Use of a Δ^1-Piperidine for the Synthesis of a Differentially Protected Diamine Intermediate for the Preparation of the Iron Siderophore Desferrioxamine

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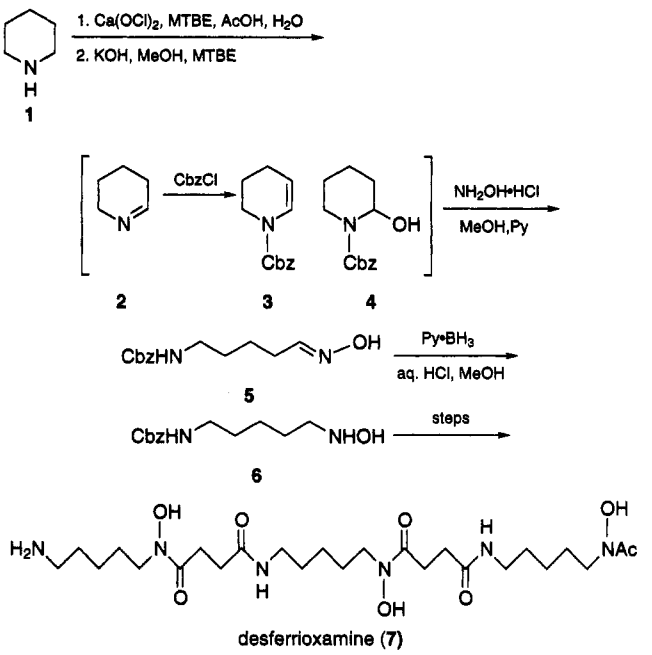
Desferrioxamine (**7**, deferoxamine, Desferal), a trihydroxamic acid isolated from *Streptomyces pilosus*, was characterized by Bickel[1] in 1960. It is used by the microorganism to sequester iron(III) for metabolism with a formation constant of 10^{31}. In man it is used to treat hemodialysis-induced aluminum accumulation in the brain and for certain iron overload conditions such as the genetically acquired hemochromatosis.[2] In a recent controversial study, it has been shown to slow the rate of mental deterioration in Alzheimers patients.[3]

Two syntheses of the compound have been reported in the literature, the original by Bickel[4] and a recent one by Bergeron.[5] The essential features of these syntheses are similar in that a differentially protected 1-amino-5-(hydroxyamino)pentane is transformed through a series of steps to form desferrioxamine (Scheme 1). The main problem with these approaches for commercial development is the bulk availability of a suitable 5-carbon piece that is easily prepared in few steps from low cost materials. As such, we felt that developing a large scale synthesis of hydroxylamine **6** from low cost readily available materials was the key to providing a commercial process for the synthesis of desferrioxamine, since **6** could readily be transformed into desferrioxamine (**7**) using modifications of the original Bickel synthesis. Several approaches were developed for the synthesis of hydroxylamine **6**, but after considering a variety of diamine sources and the processing required to convert them into the desired hydroxylamine **6**, we chose to use piperidine and take advantage of the known ability to convert it into the imine through a chlorination/dehydrochlorination protocol.[6,7] Of the various chlorine sources available, we chose to use $Ca(OCl)_2$ because it is a stable, easily handled, low cost solid.[8] Thus chloropiperidine was prepared by adding a 1:1 mixture of piperidine and acetic acid in water slowly over 2 h to a slurry of $Ca(OCl)_2$ in water and MTBE (methyl *tert*-butyl ether) at −12 °C and then separating the phases. The crude solution is used directly in the next transformation rather than concentrating it. *Since chloroamines are known to be thermally unstable, no effort was made to isolate and characterize the intermediate. The onset temperature for the decomposition of the chloroamine/MTBE solution is 110 °C as determined by differential scanning calorimetry and the neat liquid decomposes rapidly and exothermically at 65 °C.* These results show that the original procedure of ref 7 is not very safe, since in this procedure an ether–chloroamine solution is partially concentrated "on a water bath maintained below 60°". Clearly, if this is not done with the utmost care the entire mixture could decompose exothermically. We feel that the current procedure is safe and has been conducted on a pilot plant scale. Having developed a safe preparation of the chloroamine, the dehydrochlorination is affected with methanolic KOH. It should be noted that this is a high-heat, low-rate reaction. The ΔH_{rxn} is −38 kcal/mol, and the rate constant for the reaction is ~0.4 h^{-1}.[9] A critical factor in the dehydrohalogenation step is that the reaction temperature be maintained within a window of 15–25°. Lower or higher temperatures can result in a precipitous drop in yield. The imine formed from the dehydrohalogenation is trapped with CbzCl to form a mixture of carbamates **3** and **4**. Carbamate **4** can be converted completely to the enamide **3** by refluxing in toluene with a catalytic amount of acid with continuous water removal. For our purposes this was not done routinely because the crude carbamate mixture is treated with pyridine/methanol and hydroxylamine hydrochloride at 60 °C to afford the oxime **5** in 65–75% overall yield from piperidine after isolation and recrystallization. This chemistry has been used to prepare over 130 kg of the oxime. The use of sodium hypochlorite or lithium hypochlorite was not nearly as effective as $Ca(OCl)_2$. We also examined the use of chlorine, but with little success. *In fact, on one occasion we observed a runaway reaction as we sparged chlorine into a mixture of NaOH/H_2O/MTBE (0 °C to reflux in a flash).* Presumably the methyl

Scheme 1



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(6) For the use of NCS to oxidize piperidine, see: Bender, D. R.; Bjeldanes, L. F.; Knapp, D. R.; Rapoport, H. *J. Org. Chem.* **1975**, *40*, 1264 and references cited therein.
(7) Claxton, G. P.; Allen, L.; Grisar, J. M. *Org. Synth.* **1977**, *56*, 118. We have made a number of improvements to the early steps of this procedure for safety reasons.
(8) *Kirk-Othmer Encyclopedia of Chemical Technology,* Vol. 5; Grayson, M., Ed.; Wiley: New York, 1979, p 580ff.
(9) These values were obtained using a Metler RC-1 calorimeter and details will be reported elsewhere.

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tert-butyl ether was chlorinated, but in light of the nature of this reaction we were not wont to repeat it.

Reduction of the oxime was realized with pyridine·BH_3 and aqueous HCl in 90% yield.[10] The hydroxylamine **6** could be isolated as a solid by first treating with base to pH 13 and then adding sufficient water to knock the product out. The hydroxylamine can be stored for extended periods without noticeable decomposition as long as it does not come into contact with air. Preferably, the hydroxylamine is not isolated as a solid, but rather extracted with methylene chloride or MTBE/THF and used as a solution in the subsequent acylations. The use of $NaCNBH_3$ was also examined and found to be effective,[11] but safety considerations make the use of pyridine·BH_3 preferable. The entire process was also successfully carried out on pyrrolidine to provide the 4-carbon analog in an unoptimized yield of 40%. The amine **6** was then used in the Bickel synthesis of desferrioxamine to give after a number of improvements a 24% overall yield of the mesylate salt of desferrioxamine.

In conclusion we have demonstrated that calcium hypochlorite is an effective and safe oxidant for the dehydration of amines to imines on a commercial scale when careful attention is paid to the decomposition temperatures of intermediates. The chemistry described results in the preparation of differentially protected and functionalized diamines that can have further use as building blocks for such natural products as the neurotoxin NSTX-3[12] and other desferrioxamine related siderophores.[13] Furthermore, the carbamate **3** may prove valuable in other synthetic endeavors.[14]

Experimental Section

Synthesis of Oxime 11. Acetic acid (50.0 g, 0.83 mol) was added to a solution of piperidine (50.0 g, 0.58 mol) in 50 mL of water. This solution was added to a slurry of calcium hypochlorite[15] (65% available chlorine 56.5 g, 0.40 mol) in 125 mL each of water and MTBE (methyl *tert*-butyl ether) while maintaining the temperature at <−10 °C. At the end of the addition the phases were separated and to the organic phase was added KOH (56.2 g of 85%, 0.85 mol) in 125 mL of methanol, during which time the solution was allowed to warm to 15−18 °C where it was maintained. The mixture was typically allowed to stir at 15−18 °C for 16 h after the addition was complete (the temperature was maintained with a cold water). Aqueous K_2CO_3 (67.0 g, 0.48 mol in 450 mL of water) was added, followed by benzyl chloroformate (97.6 g, 0.57 mol) at 15−18 °C over about 1 h. The organic phase was concentrated to a thin oil which was added to hydroxylamine hydrochloride (38.7 g, 0.56 mol) in 88 mL of pyridine (0.85 mol) and reacted at 70 °C for about 60 min. The product crystallized on cooling, after which 125 mL of water was added to complete the precipitation and dissolve inorganic salts. The product was filtered, washed with water, and dried, typically yielding 90 g, 62%, of white flocculent oxime **11**, mp 95−99 °C (mp 125−126 °C for oxime which was recrystallized twice from methanol). ^1H NMR ($CDCl_3$−MeOH-d_4) 7.34 (bs, 5H), 6.65 (t, J = 5.4 Hz), 5.07 (s), 4.45 (bs, OH), 3.16 (t, J = 6.2 Hz), 2.38 (m), 1.52 (m). Some broadening is present because of the (*Z*)-isomer. ^{13}C NMR ($CDCl_3$−MeOH-d_4) 156.8, 151.38, 136.23, 127.96, 127.51, 127.34, 66.02, 39.99, 29.0, 24.07, 22.76 ppm. IR ($CDCl_3$) 1705, 1510 cm^{-1}. Anal. Calcd: C, 62.38; H, 7.25; N, 11.19. Found: C, 61.96; H, 7.19; N, 11.05.

Synthesis of Hydroxylamine 6. To a 500 mL 3-neck round-bottom flask, equipped with a mechanical stirrer, temperature probe, dropping funnel, and nitrogen inlet, were added 8.9 g (37 mmol) of oxime **11**, 50.0 mL of methanol, and 7.5 mL (74 mmol) of pyridine−borane complex. The reaction was cooled to 0 °C (brine−ice bath), and 50 mL of 10% aqueous HCl was added via dropping funnel over a 20 min period. The reaction temperature was maintained between 0 and 6 °C during the addition. After the addition was complete, the brine bath was removed and the reaction was stirred for an additional 2 h. The pH was then adjusted to 13 by the addition of 100 mL of 25% aqueous NaOH. The product was further precipitated by the addition of 125 mL of water. The white solids were then filtered, being careful to maintain a positive nitrogen flow since the hydroxylamine decomposes in the presence of oxygen. The white solids were then dried overnight via high vacuum at rt to give 7.6 g (86%) of 1-(carbobenzoxyamino)-5-(hydroxyamino)pentane (**6**). Mp (crude) 100−103°C (lit.[4] mp 113−115 °C). ^1H NMR (90 MHz, DMSO) 7.3 (s, 5H), 7.0 (br s, 2H), 5.4 (br s, 1H), 4.9 (s, 2H), 3.0 (m, 2H), 2.7 (m, 2H), 1.3 (m, 6H). IR (KBr, cm^{-1}) 3320, 1690, 1655.

4-(*N*-(Benzyloxycarbonylamino)butanal Oxime. To a 0 °C biphasic mixture of 31.9 g (0.223 mol) of $Ca(OCl)_2$ in 50 mL of water and 50 mL of MTBE were slowly added 30.0 mL (0.36 mol) of pyrrolidine in 35 mL of acetic acid and 50 mL of water while maintaining the temperature between 0 and 9 °C. The bath was then removed, the layers were separated, and the aqueous phase was extracted with MTBE (3 × 50 mL). The solution was concentrated on a rotary evaporator to a volume of approximately 90 mL (*caution*: *N*-chloroamines are potentially explosive. Do not heat the water bath while concentrating). The MTBE solution of the *N*-chloroamine was then slowly added to 28.6 g (0.512 mol) of KOH in 100 mL of methanol while maintaining the temperature between 10 and 15 °C. The brown mixture was then stirred overnight at room temperature. The resultant slurry was cooled to 0 °C and 47.0 mL (0.329 mol) of benzyl chloroformate dissolved in 50 mL of MTBE was slowly added while maintaining the temperature between 0 and 8 °C and a pH of 7−12 by adding 50% NaOH as needed. The cooling bath was removed, 100 mL of water was added, the insolubles were removed by filtration, and the filtrate was extracted with MTBE (2 × 100 mL). The combined organic extracts were concentrated to a brown oil. The oil was dissolved in 70 mL of MeOH and 40 mL of pyridine. Hydroxylamine hydrochloride (27.6 g, 0.397 mol) was added, and the mixture was heated to reflux for 4 h at which time the reaction was complete as determined by TLC (50% ethyl acetate/cyclohexane). Methanol was removed, 100 mL of water was added, and the resultant oil was extracted with ethyl acetate (3 × 100 mL). The ethyl acetate was removed, and toluene was added and removed twice by vacuum distillation. The resultant solids were then triturated in 30 mL of toluene at room temperature and then at 0 °C. The solids were filtered, washed with 0 °C toluene, and dried via high vacuum to give 26.8 g (34%) of the oxime as a slightly colored solid. This is an unoptimized procedure. Mp 94−96 °C (uncorrected). ^1H NMR ($CDCl_3$) 7.34 (m, 5H), 7.25 (m, 1H), 6.65 (t, J = 8.3 Hz, 1H), 5.01 (s, 2H), 3.34 (s, 1H), 3.01 (q, J = 6.2 Hz, 2H), 2.22 (m, 2H), 1.55 (qn, J = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) 156.05, 149.70, 137.22, 128.26, 127.62, 65.09, 39.48, 26.03, 22.11. HRMS (EI) calcd for $C_{12}H_{16}N_2O_3$ + H 237.1248, found 237.1239. Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.82; N, 11.86. Found: C, 60.85; H, 6.77; N, 11.76.

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