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An Efficient Total Synthesis of Desferrioxamine B

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The total syntheses of the microbial iron chelator desferrioxamine B hydrochloride and some analogues are described. The synthetic scheme is highly flexible, providing access to dihydroxamate, trihydroxamate, tetrahydroxamate, and higher homologues of desferrioxamine. The procedure also allows for access to primary amino nitrogen functionalized desferrioxamines. The scheme is predicated on the generation of the key intermediate *O*-benzyl-*N*-(4-cyanobutyl)hydroxylamine, which is acylated at the *O*-benzylhydroxylamine nitrogen with either succinic or acetic anhydride. The resulting half acid amide or amide, respectively, is subjected to a series of high-yield condensations and reductions that provide desferrioxamine in 45% overall yield. Finally a desamino analogue of desferrioxamine is prepared in order to demonstrate the synthetic utility of the scheme as applied to desferrioxamine derivatives.

The microbial iron chelator, siderophore, desferrioxamine B (Figure 1), was isolated from *Streptomyces pilosus* and characterized by Bickel[1] in 1960. It is a linear trihydroxamate ligand, which forms a very stable hexacoordinate, octahedral[2] complex with Fe(III), $K_f = 1 \times 10^{30}$ M^{-1}. The ligand employs its three bidentate hydroxamate units in chelating the metal.

Although desferrioxamine B will bind a number of different +3 cations, e.g., Al(III), Ga(III), Cr(III), it exhibits a high specificity for Fe(III), and is utilized by *S. pilosus* for the acquisition of iron from the environment. Because of the ligand's metal selectivity and low toxicity, it has been employed in the treatment of several iron-overload diseases, e.g., thalassaemia.[3] However, desferrioxamine B does not offer a completely satisfactory solution to the iron-overload problem. The drug is cleared by the kidneys and has a very short half-life in the body, and thus the patient must be maintained on constant infusion therapy. It is not at all orally effective. Because of these shortcomings, investigators have explored the potential of other ligands as therapeutic iron chelators. To date, these investigations have not included modification of the desferrioxamine molecule simply because of the lack of high-yield or facile approaches to the synthesis of molecule. In this paper, we describe a short high-yield synthesis of desferrioxamine, a scheme that lends itself to the production of a variety of analogues.

Results and Discussion

Desferrioxamine B was first synthesized in 1962 by Prelog.[4] However, because of the number of steps in the synthesis and the low yield of the sequence, the method does not allow for to the production of large quantities of the chelator or its analogues. A retrosynthetic analysis of the ligand reveals that the desferrioxamine molecule is made up of two fundamental units, 1-amino-5-(*N*-hydroxyamino)pentane and succinic acid. The key then to its synthesis is the production of this amino(hydroxyamino)pentane unit and its condensation with succinic acid. Prelog approached this problem beginning with the starting material 1-amino-5-nitropentane, an amine that was accessible in only 46% yield.[5] This compound was next N-carbobenzoxylated, and the terminal nitro group was reduced to the corresponding hydroxyamino group. This key intermediate was condensed with succinic acid followed by a series of other dicyclohexylcarbodiimide-catalyzed acylations along with several reductions to produce desferrioxamine B. The overall yield of this 11-step sequence was 6%.

Our synthesis of desferrioxamine B (Figure 2) is predicated on the production of *O*-benzyl-*N*-(4-cyanobutyl)-hydroxylamine (**2**). This compound was prepared in 85% yield by the condensation of 4-cyanobutanal[6] (**1**) with the hydrochloride salt of *O*-benzylhydroxylamine followed by

(1) Bickel, H.; Fechtig, B.; Hall, G. E.; Keller-Schierlein, W.; Prelog, V. *Helv. Chim. Acta* **1960**, *43*, 2129.
(2) Modell, B.; Berdoukas, V. *The Clinical Approach to Thalassaemia*; Grune and Stratton: London, 1984; pp 217–241.
(3) *Development of Iron Chelators for Clinical Use*; Martell, A. E., Anderson, W. F., Badman, D. J., Eds.; Elsevier/North-Holland: New York, 1981.
(4) Prelog, V.; Walser, A. *Helv. Chim. Acta.* **1962**, *45*, 631.
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(6) Izawa, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 555–558.

0022-3263/88/1953-3131$01.50/0

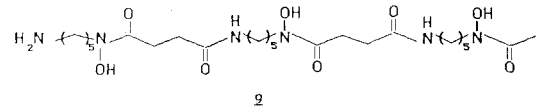

Figure 1.

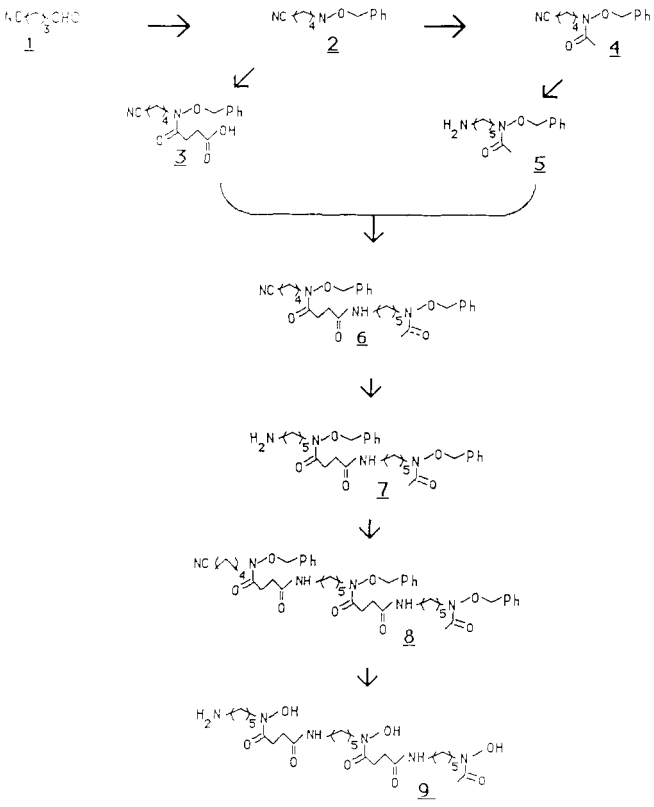

Figure 2.

reduction of the resulting oxime with sodium cyanoborohydride.[7] In the next step, the nitrile **2** was condensed either with succinic anhydride to produce the half acid amide **3** in 88% yield or with acetic anhydride to generate the corresponding cyanoacetamide **4** quantitatively. The cyanoacetamide **4** was next hydrogenated to the amine **5** in 82% yield. The reaction was carried out in methanol–ammonia, utilizing prewashed nickel catalyst.[8] We determined that if the catalyst was not first washed with water to remove residual sodium hydroxide the reaction mixture included a number of unwanted products. We next condensed the amine **5** with the half acid amide **3** in 88% yield, employing the condensing agent dicyclohexylcarbodiimide. The resulting nitrile **6** was then reduced to the corresponding amine **7** in 82% yield by employing the nickel catalyst described above. The amine **7** was treated with the half acid amide **3** in the presence of dicyclohexylcarbodiimide, and the resulting nitrile **8** was isolated in 88% yield. The nitrile **8** was reduced to the final product, desferrioxamine B (**9**), in 84% yield. It is noteworthy that the nitrile could be reduced concurrently with removal of all three benzyl protecting groups by utilizing 10% Pd/C in 0.1 N HCl and methanol.

This synthesis lends itself nicely to the modification of the desferrioxamine backbone. For example, the synthesis can be terminated at the nitrile **6**, and this compound can be reduced to the corresponding tetracoordinate ligand simply by exposing the compound to hydrogen over palladium. Alternately, the octacoordinate ligand can be generated by first reducing the nitrile of the desferrioxamine precursor **8**, followed by condensation of the product with a second equivalent of **3** and then by reduction with hydrogen over palladium. In a model study focused on demonstrating the flexibility of the synthesis, we prepared *a desamino analogue of desferrioxamine* (**6a**) (Figure 3).

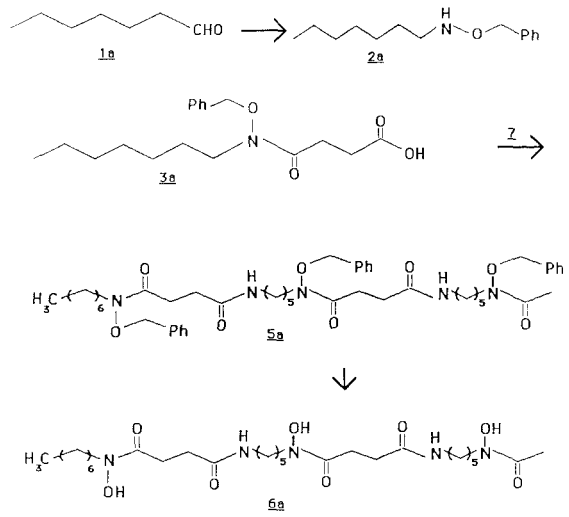

Figure 3.

The desamino analogue was prepared beginning with heptanal (**1a**). This aldehyde was treated with the hydrochloride salt of *O*-benzylhydroxylamine, and the resulting oxime was reduced with sodium cyanoborohydride to produce the *O*-benzylhydroxylamine **2a** in 22% yield.

The hydroxylamine **2a** was next condensed with succinic anhydride to generate the half acid amide **3a** in 85% yield. This amide was now condensed with amine **7** synthesized in Figure 2. The condensation product **5a** was finally reduced with hydrogen over palladium, providing the desamino analogue **6a** in 86% yield.

It is clear that the synthetic scheme described above is a viable method for the total synthesis of desferrioxamine B as well as a variety of its analogues.

Experimental Section

All reagents were purchased from Aldrich Chemical Co., Milwaukee, WI, and were used without further purification. All solvents were routinely distilled. Melting points are uncorrected. Proton NMR spectra were recorded on a Varian EM-390 or a Nicolet NT-300 instrument. IR spectra were recorded on a Beckman Acculab 1 instrument. Mass spectra were obtained on a Kratos MS80RFA spectrometer. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

4-Cyanobutanal (1) was prepared from 35.1 g (0.16 mol) of the 3-acylthiazolidine-2-thione according to the method of Izawa.[6] The aldehyde was purified by distillation at 83–84 °C (2 mm)[9] to give 9.7 g (61%) of product: ^{1}H NMR ($CDCl_3$) δ 1.80–2.15 (m, 2 H), 2.5 (t, 2 H, J = 6.3 Hz), 2.67 (t, 2 H, J = 6.3 Hz), 9.9 (s, 1 H), identical with literature values;[10] IR ($CHCl_3$) 3500, 2940, 2895, 2825, 2700, 2240, 1725, 1610, 1445, 1420, 1360 cm^{-1}.

***O*-Benzyl-*N*-(4-cyanobutyl)hydroxylamine (2).** *O*-Benzylhydroxylamine hydrochloride (4.7 g, 29.7 mmol) was mixed with 5 mL of water and 11 mL of methanol at 0 °C, and the apparent pH was adjusted to 4.7 with 6 N potassium hydroxide. The aldehyde 4-cyanobutanal[6] (2.6 mL, 27 mmol) was added to the hydroxylamine, and the mixture was allowed to warm to room temperature. The pH was maintained by the addition of further 6 N potassium hydroxide. After 1 h, the reaction mixture was

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(10) Osei-Twum, E. Y.; McCallion, D.; Nazran, A. S.; Panicucci, R.; Risbood, P. A.; Warkentin, J. *J. Org. Chem.* **1984**, *49*, 336.

cooled to 0 °C, and sodium cyanoborohydride (1.26 g, 20 mmol) was added. The pH was adjusted to 3 and maintained by addition of saturated hydrogen chloride in methanol. When the pH stabilized, the reaction was warmed to room temperature and stirred for 3 h at a pH of 3. The reaction mixture was then poured into ether and made basic with 6 N potassium hydroxide. The aqueous layer was extracted with ether (3 × 50 mL). The extracts were combined, washed with brine, and dried over magnesium sulfate. The solvents were removed, and the resulting liquid was distilled at 150–151 °C (0.6 mm) to give 4.65 g (84%) of **2**: ^{1}H NMR ($CDCl_3$) δ 1.56–1.85 (m, 4 H), 2.20–2.45 (m, 2 H), 2.85–3.10 (m, 2 H), 4.7 (s, 2 H), 5.53 (t, 1 H), 7.4 (s, 5 H); IR ($CHCl_3$) 3040, 2930, 2860, 2240, 1500, 1450, 1430, 1360, 1210 cm^{-1}. Anal. calcd for $C_{12}H_{16}N_2O$: C, 70.54; H, 7.91. Found: C, 70.51; H, 7.91.

***N*-(4-Cyanobutyl)-*N*-(benzyloxy)succinamic Acid (3).** A flask was charged with 2.8 g (13.7 mmol) of **2** in 23 mL of pyridine and 2.1 g (20.8 mmol) of succinic anhydride, initially heated at 100 °C for 1.5 h and then allowed to cool to room temperature and to stir overnight. The pyridine was removed under vacuum, and the residue was dissolved in a minimal amount of chloroform and filtered. The chloroform was removed, and the residue was dissolved in ether, which was extracted three times with 20% potassium bicarbonate (3 × 50 mL). The aqueous solutions were combined, acidified, and extracted with ether. This solution was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was then chromatographed on 70–230-mesh silica gel by eluting with 5% methanol in chloroform to give 4.12 g (98%) of product: ^{1}H NMR ($CDCl_3$) δ 1.56–1.7 (m, 2 H), 1.7–1.97 (m, 2 H), 2.36 (t, 2 H), 2.60–2.80 (m, 4 H), 3.68 (t, 2 H), 4.85 (s, 2 H), 7.4 (s, 5 H); IR ($CHCl_3$) 3670, 2930, 2240, 1710, 1650, 1415, 1200 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.17; H, 6.64. Found: C, 63.36; H, 6.74.

***N*-(4-Cyanobutyl)-*N*-(benzyloxy)acetamide (4).** A solution of 2.6 g (12.75 mmol) of **2**, 17.24 mL of pyridine, and 17.2 mL of acetic anhydride was stirred under argon at room temperature for 24 h. At the end of this period, the excess pyridine and acetic anhydride were removed by vacuum (0.05 mm). The resulting oil was taken up in chloroform, which was extracted with 1 N hydrochloric acid (2 × 50 mL), saturated sodium bicarbonate (2 × 50 mL), and brine (50 mL) and then dried over anhydrous sodium sulfate. The solution was filtered, and the solvent was removed to yield 3.14 g (100%) of product as a light oil: ^{1}H NMR ($CDCl_3$) δ 1.5–1.9 (m, 4 H), 2.1 (s, 3 H), 2.26 (t, 2 H), 3.67 (t, 2 H), 4.84 (s, 2 H), 7.41 (s, 5 H); IR ($CHCl_3$) 3040, 2940, 2880, 2240, 1650, 1450, 1410 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.26; H, 7.38. Found: C, 68.25; H, 7.44.

***N*-(5-Aminopentyl)-*N*-(benzyloxy)acetamide (5).** A 250-mL Parr shaker bottle was charged with 2.6 g (damp) Raney nickel, 1.4 g (5.7 mmol) of **4**, 15 mL of ammonia-saturated methanol, and 4 mL of saturated ammonium hydroxide. The bottle was cooled in an ice bath, and anhydrous ammonia was allowed to bubble through the solution for 10 min in order to insure saturation. The bottle was pressurized to 50 psi with hydrogen, and the reaction was allowed to proceed with shaking for 3 h. At the end of this period, the catalyst was removed by filtration through Celite, and the solvents were evaporated. The crude material was purified by chromatography on 70–230-mesh silica gel, which was prewashed with solvent to remove soluble particulates. Elution with 1% ammonium hydroxide in methanol gave a 1.25 g (88%) yield of desired material: ^{1}H NMR ($CDCl_3$) δ 1.2–1.9 (m, 8 H), 2.1 (s, 3 H), 2.53–2.83 (m, 2 H), 3.64 (t, 2 H), 4.80 (s, 2 H), 7.4 (s, 5 H); IR ($CHCl_3$) 3600, 3420, 2920, 2860, 2220, 1650, 1400 cm^{-1}. HRMS calcd for $C_{14}H_{22}N_2O_2$ 250.1680, found 250.1670. Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.15; H, 8.87. Found: C, 66.71; H, 8.79.

***N*-(4-Cyanobutyl)-3-[[5-[(benzyloxy)acetylamino]pentyl]carbamoyl]-*O*-benzylpropionohydroxamic Acid (6).** A mixture of 28 mL of chloroform, 1.46 g (4.79 mmol) of **3**, 1 g (4 mmol) of **5**, 1.24 g (6 mmol) of DCC, and 70 mg of DMAP was cooled to 0 °C for 0.5 h, allowed to warm to room temperature, and stirred for 24 h. The reaction mixture was again cooled to 0 °C and filtered. After removal of solvent the resulting oil was chromatographed on 70–230-mesh silica gel by eluting with 2.5% methanol in chloroform to yield 2.1 g (98%) of product: ^{1}H NMR ($CDCl_3$) δ 1.2–1.9 (m, 10 H), 2.1 (s, 3 H), 2.3–2.6 (m, 4 H), 2.7–3.0 (m, 2 H), 3.10–3.40 (m, 2 H), 3.55–3.80 (m, 4 H), 4.83 (s, 2 H), 4.9 (s, 2 H), 6.1–6.3 (m, 1 H), 7.45 (s, 10 H); IR ($CHCl_3$) 3665, 3450, 3350, 2940, 2880, 2250, 1660, 1520, 1410 cm^{-1}. Anal. Calcd for $C_{30}H_{40}N_4O_5$: C, 67.14; H, 7.51. Found: C, 66.70; H, 7.58.

***N*-(5-Aminopentyl)-3-[[5-[(benzyloxy)acetylamino]pentyl]carbamoyl]-*O*-benzylpropionohydroxamic Acid (7).** A 250-mL Parr shaker bottle was charged with 1.28 g of damp Raney nickel, 1.22 g (2.27 mmol) of **6**, 3 mL of ammonia-saturated methanol, and 0.7 mL of ammonium hydroxide. The bottle was cooled in an ice bath, and anhydrous ammonia was bubbled through the solution for 25 min to insure saturation. The bottle was placed on the shaker and proessurized to 50 psi with hydrogen. The reaction was allowed to proceed for 2.5 h. The catalyst was filtered off, the solvent was removed, and the crude material was chromatographed on 70–230-mesh silica gel with 0.7% ammonium hydroxide in methanol as eluant to give 1 g (82%) of product: ^{1}H NMR ($CDCl_3$) δ 1.17–1.40 (m, 4 H), 1.40–1.60 (m, 4 H), 1.60–1.77 (m, 4 H), 2.1 (s, 3 H), 2.20–2.60 (m, 4 H), 2.60–2.75 (m, 2 H), 2.75–2.87 (m, 2 H), 3.12–3.30 (m, 2 H), 3.5–3.77 (m, 4 H), 4.80 (s, 2 H), 4.88 (s, 2 H), 6.15–6.37 (m, 1 H), 7.63 (s, 10 H); IR ($CHCl_3$) 3620, 3440, 2940, 2860, 2240, 1655, 1445, 1410 cm^{-1}. Anal. Calcd for $C_{30}H_{44}N_4O_5 \cdot H_2O$: C, 64.47; H, 7.97. Found: C, 64.50; H, 8.14.

***N*-[5-[3-[(4-Cyanobutyl)(benzyloxy)carbamoyl]propionamido]pentyl]-3-[[5-[(benzyloxy)acetylamino]pentyl]carbamoyl]-*O*-benzylpropionohydroxamic Acid (8).** A mixture of 0.33 g (1.07 mmol) of **3**, 0.58 g (1.07 mmol) of **7**, 13 mg of DMAP, and 5.3 mL of chloroform was cooled to 0 °C, and 0.28 g (1.35 mmol) DCC was added. After 10 min, the reaction was allowed to warm to room temperature and stirred for 12 h. The reaction was then cooled to 0 °C and filtered. The solvent was removed, and the crude material was chromatographed on 70–230-mesh silica gel with 2.5% MeOH in chloroform as eluant to give 0.78 g (88%) of product: ^{1}H NMR ($CDCl_3$) δ 1.4–1.59 (m, 4 H), 1.59–1.70 (m, 6 H), 1.70–1.85 (m, 6 H), 2.1 (s, 3 H), 2.35 (t, 2 H), 2.40–2.55 (m, 4 H), 2.75–2.90 (m, 4 H), 3.18–3.28 (m, 4 H), 3.6–3.7 (m, 6 H), 4.8 (s, 2 H), 4.82 (s, 2 H), 4.84 (s, 2 H), 6.20–6.75 (m, 2 H), 7.4 (s, 15 H); IR ($CHCl_3$) 3680, 3440, 3340, 2990, 2940, 2870, 2250, 1660, 1520, 1455, 1415 cm^{-1}. Anal. Calcd for $C_{46}H_{62}N_6O_8$: C, 66.30; H, 7.68. Found: C, 66.44; H, 7.66.

Desferrioxamine B Hydrochloride (9). Compound **8** (0.165 g, 0.2 mmol) was reduced in 68 mL of methanol, 2.7 mL of 0.1 N hydrochloric acid, and 0.27 g of 10% palladium on carbon. The hydrogenation was carried out at 1 atm of hydrogen for 7.5 h. The solution was filtered, the solvents were removed, and the residue was washed with cold methanol, and then chloroform to give 0.1 g (84%) of product. This material had a melting point of 167–168 °C[4] and was identical with an authentic sample by 300-MHz NMR.[11] Anal. Calcd for $C_{25}H_{49}O_8N_6Cl$: C, 50.28; H, 8.27. Found: C, 50.13; H, 8.34.

***O*-Benzyl-*N*-heptylhydroxylamine (2a).** *O*-Benzylhydroxylamine (13.37 g, 83.74 mmol) was dissolved in 31 mL of methanol and 14 mL of water at 0 °C, and the apparent pH was adjusted to 4.7 with 6 N potassium hydroxide. Heptanal (10.2 mL, 76 mmol) was added, and the pH was maintained at 4.7 while the reaction warmed to room temperature. After the pH change stabilized, the mixture was again cooled to 0 °C, and 3.54 g (56.31 mmol) of sodium cyanoborohydride was added. The pH was then lowered to just below 3 and maintained there by the addition of a 2 N hydrogen chloride in methanol. When the pH change has stabilized, the solution was stirred at pH 3 for 3 h at room temperature. The mixture was then poured into ether (100 mL) and brine (50 mL) and enough 6 N potassium hydroxide was added to bring the pH to 9. The aqueous layer was extracted with ether (3 × 50 mL), and the ether solutions were combined and dried over magnesium sulfate. The solvents were then removed, and the resulting oil was distilled at 110–112 °C (0.1 mm) to give 3.6 g (22%) of **2a**: ^{1}H NMR ($CDCl_3$) δ 0.7–1.05 (m, 3 H), 1.05–1.73 (m, 10 H), 2.92 (t, 2 H), 4.7 (s, 2 H), 5.3–5.7 (m, 1 H), 7.4 (s, 5 H); HRMS calcd for $C_{14}H_{23}NO$ 221.1778, found 221.1721.

***N*-Heptyl-*N*-(benzyloxy)succinamic Acid (3a).** A solution of **2a** (2.09 g, 9.46 mmol), and succinic anhydride (1.42 g, 14.15 mmol), in 16 mL of pyridine was stirred at room temperature for 12 h. The pyridine was next removed by vacuum, and the re-

(11) We thank Dr. Heinrich H. Peter at Ciba-Geigy Basel for providing a generous sample of desferrioxamine B.

sulting material was dissolved in a minimal amount of chloroform. The solution was cooled to 0 °C and filtered. The organic solution was evaporated, and the residue was taken up in ether. The ether solution was extracted with 20% potassium bicarbonate (3 × 100 mL). The resulting aqueous solution was acidified and extracted with ether (3 × 100 mL). The ether solution was dried over anhydrous sodium sulfate, and the solvent was removed. The residue was then chromatographed on 70–230-mesh silica gel by eluting with 5% methanol in chloroform to give 2.52 g (83%) of product: ^{1}H NMR ($CDCl_3$) δ 0.8–1.1 (m, 3 H), 1.1–1.5 (m, 8 H), 1.5–1.85 (m, 2 H), 2.6–2.8 (m, 4 H), 3.63 (t, 2 H), 4.9 (s, 2 H), 7.4 (s, 5 H); HRMS calcd for $C_{18}H_{27}NO_4$ 321.1938, found 321.1952.

***N*-[5-[3-[Heptyl(benzyloxy)carbamoyl]propionamido]-pentyl]-3-[[5-[(benzyloxy)acetylamino]pentyl]carbamoyl]-*O*-benzylpropionohydroxamic Acid (5a).** The acid **3a** (0.749 g, 2.3 mmol) and **7** (1.11 g, 2.1 mmol) were dissolved in 11 mL of anhydrous dichloromethane. To this were added 0.6 g (2.9 mmol) of dicyclohexylcarbodiimide and 32 mg (0.26 mmol) of (dimethylamino)pyridine, and the solution was stirred at room temperature for 20 h. The reaction mixture was cooled to 0 °C and filtered. The solvent was removed, and the crude material was purified by chromatography on 70–230-mesh silica gel by eluting with 2% methanol in chloroform to give 1.3 g (73%) of product: ^{1}H NMR ($CDCl_3$) δ 0.70–1.05 (m, 3 H), 1.05–1.9 (m, 22 H), 2.1 (s, 3 H), 2.25–2.64 (m, 4 H), 2.64–3.0 (m, 4 H), 3.0–3.4 (m, 4 H), 3.5–3.8 (m, 6 H), 4.83 (s, 2 H), 4.87 (s, 4 H), 6.2–6.5 (m, 2 H), 7.4 (s, 15 H); FABMS calcd for $C_{48}H_{69}N_5O_8$: 843, found 843.

***N*-[5-[3-[Heptylhydroxycarbamoyl]propionamido]-pentyl]-3-[[5-(acetylhydroxyamino)pentyl]carbamoyl]-propionohydroxamic Acid (6a).** The acid **5a** (0.49 g, 0.58 mmol) was dissolved in 8.5 mL of methanol, and 50 mg of 10% Pd/C was added. The hydrogenation was carried out overnight at 1 atm of hydrogen, the reaction mixture was filtered, and the solid was washed with hot methanol. Evaporation of the methanol gave 0.284 g (85%) of product: ^{1}H NMR (DMF-d_7) δ 0.64–0.9 (m, 3 H), 0.9–1.7 (m, 22 H), 2.0 (s, 3 H), 2.2–2.5 (m, 4 H), 2.6–2.8 (m, 4 H), 2.9–3.2 (m, 4 H), 3.3–3.6 (m, 6 H), 9.7–9.95 (m, 3 H); FABMS calcd for $C_{27}H_{51}N_5O_8$: 573, found 574 (M + 1).

Registry No. **1**, 3350-74-1; **2**, 112139-59-0; **2a**, 112151-61-8; **3**, 112139-60-3; **3a**, 112139-66-9; **4**, 112139-61-4; **5**, 112139-62-5; **5a**, 112139-67-0; **6**, 112139-63-6; **6a**, 112139-68-1; **7**, 112139-64-7; **8**, 112139-65-8; **9**, 1950-39-6; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; heptanal, 111-71-7.

Main Group Conjugated Organic Anion Chemistry. 3.[1] Application of Magnesium–Anthracene Compounds in the Synthesis of Grignard Reagents

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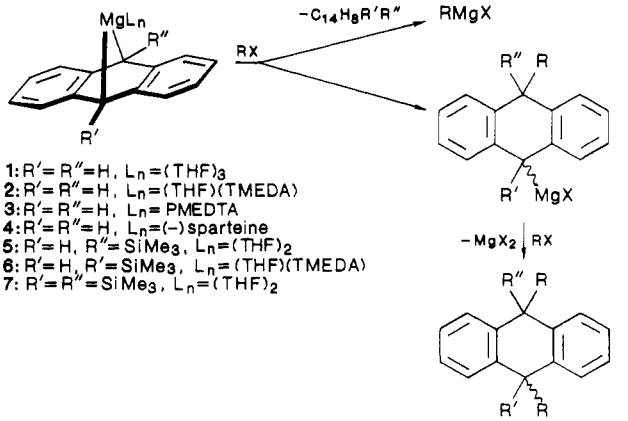
Reaction of magnesium–arene compounds, [Mg(anthracene)(THF)$_3$], **1**, and some silylanthracene, and/or tertiary amine analogues, with benzylic and allylic chlorides or bromides, and $(Me_3Si)_3CCl$, afford Grignard reagents, RMgX, in modest to high yield for chlorides and negligible to high yield for the bromides, in THF, toluene, and hexane at −10 to 20 °C. Novel benzylic-type Grignard reagents prepared in high yield include those of 9-(chloromethyl)anthracene, 2-(chloromethyl)pyridine and 8-(chloro(or bromo)methyl)quinoline, and poly-Grignard reagents derived from 1,8-bis(chloromethyl)naphthalene, 2,2′-bis(chloromethyl)-1,1′-binaphthyl, and 1,3,5-tris-(chloro(or bromo)methyl)benzene. Grignard reagent formation occurs via electron-transfer reactions. Aryl and alkyl halides yield mainly products derived from addition of the halide across the 9,10-positions of the anthracenes, via nucleophilic substitution or collapse of a diradical cage [Mg^{2+}, (anthracene)$^{\bullet-}$, $RX^{\bullet-}$.]

Introduction

Magnesium reacts with conjugated organic compounds such as polyenes, e.g. butadienes,[2,3] cyclooctatetraene[4,5] and fluoranthrene,[5] and fused aromatic compounds, e.g. anthracenes,[5-10] and isoelectronic phenazine,[1] and naphthalene,[11] in strongly coordinating solvents yielding radical anion and/or dianion species. One of the most studied is [Mg(anthracene)(THF)$_3$], **1**,[5-10,12-14] which has remarkable properties. It can act as a soluble source of magnesium, e.g. formation of MgH_2 in the presence of hydrogen,[12] or as a dinucleophile, e.g. formation of 9,10-dihydroanthracene on protonolysis.[8,12] Moreover, in some solvents it decomposes to its constituents, via Mg(anthracene)-(THF)$_2$ in benzene and toluene, and in others THF replacement prevails, e.g. with TMEDA (*N,N,N′,N′*-tetramethylethylenediamine), PMDETA (*N,N,N′,N″,N″*-pentamethyldiethylenetriamine), and (−)-sparteine,[5] resulting in compounds of higher stability in solvents other than THF. We find that **1** acts as a source of magnesium

Scheme I



with benzylic and allylic halides and $(Me_3Si)_3CCl$, affording Grignard reagents, whereas with other halides addition

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