ 300.3, found 300.3; HRMS (ESI) m/z calcd for $C_{18}H_{42}N_3$ $[M + H]^+$ 300.3369, found 300.3379; GC (FID) 97% (t_R = 11.41 min, Program 1; t_R = 9.51 min, Program 2).

Acknowledgment. The authors gratefully acknowledge Mark Hughes and Edward Rosenberg (University of Montana, Department of Chemistry) for their technical assistance in regard to the silica-polyamine-EDTA composite which is now commercially available from Purity Systems, Inc. (http://www.puritysystemsinc.com). Financial support from the United States Department of Agriculture (USDA-CSRESS Grant Nos. 2004-364463-14477 and 2005-34463-15561) is gratefully acknowledged.

Supporting Information Available: General methods, instrument details and materials, ^{13}C NMR data for all compounds, ^{1}H NMR spectra for compounds **8**−**14**, and experimental details for the synthesis of compounds **2**−**7** and **9**−**14** with full characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070245V