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Selective Cleavage of *N*-Benzyl-Protected Secondary Amines by Triphosgene

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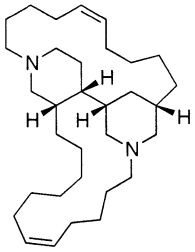
Received August 28, 2002

Abstract: A series of competition experiments has revealed that selective cleavage of *N*-benzyl-protected secondary amines can be achieved with triphosgene, thereby providing a useful range of carbamoyl chlorides.

In connection with efforts to develop synthetic routes to the marine natural product haliclonacyclamine A (**1**)[1] and its various congeners,[1,2] we sought a method that would allow for selective mono-debenzylation of the readily available bis-piperidine **2**.[3] Among the various reagents investigated for this purpose,[4] the commercially available and easily handled triphosgene [bis(trichloromethyl) carbonate][5,6] proved especially efficacious in converting, in a completely selective fashion, substrate **2** into the carbamoyl chloride **3**, which could be readily manipulated so as to give the corresponding secondary amine or a now orthogonally protected diamine. In view of this result, and the likely utility of regioselective methods for the *N*-debenzylation of amines,[4c] we have evaluated the capacity of triphosgene to effect the selective cleavage of a suite of *N*-benzyl-protected secondary amines and report the outcomes here.



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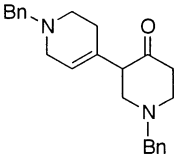

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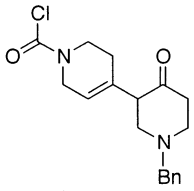

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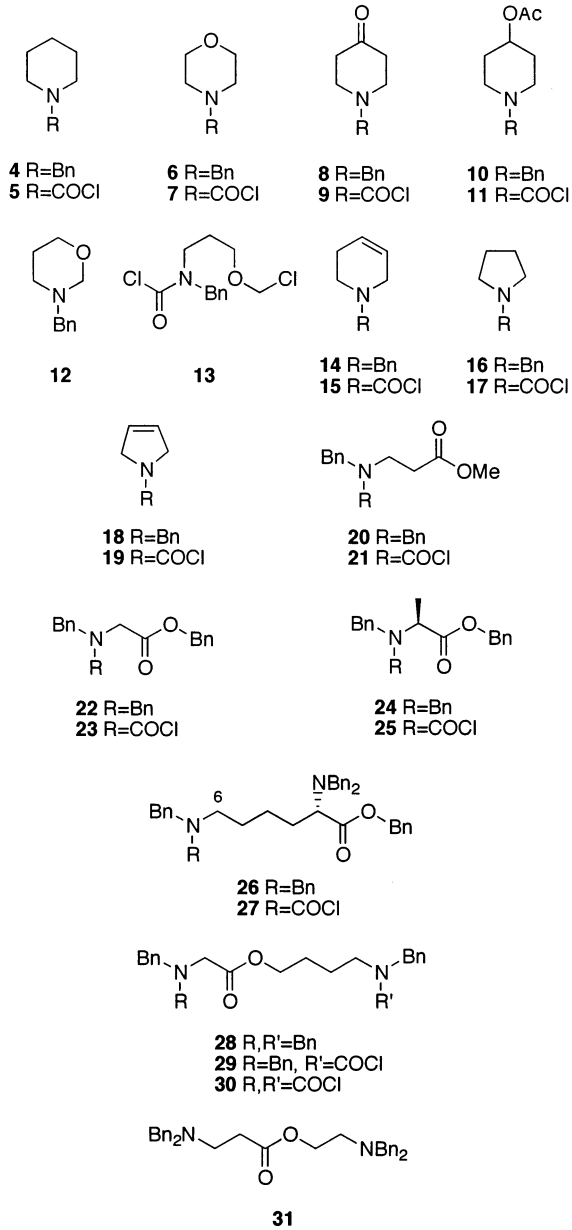
In undertaking the above-mentioned evaluation, a series of competition experiments was set up wherein equimolar quantities of various pairs of *N*-benzyl-protected secondary amines were subjected to treatment with a 0.166 molar equiv of triphosgene in dichloromethane at 0−4 °C. After 16 h, the reaction mixture was analyzed by GLC so as to determine the proportions of substrates remaining as well as the ratios of the product carbamoyl chlorides. Authentic samples of the products were prepared by independent reaction of the *N*-benzylamines with triphosgene in the manner defined by Jorand-Lebrun et al.[6] The collection of substrates investigated is shown below together with the structures of the products, while the nature and outcomes of the competition experiments are presented in Table 1.



In almost every instance a very clean reaction was observed. It is clear, as evidenced by the results presented in entries 1, 2, and 7, that it is possible to achieve very selective de-benzylation in cases where there is a significant difference in electron densities at the *N*-benzylated ring nitrogens in the two competing substrates. Thus, it would seem that the more nucleophilic nitrogen centers

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10.1021/jo0263622 CCC: $25.00
Published on Web 12/06/2002

TABLE 1. Outcomes of Competitive N-Debenzylation Experiments[a]

entry	first substrate	second substrate	major product	minor product	product ratio[b]
1	**4**	**6**	**5**	**7**	600:1
2	**4**	**8**	**5**	**9**	93:1
3	**4**	**10**	**5**	**11**	4:1
4	**4**	**14**	**5**	**15**	3:1
5	**4**	**16**	**17**	**5**	4:3
6	**6**	**12**	**13**	**7**	7:3
7	**8**	**14**	**15**	**9**	23:1
8	**16**	**18**	**17**	**19**	8:7
9	**20**	**22**	**21**	**23**	9:5[c]

[a] Reactions conducted as defined in the Experimental Section using 0.5 mmol of the first and second substrates as well as 0.166 mmol of triphosgene. [b] Unless otherwise specified, ratio determined by GLC analysis under conditions defined in the Experimental Section. [c] Ratio determined by ^{1}H NMR analysis at 300 MHz.

react preferentially with triphosgene and, thereby, set in motion the debenzylation reaction. This explanation would also account for the selective conversion of substrate **2** into product **3**. Such electron density arguments presumably also account for the preferential debenzylation of the β-amino acid derivative **20** over its α-amino acid counterpart **22** (entry 9). Further, the observation that the *N*-benzyl-protected alanine derivative **24** fails to react, even at 100 °C, with triphosgene (so as to give compound **25**) may be attributed to the increased steric congestion (relative to the glycine congener **22**) at the α-carbon, which is likely to impede attack of triphosgene at the nitrogen. The conversion **22** → **23** is notable for the lack of cleavage of the benzyl ester moiety. The observed ring cleavage of [1,3]oxazine (**12**) to give the chloromethyl ether **13** is not surprising, but this result serves to highlight one constraint (albeit a modest one) on the applicability of this type of debenzylation protocol.

In addition to the cases just mentioned, some further internal competition experiments were undertaken. Thus, treatment of the bis-dibenzylamine **26** with triphosgene gave, in 91% yield, the carbamoyl chloride **27** wherein reaction has taken place at the nitrogen remote from the ester moiety. The structure of product **27** follows from the significant change in the ^{1}H NMR chemical shift observed (δ 2.43 → 3.27) for the triplet resonance due to the C6 protons in the substrate and product. Reaction of compound **28** under the usual debenzylation conditions gave, in 87% combined yield, a ca. 5:1 mixture of the carbamoyl chloride **29** and its doubly debenzylated counterpart **30** (once again, structural assignments follow from analysis of changes in chemical shifts for key proton resonances). In contrast, the β-amino ester derivative **31** only gave a complex mixture of products on exposure to triphosgene. Nevertheless, the results just mentioned clearly add weight to the idea that electronic factors play a pivotal role in determining the selectivity of these debenzylation reactions. Such factors may be either reinforced or counterbalanced by steric effects.

On the basis of the foregoing, triphosgene would seem to be a useful reagent for the selective cleavage of *N*-benzyl-protected secondary amines even when several such groups are incorporated within the one substrate. With the developments described here, we believe the benzyl moiety can be regarded as an especially valuable protecting group for polyamines and that it warrants greater attention than it has been accorded to date. Indeed, with the increasing number of biologically active polyamine natural products[7] being discovered, benzyl protection of amines would now seem to be a useful tool in developing serviceable syntheses of these compounds and their analogues.

Experimental Section

General experimental procedures have been described previously.[8] Unless otherwise specified, NMR spectra were recorded using deuteriochloroform as solvent.

***N*-Benzyl-Protected Amines 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 31.** *N*-Benzylamines **8** and **18** were purchased from commercial suppliers while compounds **4**, **6**, and **16** were prepared by reaction of the corresponding secondary amine with benzyl chloride in the presence of ethanolic potassium carbonate according to the method of Diouf et al.[9] Compound **14** was prepared by reduction of *N*-benzylpyridinium chloride with sodium borohydride,[10] while *N*-benzylamine **20** was generated from *N*,*N*-dibenzylamine and methyl acrylate according to the method of Bartoli et al.[11] Compounds **22** and **24** were prepared by tris-benzylation of glycine and (*S*)-alanine, respectively, according to the procedure of Beaulieu and Wernic.[12] The remaining substrates were prepared according to the methods defined below.

1-Benzylpiperidin-4-yl Acetate (10). A magnetically stirred solution of 1-benzyl-4-piperidone (1.89 g, 10 mmol) in MeOH (20 mL) and maintained under nitrogen was cooled to 0 °C and then treated, portionwise over 0.25 h, with sodium borohydride (810 mg, 20 mmol). The resulting solution was stirred at 18 °C for 2 h and then diluted with H_2O (10 mL). The resulting mixture was partitioned between ethyl acetate (50 mL) and brine (50 mL), and then the separated organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was dissolved in pyridine (20 mL), and the resulting magnetically stirred solution treated, in one portion, with acetic anhydride (1.23 g, 12 mmol). After being stirred at 18 °C for 6 h, the reaction mixture was concentrated under reduced pressure and the residue partitioned between dichloromethane (50 mL) and brine (50 mL). The separated organic phase was washed with water (2 × 50 mL) and brine (2 × 50 mL) and then dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford compound **10** (2.25 g, 97%) as a clear yellow oil: ^{1}H NMR (300 MHz) δ 7.32−7.27 (5H, m), 4.77 (1H, septet, J = 4 Hz), 3.51 (2H, s), 2.70 (2H, m), 2.25 (2H, m), 2.02 (3H, s), 1.88 (2H, m), 1.71 (2H, m); ^{13}C NMR (75 MHz) δ 170.8 (C═O), 138.5 (C), 129.3 (CH), 128.4 (CH), 127.3 (CH), 70.8 (CH), 63.3 (CH_2), 51.2 (CH_2), 31.2 (CH_2), 21.8 (CH_3); IR (NaCl, film) ν_{max} 2949, 2804, 1734, 1362, 1243, 1041, 698 cm^{-1}; MS (EI) *m*/*z* 233 ($M^{\bullet+}$, 20), 190 [$(M - CH_3CO^{\bullet})^+$, 7], 174 (17), 172 (24), 156 [$(M - Ph^{\bullet})^+$, 15], 91 (100), 82 (43). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.77, H, 8.24, N, 6.01.

3-Benzyl[1,3]oxazinane (12). This compound was prepared according to the method of Booth and Lemieux[13] and obtained as a clear, colorless oil: bp 104 °C (4 mmHg); ^{1}H NMR (300 MHz) δ 7.34−7.22 (5H, m), 4.31 (2H, s), 3.87 (2H, t, J = 5.6 Hz), 3.82

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(2H, s), 2.88 (2H, t, J = 5.6 Hz), 1.72 (2H, p, J = 5.6 Hz); ^{13}C NMR (75 MHz) δ 138.7 (C), 129.2 (CH), 128.5 (CH), 127.3 (CH), 85.0 (CH_2), 68.3 (CH_2), 56.2 (CH_2), 49.9 (CH_2), 22.8 (CH_2); IR (NaCl, film) ν_{max} 2948, 2849, 1453, 1046, 737, 698 cm^{-1}; MS (EI) m/z 177 ($M^{\bullet+}$, 16), 176 [$(M - H^{\bullet})^+$, 46], 91 (100), 86 (23). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.55, H, 8.47, N, 7.86.

Benzyl (*S*)-2,6-Bis-dibenzylaminohexanoate (26). A magnetically stirred suspension of L-lysine hydrochloride (1.83 g, 10.0 mmol) in DMF/water (10:1 v/v mixture, 22 mL) was treated with anhydrous potassium carbonate (11.1 g, 80.0 mmol, 8 molar equiv) and benzyl bromide (6.5 mL, 55 mmol, 5.5 molar equiv). After being stirred at 18 °C for 4 days, the resulting white slurry was diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic portions were washed with aqueous sodium chloride (50 mL of a 15 wt % solution), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure to yield a colorless oil. Subjection of this material to flash chromatography (silica gel, 1:9 → 1:4 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f 0.5 in 1:4 v/v ethyl acetate/hexane), compound **26** (4.99 g, 84%) as a clear, colorless and highly viscous oil: $[\alpha]_D$ −52.5 (c 2.8, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.50−7.26 (25H, m), 5.33 (1H, d, J = 12.3 Hz), 5.21 (1H, d, J = 12.3 Hz), 3.99 (2H, d, J = 13.8 Hz), 3.59 (2H, d, J = 13.8 Hz), 3.57 (4H, AB_q, J = 14.1 Hz), 3.43 (1H, dd, J = 8.8 and 6.2 Hz), 2.43 (2H, t, J = 6.9 Hz), 1.86−1.25 (6H, m); ^{13}C NMR (75 MHz) δ 172.8 (C), 140.0 (C), 139.7 (C), 136.1 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.9 (CH), 126.7 (CH), 66.0 (CH_2), 60.8 (CH), 58.4 (CH_2), 54.5 (CH_2), 53.2 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 23.9 (CH_2); IR (NaCl, film) ν_{max} 3029, 2942, 2798, 1730, 1494, 1453, 1137, 745, 697 cm^{-1}; MS (EI) m/z 596 ($M^{\bullet+}$, 7%), 505 [$(M - C_7H_7^{\bullet})^+$, 46], 461 [$(M - BnOCO^{\bullet})^+$, 67], 401 (12), 308 (20), 236 (15), 210 (41), 91 (100); HRMS calcd for $C_{41}H_{44}N_2O_2$ 596.3403, found 596.3399.

4-Dibenzylaminobutyl Dibenzylaminoacetate (28). A magnetically stirred solution of 4-(*N*,*N*-dibenzylamino)butan-1-ol[14] (539 mg, 2.00 mmol) in dichloromethane (8 mL) was treated with the hydrochloride salt of *N*,*N*-dibenzylglycine[15] (929 mg, 3.00 mmol, 1.5 mole equiv), *N*,*N*-diisopropylethylamine (1.05 mL, 6.03 mmol, 3 molar equiv) and DMAP (37 mg, 0.30 mmol, 15 mol %). The resulting solution was cooled to 0 °C and EDCI (1.73 g, 9.00 mmol, 4.5 molar equiv) was added. The reaction mixture was removed from the cooling bath and allowed to stir at 18 °C for 16 h. Sodium bicarbonate (20 mL of a saturated aqueous solution) and water (10 mL) were added, and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The combined organic portions were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica gel, 1:9 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f 0.3), compound **28** (1.01 g, 100%) as a clear, colorless oil: ^{1}H NMR (300 MHz) δ 7.40−7.20 (20H, m), 4.02 (2H, t, J = 6.3 Hz), 3.80 (4H, s), 3.55 (4H, br s), 3.27 (2H, s), 2.44 (2H, br t, J = 6.3 Hz), 1.66−1.55 (4H, m); ^{13}C NMR (75 MHz) δ 171.4 (C), 139.8 (C), 139.0 (C), 128.9 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.1 (CH), 126.9 (CH), 64.3 (CH_2), 58.5 (CH_2), 57.9 (CH_2), 53.7 (CH_2), 53.0 (CH_2), 26.6 (CH_2), 23.8 (CH_2); IR (NaCl, film) ν_{max} 3027, 2945, 2798, 1734, 1494, 1453, 1367, 1184, 1148, 1028, 743, 698 cm^{-1}; MS (EI) m/z 506 ($M^{\bullet+}$, 3), 415 [$(M - C_7H_7^{\bullet})^+$, 20], 311 (3), 252 (2), 210 (69), 181 (3), 160 (21), 118 (3), 91 (100); HRMS calcd for $C_{34}H_{38}N_2O_2$ 506.2933, found 506.2934.

2-Dibenzylaminoethyl 3-Dibenzylaminopropanoate (31). A magnetically stirred solution of 2-(*N*,*N*-dibenzylamino)ethanol[16] (1.05 g, 4.37 mmol) in dichloromethane (10 mL) was treated with 3-(*N*,*N*-dibenzylamino)propanoic acid[17] (2.00 g, 6.56 mmol, 1.5 molar equiv), *N*,*N*-diisopropylethylamine (2.30 mL, 13.11 mmol, 3 molar equiv), and DMAP (80 mg, 0.65 mmol, 15 mol %). The resulting solution was cooled to 0 °C, and EDCl (3.78 g, 19.68 mmol, 4.5 molar equiv) was added. The reaction mixture was then removed from the cooling bath and allowed to stir at 18 °C for 16 h. After this time, sodium bicarbonate (40 mL of a saturated aqueous solution) and water (20 mL) were added, and the resulting mixture extracted with dichloromethane (3 × 20 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil. Subjection of this material to flash chromatography (silica gel, 1:9 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f 0.3), ester **31** (1.64 g, 76%) as white crystals: mp 62−64 °C; ^{1}H NMR (300 MHz) δ 7.42−7.20 (20H, m), 4.19 (2H, t, J = 6.0 Hz), 3.68 (4H, s), 3.64 (4H, s), 2.87 (2H, t, J = 7.0 Hz), 2.73 (2H, t, J = 6.0 Hz), 2.55 (2H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz) δ 172.3 (C=O), 139.3(4) (C), 139.3 (C), 128.8 (CH), 128.6 (CH), 128.2 (C), 127.0 (CH), 62.5 (CH_2), 58.8 (CH_2), 58.2 (CH_2), 51.8 (CH_2), 49.3 (CH_2), 33.0 (CH_2) (one peak obscured or overlapping); IR (KBr) ν_{max} 3027, 2928, 2799, 1734, 1494, 1453, 1180, 1028, 745, 698 cm^{-1}; MS (EI) m/z 492 (M^+, 10), 401 [$(M - C_7H_7^{\bullet})^+$, 45], 357 (13), 224 (13), 210 (66), 91 (100); HRMS calcd for $C_{33}H_{36}N_2O_2$ 492.2777, found 492.2775.

Carbamoyl Chlorides 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 27, 29, and 30. Authentic samples of the title carbamoyl chlorides were prepared by reaction of the corresponding *N*-benzylamines with triphosgene according to the method of Jorand-Lebrun et al.[6] The samples of compounds **5**,[18] **7**,[18] **9**,[6] **15**,[19] and **17**[18] obtained by such means gave spectroscopic data in complete accord with the same derived from authentic samples or reported previously. Data for the remaining compounds are presented below.

1-Chlorocarbonylpiperidin-4-yl Acetate (11). Obtained in 88% yield from compound **10**: ^{1}H NMR (300 MHz) δ 4.99 (1H, septet, J = 3.5 Hz), 3.84 (2H, m), 3.61 (2H, m), 2.07 (3H, s), 1.92 (2H, m), 1.74 (2H, m); ^{13}C NMR (75 MHz) δ 170.0 (C), 148.0 (C), 68.3 (CH), 45.7 (CH_2), 43.2 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 21.2 (CH_3) (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 2961, 1738, 1407, 1366, 1239, 1194, 1044 cm^{-1}; MS (EI) m/z 207 and 205 ($M^{\bullet+}$, each <1%), 170 [$(M - Cl^{\bullet})^+$, 16], 147 and 145 [$(M - HOAc)^{\bullet+}$, 45 and 100], 130 (26), 110 (38). Anal. Calcd for $C_8H_{12}ClNO_3$: C, 46.73; H, 5.88; Cl, 17.24; N, 6.81. Found: C, 46.58, H, 5.91, Cl, 17.23, N, 6.79.

***N*-Benzyl-(3-chloromethoxy-propyl)amine-1-carbonyl Chloride (13).** Obtained in 74% yield from compound **12**: ^{1}H NMR (300 MHz) δ 7.40−7.26 (5H, m), 5.46 (1H, s), 5.45 (1H, s), 4.73 (1H, s), 4.59 (1H, s), 3.70 (2H, t, J = 5.9 Hz), 3.47 (2H, m), 1.94 (2H, m); ^{13}C NMR (75 MHz) δ 150.3 (C=O), 149.8 (C=O), 135.8 (C), 135.7 (C), 131.2 (CH), 129.8 (CH), 129.1(4) (CH), 129.0-(9) (CH), 128.3 (CH), 127.3 (CH), 83.2 (CH_2), 83.1 (CH_2), 67.8 (CH_2), 67.6 (CH_2), 55.1 (CH_2), 53.1 (CH_2), 47.9 (CH_2), 47.1 (CH_2), 28.1 (CH_2), 27.1 (CH_2) (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 2950, 1732, 1403, 1190, 1131, 702 cm^{-1}; MS (EI) m/z 277 and 275 ($M^{\bullet+}$, each <1), 91 (100); HRMS calcd for $C_2H_{15}{}^{35}Cl_2NO_2$ 275.0480, found 275.0477.

2,5-Dihydropyrrole-1-carbonyl Chloride (19). Obtained in 44% yield from compound **18**: ^{1}H NMR (300 MHz) δ 5.86 (1H, m), 5.81 (1H, m), 4.38 (2H, m), 4.28 (2H, m); ^{13}C NMR (75 MHz) δ 146.8 (C), 125.3 (CH), 124.8 (CH), 56.8 (CH_2), 54.8 (CH_2) (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 2921, 2872, 1742, 1627, 1470, 1375, 1183, 883, 755 cm^{-1}; MS (EI) m/z 133 and 131 ($M^{\bullet+}$, 27 and 98), 132 and 130 [$(M - H^{\bullet})^+$, 17 and 35], 96 [$(M - Cl^{\bullet})^+$, 100], 67 (26), 63 (21); HRMS calcd for $C_5H_6{}^{35}ClNO$ 131.0138, found 131.0138.

Compound 21. Obtained in 94% yield from compound **20**: ^{1}H NMR (300 MHz) δ 7.45−7.20 (5H, m), 4.79 (1H, s), 4.63 (1H, s), 3.72 (1H, t, J = 7.2 Hz), 3.69 (3/2H, s), 3.67 (3/2H, s), 3.61 (1H, t, J = 6.9 Hz), 2.65 (2H, m); ^{13}C NMR (75 MHz) δ 171.5 (C), 171.1 (C), 149.9 (C), 149.5 (C), 135.5 (C), 135.4 (C), 128.9 (CH), 128.2 (CH), 128.1 (CH), 127.1 (CH), 55.3 (CH_2), 53.0 (CH_2),

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52.1 (CH_3), 52.0 (CH_3), 46.0 (CH_2), 45.4 (CH_2), 33.2 (CH_2), 32.0 (CH_2) (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 3032, 2953, 1733, 1438, 1402, 1374, 1323, 1207, 1174, 1048, 702 cm^{-1}; MS (EI) *m/z* 257 and 255 ($M^{\bullet+}$, each <1), 226 and 224 [$(M - CH_3O^{\bullet})^+$, each <1], 192 [$(M - ClCO^{\bullet})^+$, 76], 91 (100). Anal. Calcd for $C_{12}H_{14}ClNO_3$: C, 56.37; H, 5.52; Cl, 13.87; N, 5.48. Found: C, 56.71, H, 5.60, Cl, 13.86, N, 5.10.

Compound 23. Obtained in 92% yield from compound **22**: ^1H NMR (300 MHz) δ 7.42−7.20 (10H, m), 5.19 (1H, s), 5.17 (1H, s), 4.82 (1H, s), 4.67 (1H, s), 4.12 (1H, s), 4.06 (1H, s) (additional signals due to slow interconversion of rotamers); ^{13}C NMR (75 MHz) δ 167.6, 167.3, 150.4, 150.2, 134.9, 134.8, 134.5, 134.3, 128.9, 128.8, 128.5(2), 128.5(0), 128.4(8), 128.3(9), 128.3(3), 128.2(7), 128.2(2), 128.1(9), 128.1(4), 127.4, 67.4, 67.3, 55.1, 53.5, 51.0, 49.2 (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 3065, 3034, 2950, 1732, 1497, 1455, 1391, 1174, 1079, 991, 738, 698 cm^{-1}; MS (EI) *m/z* 281 [$(M - HCl)^{\bullet+}$, 6], 253 [$(M - CO - HCl)^{\bullet+}$, 3], 91 (100). Anal. Calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.07; Cl, 11.16; N, 4.41. Found: C, 63.24, H, 5.37, Cl, 11.19, N, 4.37.

General Procedure Used for Competition Experiments. A solution of triphosgene (49 mg, 0.166 mmol) in anhydrous dichloromethane (1.7 mL) was added to a magnetically stirred solution of the two *N*-benzylamines (0.50 mmol of each) in anhydrous dichloromethane maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was left to stand at 4 °C for 16 h and then analyzed by GLC to identify (by comparison with authentic samples) products and determine their ratios. These analyses were carried out using a Varian 3400 Gas Chromatograph fitted with an FID operating at 300 °C and a 15 m × 0.25 mm (i.d.) capillary column employing a 0.25 μm thick poly(dimethylsiloxane) (HP1) stationary phase and helium as carrier gas (linear velocity of 35 cm/sec); generally an initial temperature of 50 °C rising at 10 °C/min to a final temperature of 300 °C was employed together with an injector temperature of 250 °C and a 50:1 splitter. Dodecane was used as an internal standard in all experiments. The results of such studies are presented in Table 1.

1-Benzyl-4-oxo-1,2,3,4,5,6,3′,6′-octahydro-2′*H*-[3,4′]bipyridinyl-1′-carbonyl Chloride (3). A magnetically stirred solution of triphosgene (38 mg, 0.128 mmol) in dry dichloromethane (1.3 mL) maintained at 0 °C under nitrogen was treated with a solution of compound **2**[3] (131 mg, 0.362 mmol) in dry dichloromethane (1.2 mL). The resulting mixture was allowed to stir at 4 °C for 22 h and then concentrated under reduced pressure to give a colorless oil. Subjection of this material to flash chromatography [silica, 1:4 → 3:2 v/v ethyl acetate (containing ca. 1% ammonia)/hexane elution] provided, after concentration of the appropriate fractions (R_f 0.6 in 1% v/v ammonia/ethyl acetate), compound **3** (93 mg, 77%) as a clear, colorless oil: ^1H NMR (500 MHz, 55 °C) δ 7.34−7.25 (5H, m), 5.52 (1H, br s), 4.13−4.08 (2H, br m), 3.75−3.63 (2H, br m), 3.62 (2H, s), 3.17 (1H, br dd, J = 8.7, 5.8 Hz), 3.01−2.98 (2H, br m), 2.62−2.52 (3H, br m), 2.45−2.39 (1H, m), 2.16−2.11 (2H, m); ^{13}C NMR (125 MHz, 25 °C) δ 208.1 (C), 208.0 (C), 148.8 (C), 148.3 (C), 137.9 (C), 133.8 (C), 133.7 (C), 129.0 (CH), 128.5 (CH), 127.5 (CH), 120.8 (CH), 120.5 (CH), 62.0 (CH_2), 56.9 (CH_2), 56.7 (CH), 56.6 (CH), 53.4 (CH_2), 47.5 (CH_2), 45.8 (CH_2), 45.5 (CH_2), 43.1 (CH_2), 40.9(3) (CH_2), 40.9(1) (CH_2), 27.7 (CH_2), 27.2 (CH_2) (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 3027, 2908, 2806, 1739, 1716, 1494, 1453, 1405, 1363, 1352, 1317, 1261, 1220, 1187, 1126, 1049, 851, 741, 700, 660 cm^{-1}; MS (EI) *m/z* 334 and 332 ($M^{\bullet+}$, 17 and 45), 297 [$(M - Cl^{\bullet})^+$, 20], 278 and 276 (4 and 11), 133 (62), 91 (100); HRMS calcd for $C_{18}H_{21}{}^{35}ClN_2O_2$ 332.1292, found 332.1290.

Compound 27. A magnetically stirred solution of diamine **26** (597 mg, 1.00 mmol) in dichloromethane (3.3 mL) maintained at 0 °C was treated, via cannula, with a solution of triphosgene (104 mg, 0.35 mmol, 0.35 molar equiv) in dichloromethane (3.5 mL). The ensuing reaction mixture was allowed to stand at 4 °C for 16 h then the solvent was removed under reduced pressure to yield a colorless oil. Subjection of this material to flash chromatography (silica gel, 1:9 → 3:17 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f 0.3 in 3:17 v/v ethyl acetate/hexane), compound **27** (518 mg, 91%) as a clear, colorless oil: $[\alpha]_D$ −52.0 (*c* 2.4, $CHCl_3$); ^1H NMR (500 MHz) δ 7.54−7.31 (20H, m), 5.37 (1H, m), 5.27 (1H, m), 4.71 (1H, m), 4.58 (1H, AB_q, J = 15 Hz), 4.00 (2H, m), 3.63 (2H, m), 3.44 (1H, m), 3.37 (2H, m), 1.87−1.77 (2H, m), 1.56−1.49 (3H, m), 1.30 (1H, m); ^{13}C NMR (125 MHz) δ 172.7(4) (C), 172.7(2) (C), 150.1 (C), 149.4 (C), 139.5 (C), 136.1(1) (C), 136.0(8) (C), 135.8 (C), 135.6 (C), 128.9(4) (CH), 128.8(7) (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4(4) (CH), 128.3(7) (CH), 128.1 (CH), 128.0 (CH), 127.1(5) (CH), 127.1(0) (CH), 127.0 (CH), 66.1(0) (CH_2), 66.0(7) (CH_2), 60.5 (CH), 54.5(7) (CH_2), 54.5(2) (CH_2), 54.2 (CH_2), 52.3 (CH_2), 50.1 (CH_2), 49.2 (CH_2), 29.0 (CH_2), 27.5 (CH_2), 26.7 (CH_2), 23.3 (CH_2), 23.2 (CH_2) (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 3030, 2945, 2859, 1732, 1495, 1454, 1402, 1146, 969, 747, 698 cm^{-1}; MS (EI) *m/z* 533 [$(M - Cl^{\bullet})^+$, <1], 505 [$(M - COCl^{\bullet})^+$, 2], 477 [$(M - C_7H_7^{\bullet})^+$, <1], 433 [$(M - C_7H_7^{\bullet})^+$, 48], 307 (14), 210 (4), 174 (6), 91 (100); HRMS calcd for $C_{35}H_{37}N_2O_3$ [$(M - Cl^{\bullet})^+$] 533.2804, found 533.2804; calcd for $C_{28}H_{30}N_2O_3{}^{35}Cl$ ([$M - C_7H_7^{\bullet}$]$^+$) 477.1945, found 477.1942.

Compounds 29 and 30. A magnetically stirred solution of diamine **28** (507 mg, 1.00 mmol) in dichloromethane (3.3 mL) maintained at 0 °C was treated, via cannula, with a solution of triphosgene (104 mg, 0.35 mmol, 0.35 molar equiv) in dichloromethane (3.5 mL). The resulting mixture was allowed to stand at 4 °C for 16 h then the solvent was removed under reduced pressure to yield a clear, colorless oil. Subjection of this material to flash chromatography (silica gel, 1:2:7 v/v/v dichloromethane/ethyl acetate/hexane elution) provided three fractions, A−C.

Concentration of fraction A (R_f 0.5) gave the starting diamine **28** (26.2 mg, 5% recovery) as a clear, colorless oil which was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f 0.4) gave the carbamoyl chloride **29** (351 mg, 73%) as a colorless oil: ^1H NMR (300 MHz) δ 7.43−7.24 (15H, m), 4.70 (1H, s), 4.57 (1H, s), 4.09 (2H, m), 3.83 (4H, s), 3.40 (2H, m), 3.31 (2H, s), 1.63 (4H, m); ^{13}C NMR (75 MHz) δ 171.3 (C), 150.0 (C), 149.5 (C), 138.9 (C), 135.6 (C), 135.4 (C), 128.8 (CH), 128.3 (CH), 128.1(5) (CH), 128.0(9) (CH), 128.0(3) (CH), 127.2 (CH), 127.0 (CH), 63.6 (CH_2), 63.5 (CH_2), 57.9 (CH_2), 54.4 (CH_2), 53.6 (CH_2), 52.5 (CH_2), 50.0 (CH_2), 49.0 (CH_2), 26.0 (CH_2), 24.8 (CH_2), 24.0 (CH_2) (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 3029, 2946, 1734, 1495, 1454, 1402, 1184, 971, 740, 699 cm^{-1}; MS (EI) *m/z* 478 ($M^{\bullet+}$, 1), 443 [$(M - Cl^{\bullet})^+$, 2], 387 [$(M - C_7H_7^{\bullet})^+$, 9], 351 (5), 237 (6), 210 (94), 181 (5), 91 (100); HRMS calcd for $C_{28}H_{31}N_2O_3{}^{35}Cl$ 478.2023, found 478.2018.

Concentration of fraction C (R_f 0.2) gave the bis-carbamoyl chloride **30** (64.0 mg, 14%) as a colorless oil: ^1H NMR (300 MHz) δ 7.42−7.25 (10H, m), 4.82 (1H, s), 4.72 (1H, s), 4.66 (1H, s), 4.58 (1H, s), 4.13 (2H, m), 4.07 (1H, s), 3.99 (1H, s), 3.38 (2H, m), 1.62 (4H, m); ^{13}C NMR (75 MHz) δ 167.8 (C), 167.5 (C), 150.5 (C), 150.3 (C), 149.9 (C), 149.5 (C), 135.5 (C), 135.4 (C), 134.6 (C), 134.5 (C), 129.0(2) (CH), 128.9(6) (CH), 128.9(1) (CH), 128.5 (CH), 128.1(2) (CH), 128.0(8) (CH), 128.0(2) (CH), 127.6 (CH), 127.0(9) (CH), 127.0(5) (CH), 65.0 (CH_2), 64.9 (CH_2), 55.4 (CH_2), 54.4(2) (CH_2), 54.3(7) (CH_2), 53.7 (CH_2), 52.5 (CH_2), 51.0 (CH_2), 49.9 (CH_2), 49.3 (CH_2), 48.8 (CH_2), 25.8 (CH_2), 24.6 (CH_2), 23.7-(2) (CH_2), 23.6(8) (CH_2) (additional signals due to slow interconversion of rotamers); IR (NaCl, film) ν_{max} 3033, 2952, 1733, 1496, 1455, 1400, 1186, 989, 701 cm^{-1}; MS (EI) *m/z* 454, 452, 450 ($M^{\bullet+}$, each <1), 389 and 387 [$(M - COCl^{\bullet})^+$, 1 and 5], 325 and 323 [$(M - C_7H_7^{\bullet} - HCl)^+$, 3 and 11], 287 [$(M - C_7H_7^{\bullet} - 2HCl)^+$, 6], 261 (4), 224 (7), 125 (22), 91 (100); HRMS calcd for $C_{22}H_{24}N_2O_4Cl_2$ 450.1113, found 450.1121.

Acknowledgment. We thank the Institute of Advanced Studies for financial support including the provision of a Postdoctoral Fellowship to M.J.C. and a Summer Research Scholarship to J.M.

Supporting Information Available: Selected NMR spectra for compounds **3**, **10**−**13**, **19**, **21**, **23**, and **26**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0263622