JOC*Note*

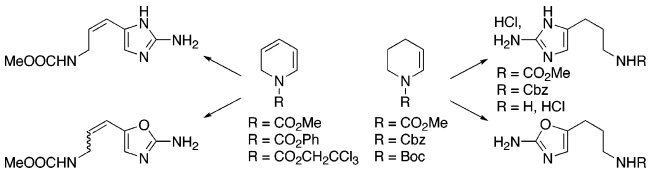
Versatile Access to C-4-Substituted 2-Amino-1,3-azoles from Hydropyridines in Oxidative Conditions

Maria del Rayo Sanchez Salvatori, Robert Abou-Jneid, Saïd Ghoulami, Marie-Thérèse Martin, Anne Zaparucha,* and Ali Al-Mourabit*

Institut de Chimie des Substances Naturelles du CNRS, BP 1, 91198Gif-sur-Yvette, France

ali.almourabit@icsn.cnrs-gif.fr

Received April 28, 2005



Various substituted 2-aminotetrahydroazolopyridines and 2-aminohexahydroazolopyridines have been prepared by bromine-mediated addition of protected guanidine or urea to hydropyridine derivatives. The pH-dependent regioselective cleavage of the resulting aminal function led to the 2-aminoazole products **III**. The yields of the bicycles of type **II**, and their conversion into azoles **III** depends on the electronic properties of the substituents on the nitrogen of the tetrahydopyridine.

2-Aminoimidazole (2AI), 2-aminooxazole (2AO), and 2-aminothiazole (2AT) constitute an important class of heterocycles, especially in medicinal chemistry. They display a broad range of interesting biological properties and serve as important precursors in drug design and natural products synthesis. The 2AI skeleton is found in various active marine metabolites isolated from sponges[1] and the 2AO moiety is the key element of a potent inhibitor of inosine monophosphate dehydrogenase,[2] while 2AT is a building block in the synthesis of anti-inflammatory agents.[3] Synthetic routes to 2AI, 2AO, and 2AT are numerous.[4] Among them, however, only a few methods are general for the preparation of these 2-amino-1,3-azoles. The first and most commonly used direct approach involves the reaction of α-halocarbonyl compounds with guanidine plus (2AI), urea plus (2AO) or thiourea plus (2AT).[5] An alternative approach is the reaction of α-amino, α-hydroxy, or α-thiohydroxy aldehydes or ketones with cyanamide to give 2AI, 2AO, and 2AT, respectively.[5d,6] However, in the case of 2AI, this reaction is pH sensitive and appears to be difficult to conduct.

In the context of a study aimed at the development of synthetic routes to marine 2AI alkaloids and analogues, we required an efficient general pathway to the 4-substituted 2-amino-1,3-azole core. Recently, we reported the biomimetic inspired synthesis of 2-aminoimidazole starting from *N*-methoxycarbonyl-1,2-dihydropyridine using bromine-promoted addition of Boc-guanidine.[7] As an extension of this work, we undertook a study of the reactivity of urea and thiourea as nucleophiles on one hand and dihydropyridines and tetrahydropyridines as enamine reactants on the other hand. The objective was the preparation of various C-4-substituted 2-amino-1,3-azoles.

Addition of electrophilic reagents to carbon−carbon double bonds is a standard procedure in organic chemistry.[8] Access to the 2-amino-1,3-azole core would necessitate the attack of the nucleophile (guanidine, urea, or thiourea) on an activated intermediate followed by an elimination step. We planned to benefit from the nucleophilic character of the enamine moiety of hydropyridine **I** to introduce the nucleophile through an oxidative addition protocol.[9−11] Opening of the bicyclic intermediate **II** by cleavage of the aminal bond would lead, in all cases, to the 2-amino-1,3-azole structure **III**, bearing a propylamine or propenamine at C-4 (Scheme 1).

During the course of our investigations, we found that *N*-carbamate-1,2-dihydropyridines **1**, **2**, and **3** reacted with 4 equiv of Boc-guanidine, in a mixture of acetoni-

(1) (a) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243. (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783.

(2) Murali Dhar, T. G.; Guo, J.; Shen, Z.; Pitts, W. J.; Gu, H. H.; Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Iwanowicz, E. J. *Org. Lett.* **2002**, *4*, 2091−2093.

(3) (a) Geronikaki, A.; Hadjipavlou-Litina, D.; Chatziopoulos, C.; Soloupis, G. *Molecules* **2003**, *8*, 472−479. (b) Lazer, E. S.; Miao, C. K.; Cywin, C. L.; Sorcek, R.; Wong, H.-C.; Meng, Z.; Potocki, I.; Hoermann, M.; Snow, R. J.; Tschantz, M. A.; Kelly, T. A.; McNeil, D. W.; Coutts, S. J.; Churchill, L.; Graham, A. G.; David, E.; Grob, P. M.; Engel, W.; Meier, H.; Trummlitz, G. *J. Med. Chem.* **1997**, *40*, 980−989.

(4) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5.

(5) For representative references, see: (a) Little, T. L.; Webber, S. E. *J. Org. Chem.* **1994**, *59*, 7299−7305. (b) Shikhaliev, K. S.; Falaleev, A. V.; Ermolova, G. I.; Solov'ev, A. S. *Chem. Heterocycl. Compd. (Engl. Trans.)* **1999**, *35*, 818−820. (c) Birman, V. B.; Jiang, X.-T. *Org. Lett.* **2004**, *6*, 2369−2371. (d) Murali Dhar, T. G.; Liu, C.; Pitts, W. J.; Guo, J.; Watterson, S. H.; Gu, H.; Fleener, C. A.; Rouleau, K.; Sherbina, N. Z.; Barrish, J. C.; Hollenbaugh, D.; Iwanowicz, E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3125−3128. (e) Crank, G.; Foulis, M. J. *J. Med. Chem.* **1971**, *14*, 1075−1077. (f) Kim, H.-O.; Kahn, M. *Synlett* **1999**, 1239−1240. (g) Herlenmeyer, J. *Helv. Chim. Acta* **1949**, *32*, 38. (h) Plouvier, B.; Houssin, R.; Bailly, C.; Hénichart, J.-P. *J. Heterocycl. Chem.* **1989**, *26*, 1643−1647. (i) Bricuté, D.; Slok, F. A.; Romming, C.; Sasckus, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 652−656.

(6) For representative references, see: (a) Lawson, A. *J. Chem. Soc.* **1956**, 307−310. (b) Lancini, G. C.; Lazzari, E.; Arioli, V.; Bellani, P. *J. Med. Chem.* **1969**, *12*, 775−780. (c) Saul, R.; Kern, T.; Kopf, J.; Pinter, I.; Koll, P. *Eur. J. Org. Chem.* **2000**, 205−209. (d) Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1997**, *63*, 77918-7919. (e) Baran, P. S.; Zografos, A. L.; O'Malley, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 3726−3727. (f) Wolf, V.; Hauschildt, P.; Loop, W. *Chem. Ber.* **1962**, *95*, 2419−2423. (g) Brown, M. D.; Gillon, D. W.; Meakins, G. D.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1982**, 444−445. (h) Kozikowski, A. P.; Campiani, G. *Heterocycles* **1994**, *39*, 101−116.

(7) Abou-Jneid, R.; Ghoulami, S.; Martin, M.-T.; Tran Huu Dau, E.; Travert, N.; Al-Mourabit, A. *Org. Lett.* **2004**, *6*, 3933−3936.

(8) (a) Block; E.; Schwan, A. L. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 329−362. (b) Rodriguez, J.; Dulcère, J.-P. *Synthesis* **1993**, 1177−1205.

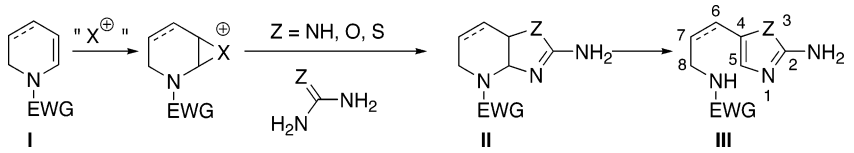
(9) Lavilla, R.; Kumar, R.; Coll, O.; Masdeu, C.; Spada, A.; Bosch, J.; Espinosa, E.; Molins, E. *Chem. Eur. J.* **2000**, *6*, 1763−1772.

(10) (a) Harris, R. L. N. *Aust. J. Chem.* **1970**, *23*, 1199−1207. (b) Grehn, L. *J. Heterocycl. Chem.* **1978**, *15*, 81−87.

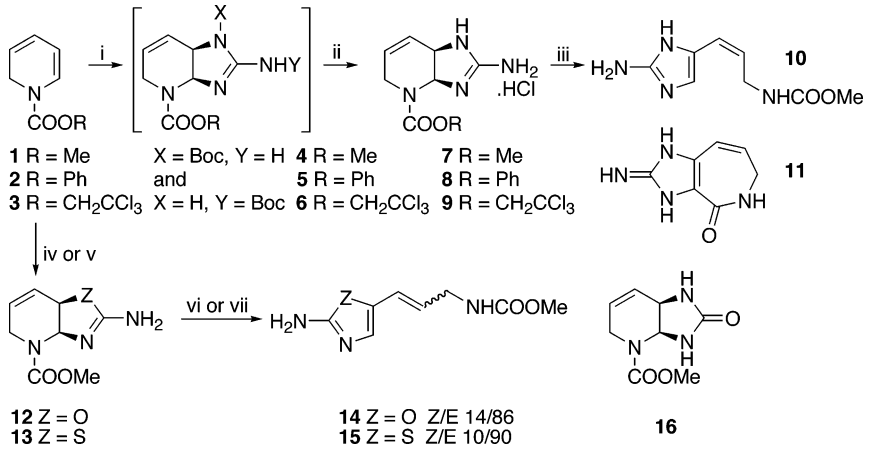
(11) Plantefeve, F.; Descotes, G. *Bull. Soc. Chim. Fr.* **1972**, 2923−2929. (b) Liu, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 9789−9797. (c) Kivits, G. A. A.; Hora, J. *J. Heterocycl. Chem.* **1975**, *12*, 577. (d) Zhao, R.; Gove, S.; Sundeen, J. E.; Chen, B.-C. *Tetrahedron Lett.* **2001**, *42*, 2101−2102.

10.1021/jo050862o CCC: $30.25
Published on Web 09/08/2005

SCHEME 1



SCHEME 2[a]



[a] Reagents and conditions: (i) BocGua, Br_2, DMF:acetonitrile, 0 °C, 15 min; (ii) HCl 2 M, **7** (71%), **8** (84%), **9** (26%) for both steps; (iii) NaOH 1 M, (*Z*)-**10** (85%, **11** (28%); (iv) urea, Br_2, DMF/acetonitrile, rt, 15 min, **12** (50%); (v) thiourea, Br_2, DMF/acetonitrile, rt, 15 min, **13** (11%); (vi) DMSO, reflux, 90−120 min, **14** *Z*/*E* 14:86 (22%), **15** *Z*/*E* 10:90 (28%); (vii) DMF, reflux, 1 h, **16** (40%).

trile−DMF (4:1), at 0 °C in the presence of 1 equiv of bromine, to give compounds **4**, **5**, and **6** respectively, as a mixture of regioisomers.[7] The *cis* stereochemistry of the ring fusion was determined by NOESY experiments. It was assumed, according to our preliminary trials and to a literature reference, that the reaction with unprotected guanidine would lead to a complex mixture because of its nucleophilicity and its sensitivity to oxidation by bromine.[12] Further deprotection of both regioisomers of **4**, **5**, and **6**, under acidic conditions, led to the *cis*-2-amino-1,3a,5,7a-dihydroimidazo[4,5-*b*]pyridine compounds **7**, **8**, and **9**. The yield of the reaction depends on the nature of the dihydropyridine protecting group. Since purification of the regioisomeric intermediates is not necessary, the addition of protected guanidine and acidic deprotection can be performed in one step improving the yield of the reaction. Aminal bond cleavage of **7** under basic conditions afforded the 2-aminoimidazole **10**. The (*Z*) allylic amine **10** could be isomerized under acidic conditions to afford the (*E*) allylic amine,[7] a key precursor of natural pyrrole−imidazole alkaloids.[1,6d,13]

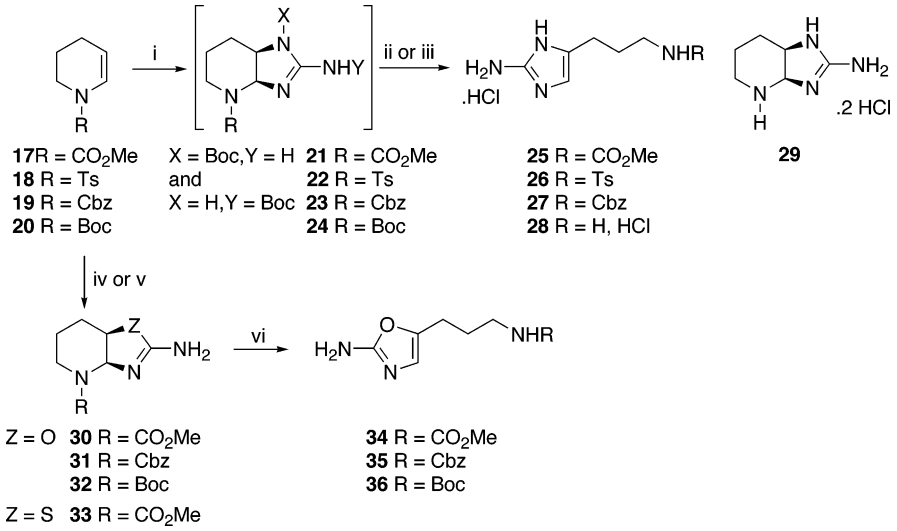
Interestingly, in the case of the carbophenoxy protecting group (**8**), the reaction with base led to the formation of the lactam **11**. The phenolate group thus appears to be a rather good leaving group in the formation of **11** from the corresponding allylic amine. When the *N*-protecting group is a Troc (**9**), reaction under basic conditions led only to a mixture of uncharacterized compounds with a trace of the bicycle **11**.

With the aforementioned success of the 2-aminoimidazole synthesis, we set about to extend the method to the preparation of the 2-aminooxazole and the 2-aminothiazole cores. Under the same reaction conditions, urea and thiourea were found to be less reactive than Boc-guanidine. Reaction of the dihydropyridine **1** with urea in the presence of one equiv. of bromine led to compound **12** in a 50% yield. The dihydropyridine ring opening was then achieved simply by heating **12** in DMSO for 90 min. The 2-aminooxazole derivative **14** was obtained in modest yield as a 14:86 mixture of *Z*/*E* stereoisomers. Attempts to improve the yield by changing the solvent to DMF did not lead to the expected product but to the bicyclic urea **16** in 40% yield as the only identifiable compound. Reaction of thiourea with dihydropyridine **1** led to the 2-aminodihydropyridinethiazole **13** with a yield of only 11%. The latter reaction suffered from the sensitivity of thiourea to oxidative conditons.[10] Heating **13** in DMSO led to the expected 2-aminothiazole compound **15** as a 10:90 mixture of *Z*/*E* stereoisomers in a 28% yield (Scheme 2).

To widen the scope of the reaction, we next examined the reactivity of various *N*-protected tetrahydropyridines toward bromine oxidation and nucleophilic addition of Boc-guanidine, urea, or thiourea (Scheme 3). As expected, tetrahydropyridines **17**, **18**, **19**, and **20** underwent oxidative coupling with Boc guanidine very rapidly and gave products **21**, **22**, **23**, and **24**, respectively, in almost quantitative yields. The crude products were reacted with hydrochloric acid to remove the guanidine Boc group and to accomplish concomitant cleavage of the aminal bond. The 2-aminoimidazoles **25**, **26**, and **27** were obtained in about 50−70% yields for the three steps. Completely deprotected **28** was isolated by heating **23** in HCl for 12 h. This compound has already been prepared from ornithine derivatives by Büchi first[14] and Horne,[6d] using the method of Lancini.[6b] Treatment of piperidine *N*-Boc-

(12) Gilchrist, T. L. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 735−756.
(13) (a) Wright, A. E.; Chiles, S. A.; Cross, S. S. *J. Nat. Prod.* **1991**, *54*, 1684. (b) Andrade, P.; Willoughby, R.; Pomponi, S. A.; Kerr, R. G. *Tetrahedron Lett.* **1999**, *40*, 4775−4778.

SCHEME 3[a]



[a] Reagents and conditions: (i) Boc-Gua, Br_2, DMF/acetonitrile, rt, 15 min; (ii) HCl 2 M, 70 °C, 5 h, **25** (72%), **26** (50%), **27** (48%), **28** from **19** (84%) for both steps; (iii) HCl 2 M, 70 °C, 12 h, **29** from **20** (42%) for both steps; (iv) urea, Br_2, DMF/acetonitrile, rt, 15 min, **30** (66%), **31** (32%), **32** (31%); (v) thiourea, Br_2, DMF/acetonitrile, rt, 15 min, **33** (4%); (vi) NaOH 1M, 100 °C, 5 min, **34** (quant), **35** (quant), **36** (quant).

protected compound **24** with HCl for 12 h gave only **29**, indicating that the presence of an electron-withdrawing group on the piperidine moiety is necessary for aminal cleavage.

Using the same procedure with urea instead of Boc-guanidine, the tetrahydrooxazolopyridine compounds **30**, **31**, and **32** were obtained in 66, 32, and 31% yields from **17**, **19**, and **20**, respectively. Attempts to run the same reaction sequence with thiourea as the nucleophile were disappointing since only a 4% yield of the bicycle **33** was obtained.

The transformation of aminals **30**, **31**, and **32** into the 2-aminooxazoles **34**, **35**, and **36** (Scheme 3) in nearly quantitative yields was achieved by refluxing in 1 M aqueous NaOH for 5 min. Attempts to open the bicycles **30** and **31** under acidic conditions did not give any reaction, the starting material was recovered. Heating in DMSO under neutral conditions led to unidentifiable degradation products. It is noteworthy that purification of 2-aminooxazoles **34**, **35**, and **36** on silica gel or by HPLC led to the partially or totally recyclized compounds **30**, **31**, and **32**.

A short procedure for the preparation of C-4-substituted 2-amino-1,3-azoles has been developed. A bromine-mediated oxidative protocol on the enamine moiety of various dihydro or tetrahydropyridines followed by nucleophilic addition of protected guanidine, urea or thiourea allowed access to various 2-amino-hydro-3-azolopyridines. The yields were found to be modest to excellent depending on the nucleophile. The method is more applicable to protected guanidine and urea than to thiourea and unprotected guanidine. The propensity of the latter to be oxidized by bromine is probably the reason for this limitation. The subsequent regioselective aminal ring-opening reactions and the rearrangement with conversion to 2-aminoimidazoles and 2-aminooxazoles were found to be pH dependent and proceeded in moderate to good yields.

Experimental Section

N-Alkoxycarbonyl-1,2-dihydropyridines **1**−**3**, *N*-alkoxycarbonyl-1,2,3,4-tetrahydropyridines **17**, **19**, and **20**, and *N*-tosyl-1,2,3,4-tetrahydropyridine (**18**) were prepared according to reported procedures:[15] **1** (71%),[15a] **2** (77%),[16] **3** (80%),[17] **17** (74%),[18] **18** (61%),[19] **19** (65%),[15c] **20** (44%).[20]

General Procedure for the Preparation of Compounds 14 and 15. Representative Procedure for [3-(2-Aminooxazol-5-yl)allyl]carbamic Acid Methyl Ester (14). A solution of **12** (6.1 mmol) in DMSO (75 mL) was stirred at 175 °C for 1.5 h. The reaction mixture was cooled to room temperature and poured into cold water, and the solution was made basic to a pH 10 or greater by addition of an aqueous 5% Na_2CO_3 solution. The solution was extracted with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The residue was purified by preparative-layer chromatography using 98:2 NH_3-saturated CH_2Cl_2−MeOH to afford **14** a brown solid (265 mg, 22%) as an inseparable mixture of isomers (*Z*/*E* 14:86): IR (Nujol) 3343, 3319, 1690, 1656; MS (ES) *m*/*z* 197.8 $(M + H)^+$; HRMS calcd for $C_8H_{11}N_3O_3$ 198.0879, found $(M + H)^+$ 198.0905; *E* isomer ^1H NMR (CD_3OD, 300 MHz) δ 3.64 (s, 3H), 3.80 (d, $J = 7$ Hz, 2H), 5.85 (dt, $J = 6$ Hz, 16 Hz, 1H), 6.22 (dd, $J = 16$ Hz, 1 Hz, 1H), 6.54 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 43.3, 52.6, 117.4, 123.8, 124.4, 144.7, 159.5, 163.1. *Z* isomer ^1H NMR (CD_3OD, 300 MHz) δ 3.64 (s, 3H), 4.06 (br d, $J = 6$ Hz, 12 Hz, 1H), 5.36 (br d, $J = 6$ Hz, 12 Hz, 1H), 6.09 (dd, $J = 12$ Hz, 1 Hz, 1 H), 6.63 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 40.9, 52.5, 115.8, 125.6, 126.7, 144.5.

(14) Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1777−1779.

(15) (a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321−1323. (b) Zapf, C. W.; Creighton, C. J.; Tomoika, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133−1136. (c) Leclercq, S.; Thirionet, I.; Broeders, F.; Daloze, D.; Vander Meer, R.; Braeckman, J. C. *Tetrahedron* **1994**, *50*, 8465−8478.

(16) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836−4842.

(17) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124−133.

(18) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.-I.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697−6703.

(19) Kim, S.; Yoon, J.-Y. *Synthesis* **2000**, 1622−1630.

(20) Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180−4184.

[3-(2-Imino-2,3-dihydrothiazol-5-yl)allyl]carbamic Acid Methyl Ester (15). Reaction conditions: compound **13** was heated for 2 h at 175 °C. Purification by silica gel flash chromatography using 95:5 NH_3 saturated CH_2Cl_2−MeOH. Inseparable 1:9 mixture of *Z*/*E* isomers as a brown solid (28%): IR (film) 1699, 1636, 1536, 1503, 1023, 949; MS (ES) *m/z* 214.1 $(M + H)^+$; HRMS calcd for $C_8H_{11}N_3O_2S$ 214.0650, found $(M + H)^+$ 214.0640; *E* isomer ^1H NMR ($CDCl_3$, 250 MHz) δ 3.64 (s, 3H), 3.8 (d, $J = 5$ Hz, 2H), 5.57 (dt, $J = 6$ Hz, 15 Hz, 1H), 6.45 (d, $J = 15$ Hz, 1H), 6.85 (s, 1H); ^{13}C NMR ($CDCl_3$−CD_3OD, 75 MHz) δ 42.3, 51.8, 121.9, 123.9, 125.7, 136.2, 167.9; *Z* isomer ^1H NMR ($CDCl_3$, 250 MHz) δ 3.64 (s, 3H), 3.77 (d, $J = 5$ Hz, 2H), 5.36 (dt, $J = 6$ Hz, 11 Hz, 1H), 6.37 (d, $J = 11$ Hz, 1H), 6.93 (s, 1H).

***cis*-2-Oxo-1,2,3,3a,5,7a-hexahydroimidazol[4,5-*b*]pyridine-4-carboxylic Acid Methyl Ester (16).** A solution of **12** (1 mmol) in DMF (10 mL) was stirred under reflux for 1 h. The solvent was evaporated in vacuo, and the residue was purified by silica gel flash chromatography using 93:7 diethyl ether/methanol to afford **16** (81 mg, 40%) as a yellow solid: mp 198 °C; IR (Nujol) 3314, 3213, 1697; ^1H NMR (CD_3OD, 250 MHz) δ 3.55 (br d, 1H), 3.65 (s, 3H), 4.06 (m, 2H), 5.56 (m, 1H), 5.86 (m, 2H), 6.52 (br s, 1H), 6.76 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 38.2, 48.0, 52.6, 61.6, 123.8, 124.3, 155.3, 160.9; MS (ES) *m/z* 219.9 $(M + H)^+$; HRMS calcd for $C_8H_{11}N_3O_3$ 220.0698, found $(M + H)^+$ 220.0681.

General Procedure for the Cleavage of the *tert*-Butyloxycarbonyl Group and the Ring Opening under Acidic Conditions (Preparation of Compounds 25−29). Representative Procedure for 5-[3-(Methoxycarbonylamino)-propyl]-1*H*-imidazol-2-ylammonium Chloride (25). The crude mixture of compounds **21** was dissolved in 2 M HCl (5 mL) and the reaction mixture was stirred at 70 °C for 5 h. The solution was cooled to room temperature, washed with diethyl ether and the solvent was evaporated in vacuo. The residue was purified by silica gel flash chromatography using 80:20 CH_2Cl_2−MeOH to afford **25** (237 mg, 72% from **17**) as a yellow oil: IR (film) 3334, 1681; ^1H NMR (CD_3OD, 300 MHz) δ 1.76 (t, $J = 7.5$ Hz, 2H), 2.51 (t, $J = 7.5$ Hz, 2H), 3.15 (t, $J = 7.5$ Hz, 2H), 3.55 (s, 3H), 6.48 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 22.7, 29.7, 40.8, 52.6, 110.0, 128.4, 141.7; MS (ES) *m/z* 199 $(M + H)^+$; HRMS calcd for $C_8H_{15}N_2O_4$ 199.1195, found $(M + H)^+$ 199.1184.

5-[3-(4-Methylbenzenesulfonylamino)propyl]-1*H*-imidazol-2-ylammonium chloride (26): colorless paste (50% from **18**); IR (film) 2924, 1155; ^1H NMR (CD_3OD, 300 MHz) δ 1.74 (t, $J = 6$ Hz, 2H), 2.42 (s, 3H), 2.52 (t, $J = 6$ Hz, 2H), 2.85 (t, $J = 6$ Hz, 2H), 6.48 (s, 1H), 7.30 (d, $J = 9$ Hz, 2H), 7.66 (d, $J = 9$ Hz, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 21.5, 22.4, 29.1, 42.8, 110.0, 128.0, 130.7, 138.6, 144.6, 148.3; MS (ES) *m/z* 295 $(M + H)^+$; HRMS calcd for $C_{13}H_{19}N_4O_2S$ 295.1229, found $(M + H)^+$ 295.1214.

5-[3-(Benzyloxycarbonylamino)propyl]-1*H*-imidazol-2-ylammonium chloride (27): yellow oil (48% from **19**); IR (film) 3307, 1681; ^1H NMR (CD_3OD, 300 MHz) δ 1.76 (q, $J = 6$ Hz, 2H), 2.50 (t, $J = 6$ Hz, 2H), 3.15 (t, $J = 6$ Hz, 2H), 5.06 (s, 2H), 6.50 (s, 1H), 7.32 (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz) δ 22.7, 29.6, 40.8, 67.4, 109.9, 128.3, 128.7, 129.0, 129.5, 138.4, 148.4, 159.0; MS (ES) *m/z* 275 $(M + H)^+$; HRMS calcd for $C_{14}H_{19}N_4O_2$ 275.1508, found $(M + H)^+$ 275.1500.

5-(3-Aminopropyl)-1*H*-imidazol-2-ylammonium Dihydrochloride (28). Reaction conditions: 12 h at 70 °C. Purification by silica gel flash chromatography using 70:30 CH_2Cl_2−MeOH: white solid (42% from **19**); mp 204−205 °C dec; IR (Nujol) 3320, 2923; ^1H NMR (CD_3OD, 300 MHz) δ 1.97 (q, $J = 6$ Hz, 2H), 2.63 (t, $J = 6$ Hz, 2H), 2.98 (t, $J = 6$ Hz, 2H), 6.60 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 22.5, 27.1, 39.9, 110.4, 127.1, 148.6; MS (ES) *m/z* 141 $(M + H)^+$.

3a,4,5,6,7,7a-Hexahydro-1*H*-imidazo[4,5-*b*]pyridin-2-ylamine (29): paste (84% from **20**); IR (film) 3390; ^1H NMR (CD_3OD, 300 MHz) δ 1.81 (m, 2H), 2.00 (m, 1H), 2.15 (br d, $J = 18$ Hz, 1H), 2.97 (dd, $J = 9$ Hz, 6 Hz, 1H), 3.28 (br m, 1H), 4.31 (br m, 1H), 5.24 (d, $J = 6$ Hz, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 17.0, 23.0, 41.3, 55.1, 66.2, 161.3; MS (ES) *m/z* 142 $(M + 2H)^+$, 141 $(M + H)^+$, 124 $(C_6H_{10}N_3)^+$; HRMS calcd for $C_6H_{13}N_4$ 141.1140, found $(M + H)^+$ 141.1141.

General Procedure for Ring Opening under Basic Conditions (Preparation of Compounds 34−36). Representative Procedure for Methyl 3-(2-Aminooxazol-5-yl)-propylcarbamate (34). A solution of compound **30** (0.66 mmol) in 1 M NaOH (5 mL) was stirred under reflux for 5 min. The solution was cooled to room temperature and poured into a mixture of phosphate buffer pH 7 and BuOH. The aqueous layer was extracted with BuOH. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was evaporated in vacuo to afford **34** (quantitative yield) as a yellow paste: ^1H NMR (CD_3OD, 300 MHz) δ 1.71 (m, 2H), 2.37 (t, $J = 7.5$ Hz, 2H), 3.12 (t, $J = 6.7$ Hz, 2H), 3.62 (s, 3H), 6.08 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 23.5, 29.7, 41.0, 52.5, 106.1, 124.4, 156.9, 159.8; MS (ES) *m/z* 165 $(M + H)^+$, 187 $(M + Na)^+$; HRMS (ES) calcd for $C_8H_{14}N_3O_3$ 200.1035, found $(M + H)^+$ 200.1023.

Benzyl 3-(2-aminooxazol-5-yl)propylcarbamate (35): off-white paste (quantitative yield); ^1H NMR (CD_3OD, 300 MHz) δ 1.71 (q, $J = 6.9$ Hz, $J = 7.5$ Hz, 2H), 2.37 (t, $J = 7.4$ Hz, 2H), 3.14 (t, $J = 6.8$ Hz, 2H), 5.06 (s, 2H), 6.06 (s, 1H), 7.33 (m, 5H); ^{13}C (CD_3OD, 75 MHz) δ 23.5, 29.7, 41.0, 49.4 (HMBC), 67.5, 106.1, 124.4, 128.9, 129.0, 129.5, 138.5, 156.9 (HMBC), 159.0 (HMBC); HRMS (ES) calcd for $C_{14}H_{17}N_3NaO_3$ 298.1168, found $(M + Na)^+$ 298.1174.

***tert*-Butyl 3-(2-aminooxazol-5-yl)propylcarbamate (36):** off-white paste (quantitative yield); ^1H (CD_3OD, 500 MHz) δ 1.43 (s, 9H), 1.68 (m, 1H), 2.36 (t, $J =$ Hz, 1H), 3.05 (t, $J =$, 1H), 6.06 (s, 1H); ^{13}C (CD_3OD, 125 MHz) δ 23.5, 28.6, 29.8, 40.6, 80.0, 106.0, 124.5, 156.9, 158.7; MS (ES) *m/z* 165 $(M + H)^+$, 187 $(M + Na)^+$; HRMS (ES) calcd for $C_{11}H_{19}N_3NaO_3$ 264.1324, found $(M + Na)^+$ 264.1333.

Acknowledgment. We thank MENRT for a grant (R.A.-J.). We gratefully acknowledge Dr. Robert Dodd for the correction of this manuscript.

Supporting Information Available: Experimental procedures and characterization data for compounds **7**−**13** and **30**−**33** and ^1H and ^{13}CNMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050862O