Condensation of Lactams with 2-Aminoacetylaldehyde Diethyl Acetal. A One-Pot Synthesis of Bicyclic Imidazoles

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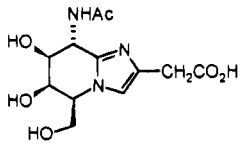
In the course of our studies of the synthesis of biologically active compounds containing the imidazole nucleus, such as nagstatin (1)[2] and other related 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines,[3] we investigated a one-pot synthesis of 1,2-fused bicyclic imidazoles **2**. Herein, we report the condensation of various lactams with 2-aminoacetaldehyde diethyl acetal (**3**) in the presence or absence of a Lewis acid



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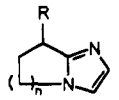


2a: n = 1, R = H
2b: n = 2, R = H
2c: n = 2, R = OH
2d: n = 3, R = H
2e: n = 4, R = H
2f: n = 5, R = H

Although many efforts have been devoted to the synthesis of imidazo[1,2-*a*]pyridines,[3,4] the synthesis of 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines and other 1,2-fused bicyclic imidazoles (such as **2**) have not been reported. Inspired by the condensation method developed at the Sagami Chemical Research Center[5] for the preparation of 2-substituted imidazoles, consisting of simply heating amides with 2-aminoacetaldehyde dimethyl acetal, we initiated a study of condensation reactions of a variety of lactams with **3**. Disappointing results were obtained after many trials when equimolar amounts of δ-valerolactam (**4b**) and **3** were heated at 175 °C for 3 days; only a 9% maximum yield of 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (**2b**) was isolated (Scheme 1). Using mesitylene as solvent did not improve the yield. The presence of a small amount of acetic acid was then found to increase the rate of the reaction, but it also promoted faster polymerization of **3**. Weak Lewis acids such as trimethyl borate, sodium sulfate, and magnesium sulfate or weak bases such as calcium carbonate all failed to improve the yield. However, the presence of strong Lewis acids such as tin tetrachloride or titanium tetrachloride promoted the formation of very good yields of the condensed product **2b** as well as those from the reaction of other lactams [**4a**–**4f** and 5,6-dihydro-2-pyridinone (**5**)]. The results are summarized in Table 1. Most of the yields range between 50 and 89.5% with $SnCl_4$ as catalyst. In most cases, the yields are slightly higher with $TiCl_4$ than $SnCl_4$. The mechanism of the reaction is proposed to involve nucleophilic attack by the lactam NH at C-1 of the oxonium ion derived from **3** and $SnCl_4$, followed by ring closure of the amino group with the lactam carbonyl group, dehydration, and elimination of ethanol.

Various functional groups such as hydroxyl and olefinic groups (see entries 3 and 4) tolerate the reaction conditions. It should be noted that all the bicyclic imidazoles **2** reported here are new compounds. 3-Hydroxy-3,4,5,6-

Scheme 1

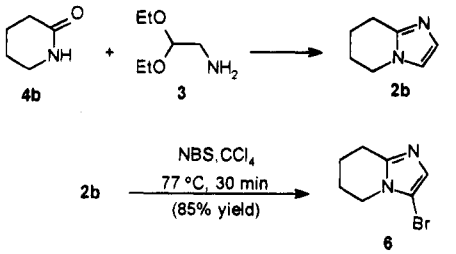
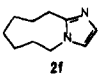


Table 1. Reaction Conditions and Yields of the Condensation of Lactams (4 and 5) with 2 Equiv of 2-Aminoacetaldehyde Diethyl Acetal (3)

Entry	Starting lactams	$SnCl_4$ as catalyst			$TiCl_4$ as catalyst			product
		temp (°C)	time (h)	yield (%)	temp (°C)	time (h)	yield (%)	
1	 **4a**	140	72	60.8	155	74	80.3	 **2a**
2	 **4b**	150	51	68	140	72	62	 **2b**
3	 **4c**	150	44	50.7	140	72	61	 **2c**
4	 **5**	150	60	59.9	140	74	68.9	 **2g**
5	 **4d**	150	45	79.9	---	---	---	 **2d**
6	 **4e**	150	53	82.6	---	---	---	 **2e**
7	 **4f**	150	72	89.5	140	74	91.2	 **2f**

(1) To whom inquires regarding the X-ray analysis should be addressed.

(2) (a) Aoyagi, T.; Suda, H.; Uotani, K.; Kojima, F.; Aoyama, T.; Horiguchi, K.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1404–8. (b) Aoyama, T.; Naganawa, H.; Suda, H.; Uotani, K.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1557–8.

(3) Many 1,2-fused bicyclic imidazoles have antiulcer, antidepressant, antibacterial, and T_xA_2 synthase inhibitory activities: (a) Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S.; Wong, S.-C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; Steinberg, M.; McPhail, A. T. *J. Med. Chem.* **1985**, *28*, 876–92. (b) Fos, E.; Bosca, F.; Mauleon, D.; Carganico, G. *J. Heterocycl. Chem.* **1993**, *30*, 473–6. (c) Stefancich, G.; Silvestri, R.; Artico, M. *J. Heterocycl. Chem.* **1993**, *30*, 529–32. (d) Shawcross, A.; Stanforth, S. P. *Ibid.* 563–5.

(4) (a) Lombardino, J. G. *J. Org. Chem.* **1965**, *30*, 2403–6. (b) Pandler, W. W.; Blewitt, H. L. *J. Org. Chem.* **1965**, *30*, 4081–90. (c) Paolini, J. P.; Robins, R. L. *J. Heterocycl. Chem.* **1965**, *2*, 53–62. (d) Paudler, W. W.; Shin, H. G. *J. Org. Chem.* **1968**, *33*, 1638–9. (e) Elliott, A. J.; Guzik, H.; Soler, J. R. *J. Heterocycl. Chem.* **1982**, *19*, 1437–40.

(5) Sagami Chemical Research Center. *Jpn. Kokai Takkyo Koho JP* 57,136,573 [82,136,573], Feb 17, 1981; *Chem. Abstr.* **1983**, *98*, 72100d.

0022-3263/94/1959-5084$04.50/0

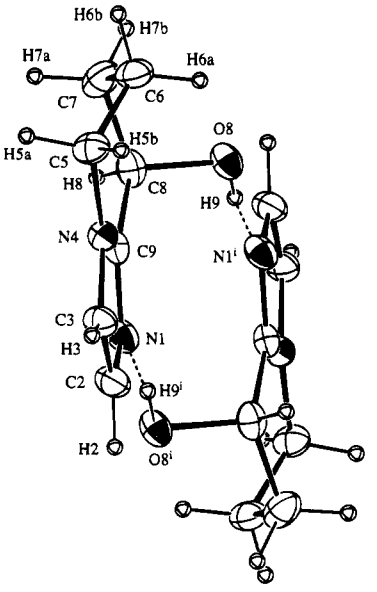


Figure 1. ORTEP drawing of X-ray crystallographically determined structure of **2c**.

Table 2. Selected Bond Lengths and Bond Angles of 2c

bond distances	Å	bond angles	deg
N1–C2	1.373(3)	N1–C2–C3	110.5(2)
C2–C3	1.342(3)	C2–C3–N4	105.9(2)
C3–N4	1.366(2)	N1–C8a–N4	110.7(2)
N4–C5	1.464(3)	C2–N1–C8a	105.3(2)
N4–C8a	1.350(2)	C5–N4–C8a	125.2(2)
C8–C8a	1.494(3)	N4–C8a–C8	122.0(2)
C8–O8	1.423(3)	C8a–C8–O8	109.7(2)

tetrahydro-2-pyridinone (**4c**) was prepared in 67% overall yields (two steps) from δ-valerolactam (**4b**) by following the same methods as those for 3-hydroxy-2-pyrrolidinone.[6] 5,6-Dihydro-2-pyridinone (**5**) was prepared in a 97% overall yield from *N*-(trimethylsilyl)-2-piperidinone[6] via selenylation (LDA, PhSeCl)[7] followed by dehydroselenylation (50% H_2O_2, THF). The structure of 8-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (**2c**) was unequivocally determined by a single-crystal X-ray analysis (Figure 1).[11] Interestingly, the crystals represent the molecular dimer, the molecules being linked to each other by two hydrogen bonds (O8–H9···N1) as shown in the ORTEP drawing. The intermolecular O8–N1 distance of 2.750 Å and the O8–H9···N1 angle of 173° are in good agreement with hydrogen bonding requirements. Selected bond lengths and bond angles are listed in Table 2. The bicyclic imidazoles such as **2b** underwent regioselective bromination reaction at C-3. For instance, treatment of **2b** with 1 equiv of *N*-bromosuccinimide (NBS) under reflux in CCl_4 for 30 min gave an 85% isolated yield of 3-bromo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (**6**) (Scheme 1). The assignment of the bromine at C-3 rather than C-2 was based on the ^1H NMR chemical shifts by comparing the aromatic protons of **2b** and **6** with those of 1-methylimidazole and 5-bromo-1-methylimidazole[8] (Chart 1).

In summary, condensation of various five- to nine-membered ring lactams with 2-aminoacetaldehyde diethyl acetal (**3**) in the presence of a Lewis acid provides a facile one-pot synthesis of various substituted 1,2-fused bicyclic imidazoles in good to excellent yields. This synthesis is general and should be amenable to large scale preparation. A regioselective reaction is found in the bromination of 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine to give exclusively C-3 brominated product.

Experimental Section

General Methods. Nuclear magnetic resonance spectra were obtained at 400 MHz for ^1H and 100 MHz for ^{13}C in deuteriochloroform, unless otherwise indicated. Infrared spectra are reported in wavenumbers (cm^{-1}). Mass spectra were obtained from a Hewlett-Packard 5989A mass spectrometer. FAB MS were taken in Xe gas, 2 KV, using glycerol and *m*-nitrobenzyl alcohol as the matrix. 2-Aminoacetaldehyde diethyl acetal (**3**) was purchased from Aldrich and used without further purification. Davisil silica gel, grade 643 (200~425 mesh), was used for the flash chromatographic separation. Amberlite (R) IR-120 (plus) (from Aldrich) was used for ion-exchange column chromatography. All of the bicyclic imidazoles are extremely hygroscopic; samples which were sent for elemental analysis, although distilled under reduced pressure and maintained under argon, contained a small amount of water. Longer drying of the samples before analysis resulted in lower water content, but most of the sample content was also lost by evaporation.

The following experiment serves to illustrate the general procedure for the preparation of bicyclic imidazoles **2** using $SnCl_4$ as catalyst.

5,6,7-Trihydroimidazo[1,2-*a*]pyrrole (2a). To 0.70 g (8.22 mmol) of 2-pyrrolidinone in 3 mL of mesitylene and 3 mL of methylene chloride under argon was added 0.29 mL (2.5 mmol) of anhydrous tin(IV) chloride ($SnCl_4$) at room temperature to form a yellow precipitate. The mixture was refluxed (150 °C oil bath), and a solution of 2.4 mL (16.5 mmol) of 2-aminoacetaldehyde diethyl acetal (**3**) in 5 mL of methylene chloride was added slowly. After the reaction mixture was stirred at this temperature for 72 h, some black tar was formed. The reaction mixture was diluted with 50 mL of 3 N HCl, and the black tar was removed by filtration. The aqueous solution was concentrated *in vacuo* to a volume of about 25 mL, brought to pH ~14 with aqueous KOH, and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a brown solid which was shown by ^1H NMR to be mainly the desired 5,6,7-trihydroimidazo[1,2-*a*]pyrrole (**2a**) and a small amount of 2-pyrrolidone. Vacuum distillation of the crude product gave 0.54 g (60.8% yield) of **2a** as a white solid: mp 72.5–75.5 °C; bp 58–60 °C/0.6 mmHg; MS (CI) *m/z* 110 (M + 2), 109 (100, M + 1), 108 (M^+); IR (Nujol) ν 1620, 1520, 1290, 1260, 1132, 1095, 1055, 944 cm^{-1}; ^1H NMR δ 7.03 (s, 1H, =CH), 6.85 (d, J = 1.2 Hz, 1 H, =CH), 3.96 (td, J = 7, 1.2 Hz, 2 H, NCH_2), 2.85 (t, J = 7 Hz, 2 H, $=CCH_2$), 2.59 (m, 2 H, CH_2); ^{13}C NMR δ 154.6 (s, C-7a), 133.1 (d, C-2), 114.3 (d, C-3), 44.5 (t, C-5), 26.3 (t, C-7), 22.9 (t, C-6); HRMS calcd for $C_6H_8N_2$ 108.0688, found 108.0683; $C_6H_9N_2$ (M + 1) 109.0767, found 109.0758. Anal. Calcd for $C_6H_8N_2$: C, 66.62; H, 7.46. Found: C, 66.45; H, 7.33. This result indicated 20% H_2O (mol) was contained in the sample.

The following experiment serves to illustrate the general procedure for the preparation of bicyclic imidazoles **2** using $TiCl_4$ as catalyst.

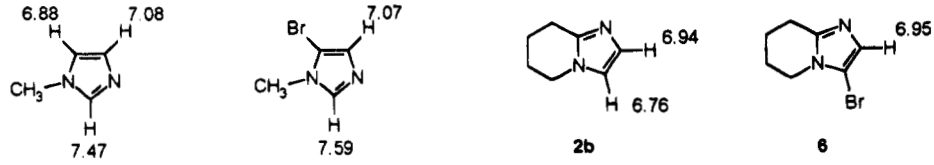
To a solution of 0.100 g (1.17 mmol) of 2-pyrrolidinone (**4a**) in 5 mL of mesitylene at 25 °C was added 0.03 mL (0.15 mmol) of $TiCl_4$. The mixture was warmed in a 140 °C bath, and 0.35 mL (2.35 mmol) of **3** in 3 mL of mesitylene was introduced dropwise over 3 h. The reaction mixture was stirred in the 140 °C bath for 90 h. Some black tar was formed. The mixture was filtered, and the black solid was washed 10 times with CH_2Cl_2. The filtrate and CH_2Cl_2 washings were combined, concentrated, and chromatographed on a ion-exchange column, using a gradi-

(6) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682–4.

(7) For a review, see: Back, T. G. In *Organoselenium Chemistry*; Liotta, D., Ed.; John Wiley & Sons: New York, 1987; pp 1–126.

(8) (a) Takeuchi, T.; Yeh, H. J. C.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3565. (b) Matthews, H. R.; Rapoport, H. *J. Am. Chem. Soc.* **1973**, *95*, 2297. Attempts to determine the regiochemistry of **6** using **2D** NOESY spectroscopy by comparing spectra of **2b** and **6** failed. No NOE was observed in the 2D NOESY spectra of **2b** between protons at C-3 and C-5.

Chart 1



ent mixture of CH_2Cl_2 and NH_4OH as eluents, to give 0.102 g (80.3% yield) of **2a**.

5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridine (2b). From 1.06 g (10.7 mmol) of δ-valerolactam (**4b**), 21.4 mmol of **3**, and 3.2 mmol of tin tetrachloride, vacuum distillation of the crude product gave 0.888 g (68.2% yield) of 5,6,7,8-tetrahydroimidazo-[1,2-*a*]pyridine (**2b**) as a colorless sticky oil: bp 68–70 °C/1 mmHg; MS (CI) *m/z* 123 (M + 1, 100), 122, 110, 108; IR (neat) ν 3010 (Ar CH), 2840, 2760, 1600, 1435, 1390, 1378, 1325, 1260, 1243, 1194, 1070, 1040, 870 cm^{-1}; ^1H NMR δ 6.96 (d, J = 1.1 Hz, 1 H, =CH), 6.76 (d, J = 1.1 Hz, 1 H, =CH), 3.94 (t, J = 6 Hz, 2 H, NCH_2), 2.86 (t, J = 6 Hz, 2 H, $=CCH_2$), 1.99~1.90 (m, 4 H, 2 CH_2); ^{13}C NMR δ 144.8 (s, C8a), 127.7 (d, C2), 117.8 (d, C3), 44.7 (t, C5), 24.5 (t, C8), 23.1 (t, C6), 21.2 (t, C7); HRMS calcd for $C_7H_{10}N_2$ 122.0845, found 122.0835; $C_7H_{11}N_2$ (M + 1) 123.0923, found 123.0917. Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25. Found: C, 66.51; H, 8.06. This result indicated 20% of H_2O (mol) was contained in the sample.

From 3.10 g (31.3 mmol) of **4b** and using titanium tetrachloride as catalyst was obtained 2.37 g (62.1% yield) of **2b**.

3-Hydroxy-2-piperidinone (4c). To 4.79 g (28.03 mmol) of *N*-(trimethylsilyl)-2-piperidinone[6] and 10 mL of distilled THF in a flame-dried flask was added 1.2 equiv of lithium diisopropylamide (LDA) [prepared from 4.71 mL of diisopropylamine and 30 mL of *n*-butyllithium (1.12 M in hexane) in 50 mL of THF at −20 °C]. After the mixture was stirred at −20 °C for 1 h, 7.43 mL (36.43 mmol) of hexamethylsilyl peroxide [$(CH_3)_3SiOOSi(CH_3)_3$] was introduced at −20 °C. The reaction mixture was stirred at −20 °C for 1 h, slowly warmed to 25 °C, and then stirred for 12 h. Then, 2.08 mL of acetic acid and 100 mL of CH_2Cl_2 were added, and the mixture was stirred at 25 °C for 1 h. The white solid was filtered out, and the filtrate was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel, using a mixture of methylene chloride and methanol (20:1) as eluent, to give 2.66 g (82.5% yield) of **4c** as a white solid: mp 143–145 °C (lit.[9] 135–137 °C); ^1H NMR δ 6.06 (broad s, 1H, NH), 4.05 (dd, J = 11 Hz, 6 Hz, 1 H, CH-O), 3.95 (broad s, 1 H, OH), 3.37~3.32 (m, 2 H, NCH_2), 2.35~2.24 (m, 1 H, C5-H), 2.00~1.90 (m, 1 H, C4-H), 1.90~1.80 (m, 1 H, C5-H), 1.80~1.68 (m, 1 H, C4H); ^{13}C NMR δ 174.6 (s, C=O), 67.6 (d, COH), 42.2 (t, NC), 38.4 (t, C4), 20.5 (t, C5).

8-Hydroxy-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (2c). From 0.330 g (2.87 mmol) of **4c**, 5.74 mmol of **3**, and 0.574 mmol of tin tetrachloride was obtained 0.2007 g (50.7% yield) of **2c**: MS (CI) *m/z* 139 (M + 1, 100), 121 (M − H_2O); IR (Nujol) ν 3350–3100 (broad s, OH), 1630, 1520, 1485, 1430, 1310, 1275, 1244, 1120, 1070, 990, 930 cm^{-1}; ^1H NMR δ 7.04 (s, 1 H, C2H), 6.80 (s, 1 H, C3H), 4.97 (t, J = 5.2 Hz, 1 H, C8H), 4.06–4.01 (m, 1 H, C5H), 4.00–3.86 (m, 1 H, C5H), 2.33–2.26 (m, 1 H, C6H), 2.14–2.04 (m, 2 H, C7H), 1.98–1.91 (m, 1 H, C6H); ^{13}C NMR δ 148.5 (s, C8a), 127.7 (d, C2), 118.3 (d, C3), 62.2 (d, C8), 45.0 (t, C5), 29.5 (t, C7), 19.3 (t, C6); HRMS calcd for $C_7H_{10}N_2O$ 138.0794, found 138.0789. Recrystallization from methylene chloride gave white crystals, mp 151.5–152.5 °C, one of which was used in the X-ray analysis; monoclinic, space group $P2_1/n$, final R of 0.035 and R_w of 0.046.

3-(Phenylselenenyl)-2-piperidinone. Lithium diisopropylamide (LDA) was prepared from 1.23 mL (8.8 mmol) of diisopropylamine and 5.5 mL (8.8 mmol) of *n*-butylithium (1.6 M in hexane) in 10 mL of THF at −50 °C. The newly prepared LDA was added to a solution of 1.00 g (5.8 mmol) of *N*-(trimethylsilyl)-2-piperidinone[6] in 4 mL of distilled THF in a flame-dried flask via a cannula under argon at −50 °C. After it was stirred at −50 °C for 45 min, the anion solution was transferred into a solution of 1.68 g (8.8 mmol) of dried phenylselenenyl chloride in 4 mL of THF at −78 °C under argon through a cannula. The reaction mixture was stirred at −78 °C for 7 h and quenched with 3 mL of water. Then, it was diluted with 50 mL of CH_2Cl_2 and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated to give 1.85 g of yellow solids which NMR indicated to be 3-(phenylselenenyl)-2-piperidinone and the selenium reagent: ^1H NMR δ 7.80–7.20 (m, Ph), 6.05 (broad s, 1 H, NH), 3.95 (t, J = 5.1 Hz, 1 H, CH-Se), 3.80 (dt, J = 5.8 Hz, 1.7 Hz, 2 H, NCH_2), 2.14~2.05 (m, 1 H, C4H), 1.91~2.01 (m, 2 H, C5H), 1.73~1.64 (m, 1 H, C4H). This material was used to prepare 5,6-dihydro-2(1*H*)-pyridinone (**5**) without further purification.

5,6-Dihydro-2(1*H*)-pyridinone (5). A 0.9-mL (14.6 mmol) sample of 50% hydrogen peroxide solution was added to a solution of the above 3-(phenylselenenyl)-2-piperidinone in 10 mL of THF at 0 °C. The reaction solution was stirred at 0 °C for 30 min and at 25 °C for 1.5 h, during which time a white solid precipitated. It was diluted with 80 mL of methylene chloride and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel, using a mixture of methylene chloride and methanol (9:1) as eluent, to give 0.554 g (97.7% overall yield) of 5,6-dihydro-2(1*H*)-pyridinone (**5**):[10] ^1H NMR δ 6.65 (dt, J = 10, 3 Hz, 1 H, =CH), 6.30 (broad s, 1 H, NH), 5.92 (ddd, J = 10, 2, 2 Hz, 1 H, =CH), 3.48–3.42 (m, 2 H, NCH_2), 2.37–2.34 (m, 2 H, CH_2); ^{13}C NMR δ 164.7 (s, C=O), 139.7 (d, =C), 123.2 (d, =C), 37.9 (t, NC), 22.2 (t, C5). Both ^1H[10a] and ^{13}C[10b] NMR spectra had been reported previously. Our data are similar to those reported but not identical; hence, they are listed here.

5,6-Dihydroimidazo[1,2-*a*]pyridine (2g). From 32.5 mg (0.34 mmol) of 5,6-dihydro-2(1*H*)-pyridone (**5**), after column chromatography on silica gel, using a mixture of methylene chloride and methanol (100:4) as eluent, 24 mg (59.9% yield) of 5,6-dihydroimidazo[1,2-*a*]pyridine (**2g**) was obtained: MS (CI) *m/z* 121 (M + 1, 100), 107, 95; ^1H NMR δ 7.03 (d, J = 1 Hz, 1 H, C2H), 6.80 (s, 1 H, C3H), 6.54 (dt, J = 10 Hz, 1 Hz, 1 H, C8H), 6.07 (dt, J = 10 Hz, 4.5 Hz, 1 H, C7H), 4.05 (t, J = 7.6 Hz, 2 H, C5H), 2.60~2.55 (m, 2 H, C6H); ^{13}C NMR δ 145.8 (s, C8a), 128.6 (d, C2), 126.3 (d, C3), 120.0 (d, C8), 118.6 (d, C7), 42.9 (t, C5), 23.8 (t, C6); HRMS calcd for $C_7H_8N_2$ 120.0688, found 120.0683; $C_7H_9N_2$ (M + 1) 121.0767, found 121.0761.

5,6,7,8,9-Pentahydroimidazo[1,2-*a*]azepine (2d). From 0.75 g (6.63 mmol) of ε-caprolactam (**4d**), 13.3 mmol of **3**, and 0.23 mL (2.0 mmol) of $SnCl_4$ was obtained 0.721 g (79.9% yield) of **2d** as a white solid after column chromatography on ion-exchange resin using a gradient mixture of CH_2Cl_2 and concd NH_4OH as eluent: mp 56.3–57.9 °C; bp 73–75 °C/1 mmHg; MS (CI) *m/z* 137 (M + 1, 100), 136, 127, 122; ^1H NMR δ 6.82 (d, J = 1.1 Hz, 1 H, C2H), 6.77 (d, J = 1.1 Hz, 1 H, C3H), 3.93 (m, 2 H, C5H), 2.90 (t, J = 5.5 Hz, 2 H, C9H), 1.86~1.66 (m, 6 H, C6H, C7H, C8H); ^{13}C NMR δ 150.5 (s, C9a), 126.0 (d, C2), 120.7 (d, C3), 48.3 (t, C5), 30.8 (t, C9), 29.4 (t), 29.0 (t), 25.7 (t); HRMS calcd for $C_8H_{12}N_2$ 136.1001, found 136.9995; $C_8H_{13}N_2$ (M + 1) 137.1080, found 137.1071. Anal. Calcd for $C_8H_{12}N_2$: C, 70.54; H, 8.89. Found: C, 69.59; H, 8.77. This result indicated 10% H_2O (mol) was contained in the sample.

5,6,7,8,9,10-Hexahydroimidazo[1,2-*a*]azocine (2e). From 0.83 g (6.5 mmol) of 2-azacyclooctanone (**4e**), 13 mmol of **3**, and 1.95 mmol of tin tetrachloride, after column chromatographic separation on ion-exchange resin using a gradient mixture of CH_2Cl_2 and concentrated NH_4OH as eluents and vacuum

(9) Hjeds, H.; Honore, T. *Acta Chem. Scand.* **1978**, *B32*, 187–192.

(10) (a) Sundberg, R. J.; Bukowick, P. A.; Holcombe, F. O. *J. Org. Chem.* **1967**, *32*, 2938–41. (b) Boll, P. M.; Hansen, J.; Simonsen, O. *Tetrahedron* **1984**, *40*, 171–5.

(11) The author has deposited atomic coordinates for **2c** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

distillation of the product, was obtained 0.81g of **2e** as a colorless sticky oil: bp 80–82 °C/0.25 mmHg; MS (CI) *m/z* 151 (M + 1, 100), 128, 111, 103; ^{1}H NMR δ 6.93 (d, J = 1.2 Hz, 1 H, C2H), 6.76 (d, J = 1.2 Hz, 1 H, C3H), 3.99 (t, J = 6.1 Hz, 2 H, C5H), 2.83 (m, 2 H, C10H), 1.81–1.72 (m, 4 H) 1.47–1.41 (m, 2 H), 1.29–1.25 (m, 2 H); ^{13}C NMR δ 149.6 (s, C10a), 127.5 (d, C2), 118.6 (d, C3), 44.3 (t, C5), 31.8 (t), 31.2 (t), 26.2 (t), 25.6 (t), 23.8 (t). HRMS calcd for $C_9H_{14}N_2$ 150.1158, found 150.1153; $C_9H_{15}N_2$ (M + 1) 151.1236, found 151.1238.

5,6,7,8,9,10,11-Heptahydroimidazo[1,2-*a*]azonine (2f). From 0.5 g (3.54 mmol) of 2-azacyclononanone (**4f**), 7.08 mmol of **3**, and 0.71 mmol of tin tetrachloride, after column chromatographic separation on ion-exchange resin, using a gradient mixture of CH_2Cl_2 and concd NH_4OH as eluents and vacuum distillation, was obtained 0.52 g (89.5% yield) of **2f** as a colorless oi: bp 82–85 °C/0.75 mmHg; MS (CI) *m/z* 166 (M + 2), 165 (M + 1, 100), 142, 127, 113, 97, 83; ^{1}H NMR δ 6.96 (d, J = 1.1 Hz, 1H, C2H), 6.74 (d, J = 1.1 Hz, 1 H, C3H), 4.04 (t, J = 6.0 Hz, 2 H, C5H), 2.86 (m, 2 H, C11H), 1.86–1.77 (m, 4H), 1.54–1.50 (m, 2 H), 1.43–1.37 (m, 2 H), 1.24–1.19 (m, 2 H); ^{13}C NMR δ 150.2 (s, C11a), 128.0 (d, C2), 118.5 (d, C3), 45.9 (t, C5), 30.2 (t, C11), 28.0 (t), 27.6 (t), 27.0 (t), 26.3 (t), 21.6 (t); HRMS calcd for $C_{10}H_{16}N_2$ 164.13148, found 164.1317; calcd for $C_{10}H_{17}N_2$ (M + 1) 165.1392, found 165.1401.

3-Bromo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (6). To a solution of 83 mg (0.68 mmol) of 5,6,7,8-tetrahydroimidazo-[1,2-*a*]pyridine (**2b**) in 3 mL of carbon tetrachloride was added 121 mg (0.68 mmol) of *N*-bromosuccinimide (NBS) at 25 °C under argon. The reaction mixture was stirred and heated under reflux for 30 min and cooled to 25 °C, and the solution portion was pipetted to another flask. This solution was concentrated to dryness and column chromatographed on silica gel, using a mixture of methylene chloride and methanol (25:1) as eluent to give 115 mg (85% yield) of **6**: MS (EI) *m/z* 202 (M + 1), 200 (M − 1), 199, 172, 159; ^{1}HNMR δ 6.95 (s, 1 H, C2H), 3.82 (t, J = 5.7 Hz, 2 H, C5H), 2.85 (t, J = 6.5 Hz, 2 H, C8H), 2.01~1.98 (m, 2 H, CH_2), 1.93~1.90 (m, 2 H, CH_2); ^{13}C NMR δ 146.1 (s, C8a), 127.5 (C2), 100.9 (C3), 43.90 (t, C5), 25.24 (t, C8), 22.81 (t, C6), 20.66 (t, C7); HRMS calcd for $C_7H_9BrN_2$ 201.9930 and 199.9950, found 201.9927 and 199.9948.

When a slight excess of NBS was used, a small amount of 2,3-dibromo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine was also isolated: MS (EI) *m/z* 282 (M + 2), 281, 280, 279, 230, 228, 203, 201; ^{1}H NMR δ 3.81 (t, J = 6 Hz, 2 H, CH_2N), 2.83 (t, J = 6 Hz, 2 H, C8H), 2.04~2.0 (m, 2 H), 1.96~1.90 (m, 2 H); ^{13}C NMR δ 146.18 (s), 115.36 (s), 101.22 (s), 44.88 (t, C8), 24.99 (t, C5), 22.56 (t, C7), 20.37 (t, C6).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **2a–g** and **6** and 2D NOESY spectra of **2b** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. The X-ray data are deposited in the Cambridge Crystallographic Centre.