A New Synthetic Approach for Imidazo[1,2-*a*]imidazoles and Pyrrolo[1,2-*a*]imidazoles

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Substituted pyrrolo[1,2-*a*]imidazoles and imidazo[1,2-*a*]imidazoles are prepared in a simple one pot reaction sequence from esters of heterocyclic or aromatic α-amino acids. The reaction involves condensation with acetoine followed by cyclization with either malonodinitrile, ethyl cyanoacetate or cyanamide.

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Our recent studies were devoted to the utilization of heterocyclic amino acids in the synthesis of various heterocyclic systems [1-5]. Now we would like to report on a simple synthetic approach for pyrrolo[1,2-*a*]- and imidazo[1,2-*a*]imidazoles.

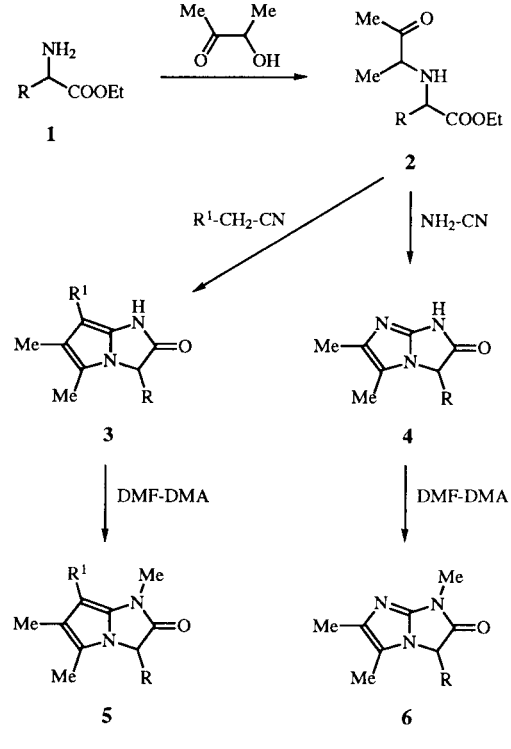
Pyrrolo[1,2-*a*]imidazoles were in general prepared from substituted imidazolium halides by a base-promoted cyclization or from imidazolium betaines by 1,3-dipolar cycloaddition of acetylenic compounds [6,7]. There are also some recent reports describing completely different approaches [8-13]. This heterocyclic system was also prepared in a two-step synthesis from ethyl glycinate and acetoine. The reaction leads first to the corresponding 1-carboxymethylpyrroles [14] which can be cyclized into the bicyclic system in the presence of a strong base (sodium hydroxide) [14,15]. On the other hand, amino acid amides react with isobutyl 4-oxobutanoate to give derivatives of the same system [16].

Imidazo[1,2-*a*]imidazoles are generally synthesized by cyclization of 1-acylmethyl- and 1-aroylmethyl-2-bromoimidazoles with amines or by acid treatment of 3-acylmethyl- or 3-aroylmethyl-2-iminoimidazoles [17]. The parent compound was prepared from 2-aminoimidazole and bromoacetaldehyde diethyl acetal [18] and substituted compounds of this system were obtained in a multistep reaction sequence starting from substituted benzaldehydes, sodium cyanide and benzhydrylamine. The last step involved condensation to the imidazole ring [19].

When esters of heterocyclic α-amino acids **1** reacted with an equivalent amount of acetoine under azeotropic elimination of water, the *in situ* formed *N*-substituted α-amino esters **2** were treated with malonodinitrile or ethyl cyanoacetate to give the corresponding pyrrolo-[1,2-*a*]imidazol-2-ones **3** in a one-step transformation. The ring formation was slower in the case of ethyl cyanoacetate and the 2-thienyl derivative **3c'** was formed in low yield after heating the xylene solution under reflux for 6 hours. Similarly, from the 3-pyridyl substituted ester **1b** only traces of the corresponding bicyclic compound **3b'** were detected by tlc.

The intermediates **2c**, **2d** and **2e**, when treated with cyanamide in the presence of *p*-toluenesulfonic acid in boiling benzene,were converted directly into the corresponding imidazo[1,2-*a*]imidazol-2-ones **4**. The reaction represents a new synthesis of this bicyclic system from esters of α-amino acids. During the reaction racemization occurred as evidenced when optically active L-phenylalanine ethyl ester **1e** gave an optically inactive product **4e**.

Both bicyclic systems, **3** and **4** were methylated with *N,N*-dimethylformamide dimethyl acetal in toluene. Exclusively *N*-methylated products **5a-c** and **6** were obtained. The formation of the corresponding *O*-methyl derivatives could not be detected. The evidence for *N*-methyl derivatives follows from the examination of the corresponding ^{1}H nmr spectra, *i.e.* the singlet for H_3 is present at about 5.6 ppm in all spectra of the methylated products. Also the ir spectra of the compounds **5** and **6** revealed the presence of an amide carbonyl group at



R = (a) 2-pyridyl, (b) 3-pyridyl, (c) 2-thienyl, (d) phenyl, (e) benzyl
R^1 = CN, COOEt

about 1760 cm^{-1}.

The described synthesis of both bicyclic heterocyclic systems allows now to prepare their derivatives with a heterocyclic ring attached to the bicyclic system by a C-C bond.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Varian 360L (60 MHz) spectrometer using TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrometer. Mass spectra were recorded on a VG Analytical Autospec Q spectrometer by electron impact ionization at 70 eV.

Microanalyses were performed on a Perkin-Elmer Elemental Analyzer model 2400. The progress of reactions was followed by tlc using Fluka TLC-Silicagel 60778 plates and a mixture of chloroform and methanol (7:3) as a mobile phase.

Ethyl D,L-α-(2-pyridyl)glycinate and ethyl D,L-α-(3-pyridyl)glycinate were obtained by catalytic hydrogenation of corresponding oximes [2,20]. Ethyl D,L-α-(2-thienyl)glycinate was prepared in a similar manner by reduction of the corresponding oxime with zinc in formic acid [3]. Ethyl esters of D,L-α-phenylglycine and L-phenylalanine were obtained from commercially available hydrochlorides after treatment with aqueous sodium hydroxide solution followed by extraction with diethyl ether.

General Procedure for the Preparation of Pyrrolo[1,2-*a*]imidazolones **3**.

To a solution of the α-amino acid ethyl ester **1** (10-15 mmoles) in 20-25 ml of anhydrous benzene the equivalent amount of acetoine (2-hydroxybutanone) was added and the reaction mixture was heated under reflux using a Dean-Stark adapter, filled with molecular sieves (Union Carbide type, 4 Å pores). After 1.5-2.5 hours the intermediate **2** was formed almost quantitatively, as could be seen by monitoring the reaction by tlc. Thereafter the equivalent amount of malonodinitrile or ethyl cyanoacetate was added and heating was continued for the time indicated for each particular compound. The reaction mixture was cooled to room temperature and 10-15 ml of ethanol was added. The separated product was filtered and crystallized from the appropriate solvent. The products **3a-c** precipated as a thick mass already from the hot reaction mixture, which was cooled, diluted with 10-15 ml of ethanol, filtered and then crystallized. In this manner the following compounds were prepared.

7-Cyano-5,6-dimethyl-3-(2-pyridyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**3a**).

The reaction time was 0.5 hours, yield 59%, mp 244-247° (from ethanol); ir: ν 3180 (NH), 2210 (CN), 1760 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.56 (s, 3H, Me), 1.85 (s, 3H, Me), 5.69 (s, 1H, CH), 6.96 (m, 2H, $H_{3'}$,$H_{5'}$), 7.60 (ddd, 1H, $H_{4'}$), 8.24 (dm, 1H, $H_{6'}$), 11.44 (broad s, 1H, NH), $J_{3',4'} = J_{4',5'} = 7.7$, $J_{5',6'} = 6.5$, $J_{4',6'} = 1.9$ Hz; ms: m/z = 252 (M^+, 100%).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.35; H, 4.56; N, 22.63.

7-Cyano-5,6-dimethyl-3-(3-pyridyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**3b**).

The reaction time was 0.75 hour, yield 49%, mp 251-253° dec (from ethanol); ir: ν 3180 (NH), 2210 (CN), 1760 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.72 (s, 3H, Me), 1.98 (s, 3H, Me), 5.78 (s, 1H, CH), 7.27-7.53 (m, 2H, $H_{4'}$, $H_{5'}$), 8.28-8.54 (m, 2H, $H_{2'}$, $H_{6'}$); ms: m/z = 252 (M^+, 86%).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.29; H, 4.79; N, 22.69.

7-Cyano-5,6-dimethyl-3-(2-thienyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**3c**).

The reaction time was 0.75 hour, yield 37%, mp 243-246° dec (from ethanol); ir: ν 3200 (NH), 2220 (NH), 1760 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.75 (s, 3H, Me), 1.95 (s, 3H, Me), 6.09 (s, 1H, CH), 6.95-7.22 (m, 2H, $H_{3''}$,$H_{4'}$), 7.58 (m, 1H, $H_{5'}$), 11.95 (broad s, 1H, NH); ms: m/z = 257 (M^+, 45%).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.45; H, 4.22; N, 16.14.

7-Ethoxycarbonyl-5,6-dimethyl-3-(2-pyridyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**3a'**).

The reaction time was 2 hours, yield 18%, mp 240-243° dec (from ethanol); ir: ν 3180 (NH), 1760, 1700 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.24 (t, 3H, $COOCH_2CH_3$), 1.72 (s, 3H, Me), 2.12 (s, 3H, Me), 4.17 (q, 2H, $COOCH_2CH_3$), 5.34 (s, 1H, CH), 6.94-7.30 (m, 2H, $H_{3'}$, $H_{5'}$), 7.59 (ddd, 1H, $H_{4'}$), 8.50 (m, 1H, $H_{6'}$), $J_{Et} = 7.4$, $J_{3',4'} = J_{4',5'} = 7.8$, $J_{4',6'} = 1.9$ Hz; ms: m/z = 299 (M^+, 75%).

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.11; H, 5.43; N, 14.02.

7-Ethoxycarbonyl-5,6-dimethyl-3-(2-thienyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**3c'**).

Ethyl D,L-α-(2-thienyl)glycinate (1.98 g, 10.7 mmoles) and acetoine (0.99 g, 11.2 mmoles) were heated under reflux in 17 ml of anhydrous benzene as described under general procedure for 1.5 hours. The reaction mixture was evaporated *in vacuo* and the orange-red oily residue was dissolved in 3 ml of xylene, ethyl cyanoacetate (1.57 g, 13.9 mmoles) was added and heated under reflux for 6 hours. Upon cooling about 15 ml of ethanol was added and the separated product was filtered and crystallized from ethanol (0.27 g, 8%), mp 214-216° dec; ir: ν 3100 (NH), 1720, 1680 (CO) cm^{-1}; ^1H nmr: δ 1.35 (t, 3H, $COOCH_2CH_3$), 1.91 (s, 3H, Me), 2.21 (s, 3H, Me), 4.28 (q, 2H, $COOCH_2CH_3$), 5.53 (s, 1H, CH), 6.91-7.07 (m, 2H, $H_{3'}$, $H_{4'}$), 7.43 (m, 1H, $H_{5'}$), 8.59 (broad s, 1H, NH); ms: m/z = 304 (M^+, 100%).

Anal. Calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 58.94; H, 5.04; N, 8.99.

General Procedure for the Preparation of Imidazo[1,2-*a*]imidazolones **4**.

The necessary intermediates **2** were prepared as described above in the case of pyrrolo[1,2-*a*]imidazoles. To the solution of **2**, prepared from 10-15 mmoles of starting esters of α-amino acids, cyanamide (14-21 mmoles) and *p*-toluenesulfonic acid (200-300 mg) were added. The reaction mixture was heated under reflux using the same Dean-Stark condenser as described for the preparation of intermediates **2**. After the time indicated for each particular compound the product was isolated in one of the following manners: [a] in the cases when some product has

started to precipitate already during heating, the reaction mixture was cooled and a mixture of ethanol and diethyl ether (1:1) for **4a** or ethyl acetate for **4b** was added and the product was filtered; [b] to the cooled reaction mixture diethyl ether was added carefully by stirring; after the addition of about 5-7 ml the tlc pure product **4c** separated.

In this manner the following compounds were prepared:

5,6-Dimethyl-3-(2-pyridyl)-2-oxo-2,3-dihydro-1*H*-imidazo-[1,2-*a*]imidazole (**4a**).

The reaction time was 0.5 hour, yield 52%, mp 233-235° dec (from ethanol); ir: ν 3480 (NH), 1700 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.65 (s, 3H, Me), 1.97 (s, 3H, Me), 5.43 (s, 1H, CH), 7.02-7.14 (m, 2H, $H_{3'}$,$H_{5'}$), 7.64 (ddd, 1H, $H_{4'}$), 8.28 (dm, 1H, $H_{6'}$), $J_{3',4'} = J_{4',5'} = 7.7$, $J_{4',6'} = 1.9$, $J_{5',6'} = 5.8$ Hz; ms: m/z = 228 (M^+, 100%).

Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.14; H, 5.30; N, 24.55. Found: C, 62.83; H, 5.06; N, 24.83.

5,6-Dimethyl-3-phenyl-2-oxo-2,3-dihydro-1*H*-imidazo-[1,2-*a*]imidazole (**4d**).

The reaction time was 3 hours, yield 37%, mp 229-231° dec (from ethyl acetate); ir: ν 3400 (NH), 1720 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.71 (s, 3H, Me), 2.00 (s, 3H, Me), 5.32 (s, 1H, CH), 6.77-7.03 (m, 2H, Ph), 7.05-7.73 (m, 3H, Ph); ms: m/z = 227 (M^+, 80%).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.94. Found: C, 68.55; H, 5.63; N, 18.47.

3-Benzyl-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazo-[1,2-*a*]imidazole (**4e**).

The reaction time was 5 hours, yield 35%, mp 152-154°; ir: ν 3400 (NH), 1720 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.75 (s, 3H, Me), 2.05 (s, 3H, Me), 2.86-3.60 (m, 2H, CH_2CH), 4.45 (dd, 1H, CH_2CH), 7.08 (broad s, 5H, Ph), 9.38 (broad s, 1H, NH), $J_{CH-CH2} = 5.5$ and 6.6 Hz; ms: m/z = 241 (M^+, 31%).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.81; H, 6.15; N, 17.28.

General Procedure for the Methylation of **3a-c** and **4a**.

A corresponding pyrrolo- or imidazo[1,2-*a*]imidazolone **3a-c** and **4a** (2.0-5.3 mmoles) was heated under reflux in anhydrous toluene with *N,N*-dimethylformamide dimethyl acetal (10% excess) for 2 hours. The reaction mixture was evaporated *in vacuo* to give an oily residue which crystallized upon the addition of ethanol, **5a-c** or diethyl ether, **6**. The separated product was filtered and crystallized from the appropriate solvent. In this manner the following compounds were prepared:

7-Cyano-1,5,6-trimethyl-3-(2-pyridyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**5a**).

This compound was obtained in yield 46%, mp 141-143° (from ethanol); ir: ν 2210 (CN), 1720 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.72 (s, 3H, Me), 2.01 (s, 3H, Me), 3.31 (s, 3H, N-Me), 5.32 (s, 1H, CH), 6.91 (m, 2H, $H_{3'}$, $H_{5'}$), 7.56 (ddd, 1H, $H_{4'}$), 8.41 (dm, 1H, $H_{6'}$), $J_{3',4'} = 7.4$, $J_{4',6'} = 1.9$, $J_{5',6'} = 5.8$ Hz; ms: m/z = 266 (M^+, 100%).

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.16; H, 5.02; N, 20.56.

7-Cyano-1,5,6-trimethyl-3-(3-pyridyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**5b**).

This compound was obtained in yield 84%, mp 162-163° (from ethanol); ir: ν 2210 (CN), 1720 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.85 (s, 3H, Me), 2.12 (s, 3H, Me), 3.51 (s, 3H, N-Me), 5.43 (s, 1H, CH), 7.37-7.73 (m, 2H, $H_{4'}$, $H_{5'}$), 8.53-8.99 (m, 2H, $H_{2'}$, $H_{6'}$); ms: m/z = 266 (M^+, 100%).

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.49; H, 5.10; N, 21.20.

7-Cyano-1,5,6-trimethyl-3-(2-thienyl)-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**5c**).

This compound was obtained in yield 63%, mp 139-141° (from a mixture of ethanol and diethyl ether); ir: ν 2210 (CN), 1730 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.89 (s, 3H, Me), 2.09 (s, 3H, Me), 3.34 (s, 3H, N-Me), 5.56 (s, 1H, CH), 6.89-7.05 (m, 2H, $H_{3'}$, $H_{4'}$), 7.32 (m, 1H, $H_{5'}$); ms: m/z = 271 (M^+, 66%).

Anal. Calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 62.27; H, 4.64; N, 15.31.

1,5,6-Trimethyl-3-(2-pyridyl)-2-oxo-2,3-dihydro-1*H*-imidazo-[1,2-*a*]imidazole (**6**).

This compound was obtained in yield 38%, mp 148-150° (from ethyl acetate); ir: ν 1740 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.82 (s, 3H, Me), 2.15 (s, 3H, Me), 3.26 (s, 3H, N-Me), 5.34 (s, 1H, CH), 6.97-7.33 (m, 2H, $H_{3'}$, $H_{5'}$), 7.65 (ddd, 1H, $H_{4'}$), 8.47 (m, 1H, $H_{6'}$), $J_{4',6'} = 1.9$, $J_{3',4'} = J_{4',5'} = 7.7$ Hz; ms: m/z = 242 (M^+, 100%).

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.44; H, 5.82; N, 23.13. Found: C, 64.66; H, 5.83; N, 22.83.

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