overnight. The excess methanol was distilled out of the reaction mixture at atmospheric pressure. The residue was cooled to room temperature and extracted with ether (3 × 35 mL). The ether was dried (K_2CO_3) and evaporated to yield the crude ester, which were found to be a mixture of the desired product and the phenol **12c**. Separation of the two compounds on preparative TLC (silica gel, hexane–EtOAc, 9:1) afforded **12b**, 18 mg, 0.065 mmol (21%), and phenol **12c**, 18 mg, 0.069 mmol (23%). The dimethoxy ester was recrystallized from pentane to yield **12b** a white solid: mp 65.5–67 °C; $[\alpha]^{23}_D$ −37.7° (*c* 1.0, abs EtOH); ^{1}H NMR ($CDCl_3$) δ 6.77 (s, 1 H), 6.68 (s, 1 H), 5.72 (d, *J* = 1.31 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.66 (s, 3 H), 3.19 (d, *J* = 15.42 Hz, 1 H), 2.68 (d, *J* = 15.44 Hz, 1 H), 2.04 (d, *J* = 1.45 Hz, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.19, 148.33, 147.55, 131.73, 127.05, 126.89, 126.72, 111.92, 107.76, 56.28, 56.07, 52.16, 43.45, 38.20, 23.93, 19.51; IR (cm^{-1}) 2953, 2932, 2866, 1730, 1605, 1512; MS (*m/z*) 276 (9.1), 217 (86.3), 202 (36.4), 186 (14.7); HRMS found 276.1371.

The phenolic product, **12c**, isolated above gave the following spectral properties: ^{1}H NMR ($CDCl_3$) δ 6.74 (s, 1 H), 6.73 (s, 1 H), 5.72 (s, 1 H), 5.55 (s, 1 H (OH)), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.16 (d, *J* = 15.40 Hz, 1 H), 2.66 (d, *J* = 15.41 Hz, 1 H), 2.03 (d, *J* = 1.42 Hz, 3 H), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.20, 145.08, 144.93, 131.65, 127.60, 126.69, 114.79, 106.72, 56.26, 52.13, 43.40, 37.98, 23.75, 19.56; IR (cm^{-1}) 3444, 2954, 2932, 1730, 1583, 1512; (*m/e*) 262 (10.0), 203 (73.4).

This material was converted into dihydronaphthalene **12b** by the following reaction conditions:

Ester **11c** (10 mg, 0.038 mmol) was dissolved in THF (3 mL) and added to NaH (0.0017 g, 0.071 mmol, washed free of oil with pentane) in THF (2 mL). The reaction was stirred at room temperature for 1 h, at this time methyl iodide (0.057 mL, 0.090 mmol) was added. The reaction was stirred for 2 h at room temperature and was worked up by pouring into NH_4Cl and extracting with ether (2 × 25 mL). The ether was dried (K_2CO_3) and evaporated to yield 7 mg (0.025 mmol, 67%) of pure **12b**.

(*S*)-2-Methyl-2-carbomethoxy-4-phenyl-1,2-dihydronaphthalene, 15a. A solution of 300 mg of lactam **13a** in 10 mL of 48% hydrobromic acid was heated to reflux for 24 h. After cooling to room temperature, the solution was diluted with water and extracted three times with ethyl acetate. The extracts were dried (Na_2SO_4) and concentrated in vacuo, and the residue was dissolved in ether. The ethereal solution was treated with excess diazomethane, and the solution was filtered and then concentrated. The residue was purified by preparative TLC and then distilled via Kugelrohr, to give 200 mg (85%): bp 120 °C (0.07 Torr); $[\alpha]^{23}_D$ +12.79° (*c* 1.15, $CHCl_3$); IR (film) 3050, 3020, 2942, 1736, 1598, 1492, 1483, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–7.00 (m, 9 H), 6.05 (s, 1 H), 3.7 (s, 3 H), 3.38 (d, *J* = 15.5 Hz, 1 H), 2.85 (d, *J* = 15.5 Hz, 1 H), 1.35 (s, 3 H). Anal. Calcd for $C_{19}H_{18}O_2$: C, 82.00; H, 6.52. Found: C, 82.80; H, 6.76. The *R* enantiomer of the above, **15b** was prepared in the same manner, affording 190 mg (79%) of a clear oil whose boiling point and spectral properties were identical with those of **15a**: $[\alpha]^{23}_D$ −12.56° (*c* 1.15, $CHCl_3$). Anal. Found: C, 81.73; H, 6.69.

Dehydropyrrolidone, 17. This material was isolated from the chromatographic separation of **5b** (vide supra), affording 260 mg (17%): ^{1}H NMR ($CDCl_3$) δ 8.37–8.35 (m, 1 H), 7.55–7.49 (m, 1 H), 7.07–7.03 (m, 2 H), 4.91 (d, *J* = 1.37 Hz, 1 H), 4.58 (s, 1 H, (OH)), 4.27–4.21 (m, 1 H), 3.76–3.61 (m, 1 H), 3.29 (d, *J* = 13.99 Hz, 1 H), 3.05–2.98 (m, 1 H), 2.83 (d, *J* = 13.99 Hz, 1 H), 2.63–2.53 (m, 1 H), 1.72 (d, *J* = 1.34 Hz, 3 H), 1.23 (s, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.79 (d, *J* = 6.59 Hz, 3 H); ^{13}C NMR (ppm) 183.67, 158.18, 148.96, 140.39, 136.34, 123.91, 121.59, 110.50, 63.00, 61.94, 49.03, 45.19, 26.69, 24.03, 20.45, 20.01, 14.33; IR 3383, 2964, 2928, 2868, 1704, 1548 cm^{-1}; *m/e* 288 (3.2), 272 (9.2), 147 (20.6), 118 (6.8), 93 (57.4), 69 (5.3).

(3*S*,6*R*,7a*R*)-3-Isopropyl-6,7a-dimethyl-5-oxo-6-(2-pyridylmethyl)-2,3,5,6,7,7a-hexahydro[2,1-*b*]oxazole, 18. Trifluoroacetic acid (0.13 mL, 1.5 mmol) was dissolved in 20 mL of dichloromethane at 0 °C, and 100 mg of **17** in 5 mL of dichloromethane was added. The solution was warmed to room temperature and stirred for 3 h. The mixture was poured in 10 mL of $NaHCO_3$ solution and extracted with dichloromethane (2 × 25 mL), and the extracts were dried (K_2CO_3) and concentrated, leaving the bicyclic lactam in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 8.52–8.49 (m, 1 H), 7.57–7.51 (m, 1 H), 7.15–7.09 (m, 2 H), 4.10 (dd, *J* = 7.20, 7.80 Hz, 1 H), 3.63–3.51 (m, 2 H), 3.13 (d, *J* = 12.88 Hz, 1 H), 2.81 (d, *J* = 12.83 Hz, 1 H), 2.51 (d, *J* = 14.29 Hz, 1 H), 1.97 (d, *J* = 14.30 Hz, 1 H), 1.47–1.39 (m, 1 H), 1.24 (s, 3 H), 0.96 (d, *J* = 6.56 Hz, 3 H), 0.84 (s, 3 H), 0.80 (d, *J* = 6.53 Hz, 3 H); ^{13}C NMR 184.00, 158.12, 148.92, 136.02, 124.75, 121.76, 96.77, 69.98, 62.58, 48.63, 46.88, 42.99, 34.19, 26.84, 24.08, 20.69, 18.89; IR 2967, 2933, 2877, 1705, 1377, 1355 cm^{-1}; (*m/e*) 288 (7.4), 273 (16.2), 245 (3.9), 146 (45.5), 134 (8.3), 118 (8.7), 93 (79.6).

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Registry No. 1, 88670-16-0; **2** (R = H, R′ = Me), 88670-17-1; **2** (R = H, R′ = $PhCH_2$), 88670-18-2; **2** (R = H, R′ = Et), 88670-19-3; **2** (R = H, R′ = 4-$MeOC_6H_4CH_2$), 88670-20-6; **2** (R = H, R′ = *i*-Pr), 88670-21-7; **2** (R = Me, R′ = $PhCH_2$), 88670-22-8; **2** (R = $PhCH_2$, R′ = Me), 88728-90-9; **2** (R = Me, R′ = Et), 88670-23-9; **2** (R = Et, R′ = Me), 88728-91-0; **2** (R = 4-$MeOC_6H_4CH_2$, R′ = Me), 88728-92-1; **2** (R = Me, R′ = 4-$MeOC_6H_4CH_2$), 88670-24-0; **2** (R = Me, R′ = *i*-Pr), 88670-25-1; **3** (R = Me, R′ = $PhCH_2$), 88685-64-7; **3** (R = $PhCH_2$, R′ = Me), 88670-26-2; **3** (R = Me, R′ = Et), 88670-27-3; **3** (R = Et, R′ = Me), 88670-28-4; **3** (R = 4-$MeOC_6H_4CH_2$, R′ = Me), 88670-30-8; **3** (R = Me, R′ = 4-$MeOC_6H_4CH_2$), 88670-29-5; **4**, 98203-44-2; **5a**, 126062-89-3; **5b**, 126062-90-6; **7a**, 126062-91-7; **7b**, 126062-92-8; **8a**, 126062-93-9; **8b**, 126062-94-0; **9a**, 112522-04-0; **9b**, 126062-95-1; **11a**, 126062-96-2; **11b**, 126062-97-3; **12a**, 126062-98-4; **12b**, 126062-99-5; **12c**, 126063-02-3; **15a**, 88670-33-1; **15b**, 88670-34-2; **16**, 126082-45-9; **17**, 126063-00-1; **18**, 126109-26-0; (*S*)-(+)-$Me_2CHCH(NH_2)CH_2OH$, 2026-48-4; $PhC(O)CH_2CH_2CO_2H$, 2051-95-8; (*S*)-$MeOC(O)CH_2C(Me)(Et)C(O)OMe$, 4727-78-0.

One-Pot Synthesis of *N*-(2-Heteroaryl)-α-amino Esters by the Regiospecific 2-*N*-(α-Alcoxycarbonyl)alkylation of 2-Aminoazines and -azoles with Glyoxals and Alcohols Promoted by Perchloric Acid

Benito Alcaide,* Joaquin Plumet, and Miguel A. Sierra

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

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2-Amino heterocycles, including pyridine, diazine, andd azole derivatives, are readily converted into *N*-(2-heteroaryl)-α-amino esters **4** in a one-pot sequence by reaction with glyoxals and alcohols in the presence of perchloric acid. In addition, the corresponding α-amino acids **5** are quantitatively obtained by acidic hydrolysis of compounds **4**.

Naturally occurring *N*-alkyl-α-amino acids are widely distributed, being metabolically important in some cases.[1,2] Furthermore, *N*-alkyl- and *N*-aryl-α-amino acids have been used as starting materials both in drug[3] and heterocyclic

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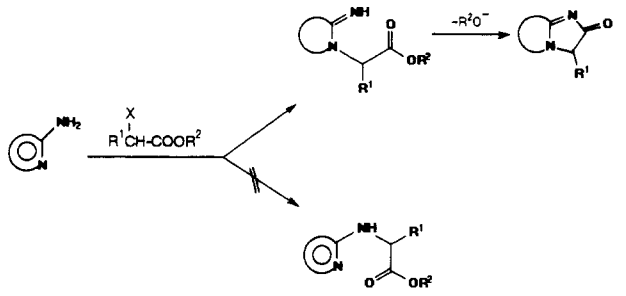
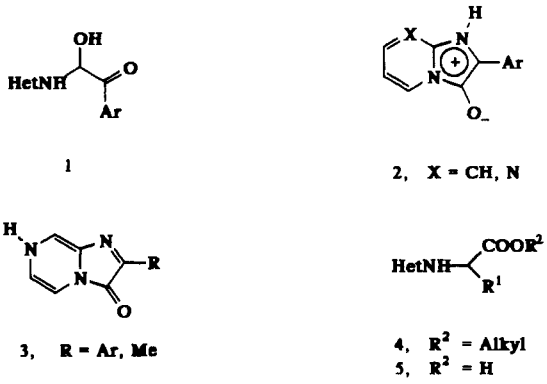
Scheme I



synthesis.[4] In addition, some *N*-arylalanine derivatives such as Ridomil are selective herbicides.[5] Due to these properties, interest in the synthesis of *N*-aryl-α-amino acid derivatives has increased in recent years.[6] In spite of their potential interest, efficient general procedures for the synthesis of *N*-(2-heteroaryl)-α-amino acids and their derivatives have not yet been developed. The lack of a general methodology for the synthesis of this class of compounds is probably due to the fact that the straightforward synthetic approach, namely, the direct alkylation of the exocyclic nitrogen by α-halo acid or α-halo esters, is known to occur at the ring nitrogen, giving the related imidazo[1,2-*a*] derivatives through the corresponding intermediate pyridone imines[7] (Scheme I).

Compounds of the *N*-(2-heteroaryl)-α-amino acid type have seldom been described. Bristow[8] reported the synthesis of *N*-(2-pyridyl)glycine in moderate yield by reaction of 2-aminopyridine with formaldehyde, sodium hydrogen sulfite, and sodium cyanide followed by hydrolysis of the *N*-(2-pyridyl)aminoacetonitrile thus formed. By the same procedure, the synthesis in low yield of *N*-(2-pyrazinyl)-glycine and some derivatives has been reported by Goto et al.[9] in studies related to *Cypridine luciferine* synthesis. The synthesis in moderate yield of *N*-(2-pyridyl)-α-alanine and its ethyl ester has been described by Yamaguchi.[10] We have recently reported the synthesis of some *N*-(2-pyridyl)aminodiphenylacetic acid derivatives by reaction of 2,2-diphenylimidazo[1,2-*a*]pyridin-3(2*H*)-ones with nucleophiles.[11]

The reaction of some glyoxal derivatives with different 2-amino heterocycles in acidic media has been investigated by several authors in connection with the synthesis of imidazo[1,2-*a*]azine derivatives.[12] Recently, we have reported the reaction of some arylglyoxals with 2-amino heterocycles in the presence or in the absence of $BF_3{\cdot}Et_2O$ complex.[13] Either carbinolamines **1** or imidazo[1,2-*a*]azine derivatives **2** and **3** (R = Ar) were obtained, depending on the nature of both the arylglyoxal and the 2-amino heterocycle. In clear contrast, we show now that the use of concentrated perchloric acid in alcoholic solution affords in a simple and efficient fashion *N*-(2-heteroaryl)-α-amino esters **4**, which in turn can be quantitatively hydrolyzed to the parent *N*-(2-heteroaryl)-α-amino acids.



1 **2**, X = CH, N

3, R = Ar, Me **4**, R^2 = Alkyl **5**, R^2 = H

The reaction of 2-aminopyridines, 2-aminopyrimidine, and 2-aminothiazole with various glyoxal derivatives[14] (Scheme II, R^1 = H, Me, Ph), in boiling alcohol as solvent (R^2 = Me, Et, *i*-Pr) and in the presence of excess aqueous 60% perchloric acid, forms regiospecifically *N*-(2-heteroaryl)-α-amino esters **4** in fair to excellent yields. Spectroscopic and analytical data for compounds **4** are in accordance with the α-amino ester structure proposed for these compounds.

Other aqueous acids such as hydrochloric acid or hydrobromic acid gave lower yields. Of the different glyoxals tested, only glyoxal itself failed to react with 2-aminopyrimidine and 2-aminothiazole. In these cases only unreacted 2-amino heterocycle and unidentified minor byproducts were obtained. Tertiary alcohols such as *tert*-butyl alcohol also failed to produce the corresponding compounds **4**.

The formation of compounds **4** may be accounted for by the two reaction pathways shown in Scheme III. Path **a** would involve bicyclic intermediate **6**, which will undergo imidazole ring opening by alcohol promoted by the aromatization of the heteroaromatic ring. The recovery of aromaticity appears to be the driving force for the process.[15] Alternatively, path **b** would imply formation of α-ketimine acetal **7**[16] followed by isomerization to the aminoketene acetal intermediate **8** and its hydrolysis. Evidence for path **a** arises from isolation in moderate yield of 2-methylimidazo[1,2-*a*]pyrazin-3-one, as its perchlorate, in the reaction of 2-aminopyrazine and pyruvaldehyde.[17]

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(6) See, for example: (a) Barrett, G. C. In *Chemistry and Biochemistry of the Amino acid*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; p 354 and references therein. (b) Sasadi, T.; Mori, K.; Ohno, M. *Synthesis* **1985**, 314. (c) Effenberger, F.; Burkard, U.; Willfahrt, J. *Liebigs Ann. Chem.* **1986**, 314. (d) Pirkle, W. H.; Pochapsky, T. C. *J. Org. Chem.* **1986**, *51*, 102. (e) Barton, D. H. R.; Finet, J. P.; Khamai, J. *Tetrahedron Lett.* **1989**, *30*, 937.

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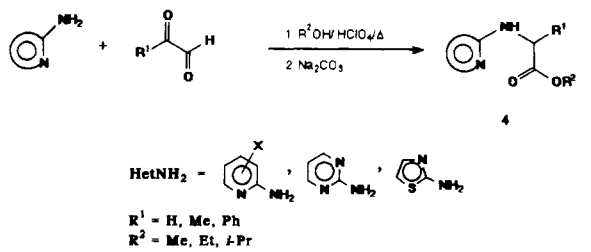
(14) Glyoxal was used as an aqueous 30% solution, phenylglyoxal as its hydrate, and pyruvaldehyde either as an aqueous 40% solution or as its dimethyl acetal with similar results.

(15) Imidazo[1,2-*a*]pyridin-3(2*H*)-one derivatives and imidazo[1,2-*a*]-pyridinium-3-olates undergo imidazole ring opening by reaction with nucleophiles easily. See ref 11 and 13.

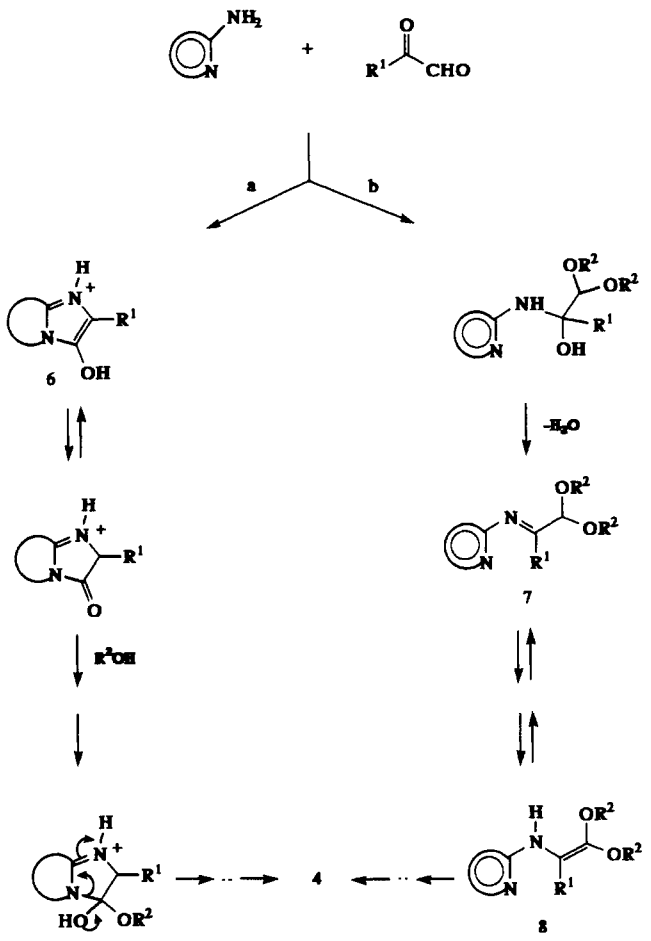
(16) Related imines derived from pyruvaldehyde dimethyl acetal and aliphatic or aromatic amines are easily prepared as stable compounds. Alcaide, B.; Plumet, J.; Sierra, M. A. To be published.

(17) The corresponding 2-aryl-7*H*-imidazo[1,2-*a*]pyrazin-3-ones prepared independently (ref 13) do not undergo imidazole ring opening in the reaction conditions for which compounds **4** are formed.

Scheme II



Scheme III



The isolation of compound **2** (X = CH, Ar = Ph), as a minor product, in the reaction of 2-aminopyridine and phenylglyoxal at short reaction times and its independent conversion to amino ester **4g** by reaction with methanol/perchloric acid[13] also support path **a**. Furthermore, aniline and 3-aminopyridine failed to give the corresponding α-amino esters in their reactions with glyoxals under identical experimental conditions. Thus, we believe that path **b** should be ruled out on account of the above evidence at least as the main reaction path.

In addition, acidic hydrolysis of amino esters **4** formed cleanly the corresponding 2-amino acids **5** as hydrochlorides in nearly quantitative yields. The free amino acid was obtained in some cases upon neutralization with aqueous sodium bicarbonate of the salt. Surprisingly, hydrolysis of **4g** yielded compound **2** (X = CH, Ar = Ph) instead of the expected amino acid. This product was identical with an authentic sample prepared independently,[13] and its formation may be explained by intramolecular cyclization of the amino acid formed during hydrolysis of **4g**.

In summary, the straightforward procedure described herein for the synthesis of compounds **4** is performed under simple conditions and is a rather general and efficient method for the regiospecific synthesis of N-(2-heteroaryl)-α-amino acid derivatives starting from 2-amino nitrogen heterocycles. Use of compounds **4** in synthesis of heterocycles is currently in progress.

Experimental Section

Melting points were taken on a Büchi 512 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian T-60 and on Varian XL-300 instruments at 60 and 300 MHz, respectively. ^{13}C NMR spectra were obtained on Varian FT-80 and on Varian XL-300 instruments at 20.15 and 75.43 MHz, respectively. ^{1}H and ^{13}C NMR chemical shifts are given in ppm relative to TMS (^{1}H, 0 ppm) or $DCCl_3$ (^{13}C, 66.90 ppm). IR spectra were recorded on a Perkin-Elmer 781 grating spectrophotometer. Mass spectra were determined on a Varian MAT 711 spectrometer. Elemental analyses were preformed at the Instituto de Química Bio-Orgánica, CSIC, Barcelona, Spain. Silica gel, Merck 60 (230–400 mesh), was used in flash chromatography purifications.

2-Amino heterocycles, glyoxal (aqueous solution, 30%), pyruvaldehyde (aqueous solution 40%), pyruvaldehyde dimethyl acetal, and perchloric acid (aqueous solution, 60%, analytical grade) were purchased from Merck and used as received. Phenylglyoxal hydrate was prepared according to the literature method.[18]

General Procedure for the Synthesis of N-(2-Heteroaryl)-α-amino Esters 4. A solution of ketoaldehyde[14] (10.5 mmol) in the corresponding alcohol (10 mL) was added in one portion over a slurry of the 2-amino heterocycle (10.5 mmol) in 60% aqueous perchloric acid (3 mL) (*CAUTION*: perchloric acid is explosive and must be handled carefully). The resulting clear solution was heated under smooth reflux for the indicated time. After this time the reaction mixture was cooled to 0 °C and neutralized with an aqueous saturated sodium carbonate solution, and the resulting mixture was extracted (methylene chloride, 3 × 15 mL). The collected organic layers were washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum. The crude material (solid or oil) thus obtained was purified by flash chromatography, evaporative distillation, or crystallization.

Methyl N-(2-pyridyl)glycinate (4a); reaction time 48 h; colorless oil; yield 60%; bp 84–88 °C (0.01 Torr); ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3 H, CH_3), 4.14 (d, 2 H, J = 5.74 Hz, CH_2), 5.24 (br s, NH), 6.44 (d, 1 H), 6.56–6.60 (m, 1 H), 7.34–7.40 (m, 1 H), 8.08 (dd, 1 H); ^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 171.6 (CO), 157.3, 147.2, 136.6, 112.9, 108.0, 51.5 (CH_2), 42.8 (OCH_3); IR (neat oil) ν 3400, 3270 (NH), 1740 (CO), 1605, 1585, 1420, 1210, 1155 cm^{-1}. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.86. Found: C, 57.58; H, 6.31; N, 16.97.

Ethyl N-(2-pyridyl)glycinate (4b): reaction time 64 h; colorless oil; yield 55%; bp 100 °C (0.05 Torr); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7.20 Hz, CH_3), 4.13 (d, 2 H, J = 5.49 Hz, CH_2), 4.22 (q, 2 H, J = 7.20 Hz, OCH_2), 5.09 (br s, NH), 6.45 (dd, 1 H), 6.57–6.61 (m, 1 H), 7.28–7.42 (m, 1 H), 8.09 (dd, 1 H); IR (neat oil) ν 3400, 3240 (NH), 1730 (CO), 1600, 1570, 1495, 1410, 1370 cm^{-1}. Anal. Calcd for $C_9H_{12}N_2O_2$: C, 60.00; H, 6.66; N, 15.55. Found: C, 60.27; H, 6.39; N, 15.61.

Isopropyl N-(2-pyridyl)glycinate (4c): reaction time 44 h; crude **4c** was purified by flash chromatography (hexane/ethyl acetate 2:1); yield 61%; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 6 H, J = 7.32 Hz, 2 × CH_3), 4.08 (d, 2 H, J = 6.47 Hz, CH_2), 5.07 (m, 2 H, NH + CH), 6.44 (dd, 1 H), 6.55–6.59 (m, 1 H), 7.34–7.40 (m, 1 H), 8.07 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.43 MHz) δ 170.6 (CO), 157.6, 147.6, 137.0, 113.3, 108.1, 68.6 (CH_2), 43.8 (CH), 21.6 (2 × CH_3); IR (neat oil) ν 3400 (NH), 1740 (CO), 1610, 1490, 1210 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.85; H, 7.21; N, 14.43. Found: C, 61.90; H, 7.35; N, 14.65.

Methyl N-(2-pyridyl)-α-alaninate (4d): reaction time 25 h; colorless solid; yield 80%; bp 90–94 °C (0.05 Torr); mp 62–64 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (d, 3 H, J = 7.08 Hz, CH_3), 3.72 (s, 3 H, OCH_3), 4.58 (q, 1 H, J = 7.08 Hz, CH), 4.98 (d, 1 H, J = 7.08

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Hz, NH), 6.41 (d, 1 H), 6.53–6.59 (m, 1 H), 7.27–7.39 (m, 1 H), 8.06 (dd, 1 H); ^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 174.8 (CO), 157.1, 147.5, 136.7, 113.0, 108.1, 51.7 (CH), 49.5 (OCH_3), 18.1 (CH_3); IR (KBr) ν 3360, 3260 (NH), 1740, 1725 (CO), 1605, 1575, 1515, 1420, 1300, 1115 cm^{-1}. Anal. Calcd for $C_9H_{12}N_2O_2$: C, 60.00; H, 6.66; N, 15.55. Found: C, 60.08; H, 6.69; N, 15.59.

Ethyl *N*-(2-pyridyl)-α-alaninate (4e): reaction time 88 h; crude **4e** was purified by flash chromatography (benzene/ethyl acetate 1:1); colorless oil; yield 55%; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.20 Hz, CH_2CH_3), 1.47 (d, 3 H, J = 7.44 Hz, $CHCH_3$), 4.18 (q, 2 H, J = 7.20 Hz, CH_2), 4.54–4.59 (m, 2 H, CH + NH), 6.41 (dd, 1 H), 6.45–6.59 (1 H), 7.33–7.39 (m, 1 H), 8.06 (dd, 1 H); ^{13}C NMR ($CDCl_3$, 75.43 MHz) δ 174.4 (CO), 157.2, 147.6, 136.8, 113.4, 108.4, 60.8 (OCH_2), 49.7 (CH), 18.30 ($CHCH_3$), 13.9 (CH_2CH_3); IR (neat oil) ν 3370 (NH), 1730 (CO), 1600, 1570, 1480, 1160 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.85; H, 7.21; N, 14.43. Found: C, 62.02; H, 7.16; N, 14.22.

Isopropyl *N*-(2-pyridyl)-α-alaninate (4f): reaction time 50 h; crude **4f** was purified by flash chromatography (hexane/ethyl acetate 2:1); pale yellow oil; yield 65%; ^{1}H NMR ($CDCl_3$) δ 1.21 (d, 3 H, J = 6.03 Hz, CH_3), 1.25 (d, 3 H, J = 6.03 Hz, CH_3), 1.46 (d, 3 H, J = 7.60 Hz, $CHNHCH_3$), 4.51 (m, 1 H, J = 7.60 Hz, $CHNHCH_3$), 4.94 (br d, 1 H, J = 7.60 Hz, NH), 4.93 (m, 1 H, J = 6.03 Hz, $OCH(CH_3)_2$), 6.42 (dd, 1 H), 6.55–6.60 (m, 1 H), 7.27–7.41 (m, 1 H), 8.09 (dd, 1 H); ^{13}C NMR ($CDCl_3$, 75.43 MHz) δ 173.8 (CO), 157.3, 147.7, 137.0, 113.3, 108.1, 68.3 ($OCH(CH_3)_2$), 50.0 ($CHNHCH_3$), 21.6, 21.5 ($CH(CH_3)_2$), 18.46 ($CHNHCH_3$); IR (neat oil) ν 3390 (NH), 1730 (CO), 1610, 1490, 1380, 1210, 1110 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.46; H, 7.69; N, 13.46. Found: C, 63.49; H, 7.41; N, 13.62.

Methyl *N*-(2-pyridyl)phenylglycinate (4g): reaction time 40 h; pale yellow needles; yield 80%; mp 101–102 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3 H, CH_3), 5.41 (br d, 1 H, J = 6.84 H, NH), 5.52 (d, 1 H, J = 6.84 Hz, CH), 6.35 (d, 1 H), 6.52–6.56 (m, 1 H), 7.21–7.35 (m, 5 H), 7.42–7.45 (m, 1 H), 8.04 (dd, 1 H); ^{13}C NMR (DMSO-d_6, 20.15 MHz) δ 172.2 (CO), 157.6, 147.2, 137.5, 136.7, 128.7, 128.1, 127.9, 112.2, 109.6, 58.1 (CH), 51.9 (CH_3); IR (KBr) ν 3240 (NH), 1750 (CO), 1600, 1570, 1510, 1415, 1150, 1130 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.78; N, 11.57. Found: C, 69.31; H, 5.55; N, 11.34.

Isopropyl *N*-(2-pyridyl)phenylglycinate (4h): reaction time 44 h; crude **4h** was purified by flash chromatography (hexane/ethyl acetate 2:1); colorless oil; yield 62%; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, 3 H, J = 6.23 Hz, CH_3), 1.26 (d, 3 H, J = 6.23 Hz, CH_3), 5.03 (m, 1 H, J = 6.23 Hz, OCH), 5.49 (br s, 2 H, CH + NH), 6.36 (d, 1 H), 6.54–6.58 (m, 1 H), 7.25–7.36 (m, 5 H), 8.06 (dd, 1 H); ^{13}C NMR ($CDCl_3$, 75.43 MHz) δ 171.1 (CO), 156.7, 147.6, 137.4, 128.4, 127.8, 127.0, 113.4, 107.9, 68.9 (OCH), 58.6 (CH), 21.4, 21.1 (CH_3); IR (neat oil) ν 3400 (NH), 1740 (CO), 1610, 1490, 1380, 1210, 1110 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.66; N, 10.37. Found: C, 71.41; H, 6.71; N, 10.25.

Methyl *N*-(4-methyl-2-pyridyl)-α-alaninate (4i): reaction time 30 h; colorless needles; yield 75%; mp 84–86 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.46 (d, 3 H, J = 7.08 Hz, CH_3), 2.19 (s, 3 H, $HetCH_3$), 3.72 (s, 3 H, OCH_3), 4.60 (m, 1 H, J = 7.10 Hz, CH), 4.95 (br d, 1 H, J = 7.02 Hz, NH), 6.24 (s, 1 H), 6.42 (d, 1 H), 7.62 (d, 1 H); ^{13}C NMR ($CDCl_3$, 75.43 MHz) δ 175.0 (CO), 157.4, 147.9, 147.3, 115.0, 108.4, 51.9 (OCH_3), 49.6 (CH), 20.7 ($HetCH_3$), 18.4 (CH_3); IR (KBr) ν 3240 (NH), 1740 (CO), 1620, 1525, 1495, 1395, 1190 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.85; H, 7.21; N, 14.43. Found: C, 62.06, H, 7.35, N, 14.25.

Methyl *N*-(5-chloro-2-pyridyl)-α-alaninate (4j): reaction time 30 h; pale yellow needles; yield 78%; mp 77–79 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.47 (d, 3 H, J = 6.90 Hz, CH_3), 3.74 (s, 3 H, OCH_3), 4.55 (m, 1 H, J = 6.90 Hz, CH), 5.00 (br d, 1 H, J = 6.90 Hz, NH), 6.38 (d, 1 H), 7.33 (dd, 1 H), 8.01 (d, 1 H); ^{13}C NMR ($CDCl_3$, 75.43 MHz) δ 174.7 (CO), 155.5, 146.0, 136.9, 120.4, 109.2, 52.1 (OCH_3), 48.8 (CH), 18.3 (CH_3); IR (KBr) ν 3450, 3300 (NH), 1740 (CO), 1600, 1510, 1485, 1375, 1200, 1160 cm^{-1}. Anal. Calcd for $C_9H_{11}N_2O_2Cl$: C, 50.35; H, 5.13; N, 13.05; Cl, 16.55. Found: C, 50.55; H, 5.16; N, 13.30; Cl, 16.23.

Methyl *N*-(2-pyrimidinyl)-α-alaninate (4k): reaction time 73 h; colorless needles; yield 85%; mp 120–121 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3 H, J = 7.03 Hz, Me), 3.73 (s, 3 H, OCH_3), 4.66 (m, 1 H, J = 7.03 Hz, CH), 6.29 (br d, 1 H, J = 7.03 Hz, NH), 6.57 (t, 1 H), 8.29 (d, 1 H); ^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 174.1 (CO), 161.3, 157.6, 120.8, 51.8 (OCH_3), 49.5 (CH), 18.0 (CH_3); IR (KBr) ν 3240 (NH), 1750 (CO), 1590, 1575, 1520, 1460, 1270, 1050 cm^{-1}. Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.07; N, 23.20. Found: C, 53.17; H, 6.06; N, 23.40.

Methyl *N*-(2-pyrimidinyl)phenylglycinate (4l): reaction time 24 h; colorless needles; yield 90%; mp 90–92 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3 H, OCH_3), 5.65 (d, 1 H, J = 6.90 Hz, CH), 6.44 (t, 2 H), 7.16 (d, 1 H, J = 6.90 Hz, NH), 7.15–7.35 (m, 5 H), 7.46 (d, 2 H); ^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 171.9 (CO), 161.0, 157.8, 136.9, 128.6, 128.2, 127.3, 112.2, 58.3 (CH), 52.3 (OCH_3); IR (KBr) ν 3120 (NH), 1750 (CO), 1595, 1570, 1520, 1450, 1210, 1170 cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.35; N, 17.28. Found: C, 64.41; H, 5.62; N, 17.51.

Methyl *N*-(2-thiazolyl)-α-alaninate (4m): reaction time 75 h; crude **4m** was purified by flash chromatography (ethyl acetate); colorless crystals; yield 84%; mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (d, 3 H, J = 7.08 Hz, CH_3), 3.75 (s, 3 H, OCH_3), 4.45 (br s, 1 H, CH), 5.88 (br s, 1 H, NH), 6.48 (d, 1 H), 7.10 (d, 1 H); ^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 173.7 (CO), 168.3, 138.5, 106.8, 53.0 (CH), 52.0 (OCH_3), 18.0 (CH_3); IR (KBr) ν 3200–2700 (NH), 1740 (CO), 1580, 1460, 1200, 1150, 1055 cm^{-1}. Anal. Calcd for $C_7H_{10}N_2O_2S$: C, 45.16; H, 5.37; N, 15.05; S, 17.20. Found: C, 45.16; H, 5.68; N, 15.19; S, 17.35.

Methyl *N*-(2-thiazolyl)phenylglycinate (4n): reaction time 48 h; crude **4n** was purified by flash chromatography (hexane/ethyl acetate 2:1); colorless crystals; yield 55%; mp 112–114 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3 H, OCH_3), 5.36 (br s, 1 H, CH), 6.43 (d, 1 H), 6.65 (br s, 1 H, NH), 7.06 (d, 1 H), 7.28–7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 171.2 (CO), 167.6, 138.8, 136.1, 128.7, 128.4, 127.2, 107.4, 61.3 (CH), 52.6 (OCH_3); IR (KBr) ν 3170 (NH), 1740 (CO), 1610, 1550, 1510, 1210, 1160 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.06; H, 4.83; N, 11.29; S, 12.90. Found: C, 58.31; H, 5.01; N, 11.26; S, 12.78.

Isolation of 2-Phenyl-1*H*-imidazo[1,2-*a*]pyridinium-3-olate (2, X = CH). Following the general procedure for the synthesis of compounds **4**, 2-aminopyridine (1.0 g, 10.6 mmol) and phenylglyoxal hydrate (1.6 g, 10.6 mmol) in methanol (5 mL) and perchloric acid (3 mL) were heated under reflux for 3 h. After cooling and neutralization, a powdered yellow solid (0.2 g) was obtained. This compound was identical with an authentic sample of 2-phenyl-1*H*-imidazo[1,2-*a*]pyridinium-3-olate prepared independently.[13] α-Amino ester **4g** (2.12 g, 70%) was isolated, upon standard treatment, from the mother liquors of compound **2**.

2-Methyl-3-oxo-7*H*-imidazo[1,2-*a*]pyrazinium Perchlorate (3·HClO$_4$, R = Me). 2-Aminopyrazine (1.0 g, 10 mmol) and pyruvaldehyde (1.9 g, 40% aqueous solution, 10 mmol) in methanol (5 mL) and perchloric acid (3 mL) were heated under reflux for 1 h. After this time the alcohol was eliminated carefully under vacuum and enough solid sodium carbonate to form a solid paste was added. The resulting dark orange-brown paste was taken up in methanol, the solid filtered, and the alcohol removed under vacuum. The dark orange solid thus obtained was purified by flash chromatography (methanol). In this way 1.0 g (40%) of compound **3** as the perchlorate, a deep yellow powdered solid that decomposes before melting above 270 °C, was isolated. Correct analytical data could not be obtained. Attempts to obtain the free base were fruitless due to total decomposition of the perchlorate upon basic treatment or stronger basic workup.

^{1}H NMR (CD_3OD) δ 2.3 (s, 3 H, CH_3), 6.9 (d, 1 H, J = 6.0 Hz, H6), 7.3 (d, 1 H, J = 6.0 Hz, H5), 7.7 (s, 1 H, H8); ^{13}C NMR (CD_3OD, 20.15 MHz) δ 152.8 (C3), 145.9 (C9), 129.9 (C2), 125.2, 117.7, 111.6 (C5, C6, C8), 13.46 (CH_3); IR (KBr) ν 3600–2600 (NH), 1670 (CO), 1600, 1685, 1150, 1090, 990 cm^{-1}.

General Procedure for the Hydrolysis of Compounds 4. A slurry of α-amino ester **4** (1.0 g) in 5 N hydrochloric acid (5 mL) was heated under reflux for 2 h. After this time the solvent was removed in vacuo and the solid residue was dried under high vacuum (10^{-3} Torr). The corresponding α-amino acid as its hydrochloride was obtained in nearly quantitative yield. All compounds **5** as the hydrochloride salts were crystalline colorless solids that melted with decomposition in a wide range, always being isolated as analitically pure compounds. Free amino acids **5** (R^1 = H, Het = pyridyl and R^1 = Me, Het = pyrimidinyl) were obtained upon treatment of their salts (1.0 g) with boiling water (3 mL) containing sodium carbonate (0.44 g). After cooling, the free amino acid crystallized in nearly quantitative yield.

***N*-(2-Pyridyl)glycine hydrochloride**: mp 200–205 °C dec (lit.[19] mp 190 °C).

***N*-(2-Pyridyl)glycine**: mp 170–174 °C (lit.[19] mp 175 °C).

***N*-(2-Pyridyl)-α-alanine hydrochloride**: mp 198–210 °C dec; ^{1}H-NMR (DMSO-d_6, 60 MHz) δ 1.5 (d, 3 H, J = 7.8 Hz, Me), 4.8 (q, 1 H, J = 7.8 Hz, CH), 7.4 (m, 2 H), 7.7–8.1 (m, 2 H), 8.8–9.6 (m, 1 H); IR (KBr) ν 1730, 1650 (CO) cm^{-1}. Anal. Calcd for $C_8H_{11}N_2O_2Cl$: C, 47.40; H, 5.43; N, 13.83, Cl, 17.53. Found: C, 47.12; H, 5.67; N, 13.96; Cl, 17.79.

***N*-(2-Pyrimidinyl)-α-alanine**: mp 180–183 °C (H_2O); ^{1}H NMR (DMSO-d_6, 60 MHz) δ 1.3 (d, 3 H, J = 7.0 Hz, Me), 4.2 (qt, 1 H, $J_1 = J_2$ = 7.0 Hz, CH), 6.3 (t, 1 H), 7.0 (d, 1 H, NH), 7.9 (d, 2 H); IR (KBr) ν 1695 (CO) cm^{-1}. Anal. Calcd for $C_7H_9N_3O_2$: C, 50.30; H, 5.38; N, 25.10. Found: C, 49.98; H, 5.65; N, 25.04. The corresponding hydrochloride salt was a viscous yellow oil.

***N*-(2-Thiazolyl)-α-alanine hydrochloride**: mp 170–190 °C dec; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 1.5 (d, 3 H, J = 7.2 Hz, Me), 4.7 (q, 1 H, J = 7.2 Hz, CH), 7.0 (d, 1 H), 7.3 (d, 1 H); IR (KBr) ν 1740 (CO) cm^{-1}. Anal. Calcd for $C_6H_9N_2O_2SCl$: C, 34.53; H, 4.31; N, 13.43; S, 15.34; Cl, 17.02. Found: C, 34.34; H, 4.36; N, 13.58; S, 15.32; Cl, 17.29.

***N*-(2-Pyrimidinyl)phenylglycine hydrochloride**: mp 185–190 °C; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 5.7 (s, 1 H, CH), 7.0 (t, 1 H), 7.2–8.0 (m, 5 H), 8.6 (d, 2 H); IR (KBr) ν 1730, 1640 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_3O_2Cl$: C, 54.23; H, 4.52; N, 15.82; Cl, 13.37. Found: C, 54.51; H, 4.43; N, 15.52; Cl, 13.12.

***N*-(2-Thiazolyl)phenylglycine hydrochloride**: mp 86–92 °C; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 5.8 (s, 1 H, CH), 6.9 (d, 1 H), 7.1–7.7 (m, 6 H); IR (KBr) ν 1730 (CO) cm^{-1}. Anal. Calcd for $C_{11}H_{11}N_2O_2SCl$: C, 48.79; H, 4.06; N, 10.35; S, 11.83; Cl, 13.12. Found: C, 48.52; H, 4.37; N, 10.32; S, 11.90; Cl, 12.87.

Hydrolysis of α-Amino Ester 4g. Following the general procedure for the hydrolysis of α-amino esters **4**, 0.2 g of compound **4g** in 5 N hydrochloric acid (2 mL) were heated under reflux for 3 h. After this time the solvent was removed under vacuo and the white crystalline solid thus obtained was treated with saturated sodium carbonate solution (4 mL). In this way 0.19 g of a yellow powdered solid was obtained. This compound was identical with an authentic sample of 2-phenyl-1*H*-imidazo[1,2-*a*]pyridinium-3-olate (**2**, X = CH).[13]

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Registry No. **2** X = CH, Ar = Ph, 106492-20-0; **3** R = Me·$HClO_4$, 126190-30-5; **4a**, 100377-28-4; **4b**, 53051-79-9; **4c**, 126190-19-0; **4d**, 126190-20-3; **4e**, 28036-34-2; **4f**, 126190-21-4; **4g**, 126190-22-5; **4h**, 126190-23-6; **4i**, 126190-24-7; **4j**, 126190-25-8; **4k**, 126190-26-9; **4l**, 126190-27-0; **4m**, 126190-28-1; **4n**, 126190-29-2; **5a**, 52946-88-0; **5a**·HCl, 112656-88-9; **5d**·HCl, 122886-09-3; **5k**, 126190-31-6; **5l**·HCl, 126190-33-8; **5m**·HCl, 126190-32-7; **5n**·HCl, 126190-34-9; glyoxal, 107-22-2; pyruvaldehyde, 78-98-8; phenylglyoxal, 1074-12-0; 2-aminopyridine, 504-29-0; 4-methyl-2-aminopyridine, 695-34-1; 5-chloro-2-aminopyridine, 1072-98-6; 2-aminopyrimidine, 109-12-6; 2-aminothiazole, 96-50-4; 2-aminopyrazine, 5049-61-6.

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Synthesis of Complex 6′-Alkynyl-6′-dethia Nucleoside Analogues of *S*-Adenosylhomocysteine as Potential Inhibitors of Methyltransferases

Eric K. Yau and James K. Coward*

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180, and Departments of Medicinal Chemistry and Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

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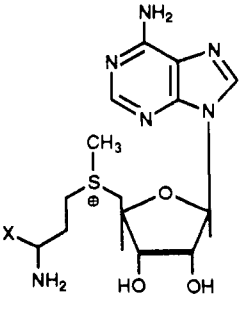
The synthesis of complex acetylenic nucleosides containing a 5′,6′ carbon–carbon bond has been investigated. Two synthetic routes were studied, both starting with an α-substituted butyrolactone. The lactone could be converted to an β-keto sulfone and then to the corresponding enol phosphate diphenyl ester. Reductive elimination to yield the desired aryl acetylene could not be effected without some overreduction to the substituted olefin. Alternatively, the lactone could be converted to an appropriately protected γ-hydroxy aldehyde which was then homologated to a terminal acetylene. The successful synthesis of a prototypic member of the target class of compounds involved a Pd-mediated coupling of an aryl iodide to the appropriately functionalized terminal acetylene. The resulting aryl acetylene was then further elaborated to the target amino acid derivative; viz, a 6′-alkynyl-6′-dethia analogue of *S*-adenosylhomocysteine.

Introduction

The reaction of a variety of cellular nucleophiles with electrophilic biochemical alkylating agents such as *S*-adenosylmethionine (AdoMet, **1**) or its decarboxylated derivtive, dcAdoMet, **2**, is extremely important in cellular metabolism. AdoMet acts as a methyl donor in the methylation of molecules as diverse as catecholamines and nucleic acids.[1] Similarly dcAdoMet acts as an aminopropyl donor in the biosynthesis of the cationic polyamines, spermidine and spermine, which are known to interact with anionic nucleic acids[2] and otherwise affect cell growth and differentiation.



1, X=CO_2H
2, X=H

Stereochemical studies of the reactions catalyzed by methyltransferases, e.g., catechol *O*-methyltransferase (COMT),[3] and aminopropyltransferases, e.g., spermidine

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