Synthesis of Substituted 2-Amino-3-cyano-4-methylpyrroles

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A facile route for the synthesis of substituted 2-amino-3-cyano-4-methylpyrroles from *N*-acetyl-α-amino ketones and malononitrile is reported.

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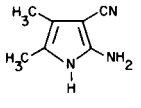
Gewald (2) first reported the synthesis of 2-amino-3-cyano-4,5-dimethylpyrrole (**1**) by the base catalyzed condensation of 3-amino-2-butanone with malononitrile.



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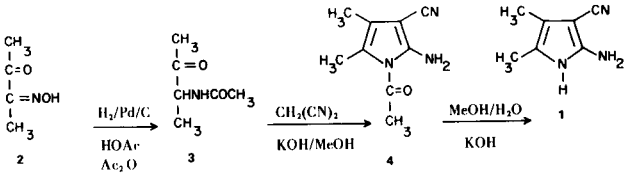
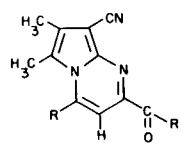
More recently (3,4), modification of this procedure has resulted in the synthesis of **1**. In the modified procedure, 2,3-butanedione monoxime (**2**) was reductively acetylated by the procedure of Hayes and Gever (5) to yield 2-acetamido-3-butanone (**3**). The *N*-acetyl-α-amino ketone (**3**) was condensed with malononitrile, in methanol using potassium hydroxide as the base catalyst, to yield 1-acetyl-2-amino-3-cyano-4,5-dimethylpyrrole (**4**). Deacylation of **4** to yield **1** was achieved by alkaline hydrolysis. The modified procedure is illustrated in scheme I.

Scheme I



In our laboratory we are particularly interested in analogs of **1** as precursors to potentially active medicinal agents. Recently compound **1** has been used as a precursor in the synthesis of substituted pyrrolo[1,2-*a*]-pyrimidines (**5**) (6) and a substituted 2,3,4,5-tetrahydro-pyrrolo[1,2-*a*][1,3]diazepine (**6**) (7).



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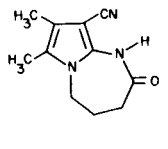

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The desire to expand the scope of synthetic possibilities and more adequately study the structure-activity relationships of **5** and **6**, has resulted in the development of an economical and facile route to 5-substituted analogs of **1**. In this route (Scheme II), L- or DL-α-amino acids (**7a-f**) are converted into their corresponding *N*-acetyl-α-amino ketones (**8a-f**) by the procedure described by Dakin and West (8). In this procedure, the amino acids are heated in a mixture of pyridine and acetic anhydride until the evolution of carbon dioxide has ceased. The solvents are removed *in vacuo* to yield the crude *N*-acetyl-α-amino ketones. The *N*-acetyl-α-amino ketones (**8a-f**) are condensed with malononitrile according to the modified Gewald procedure, described previously, to yield 5-substituted analogs (**9a-f**) of **4**. Compounds (**9a-e**) were hydrolyzed during the condensation procedure

Scheme II

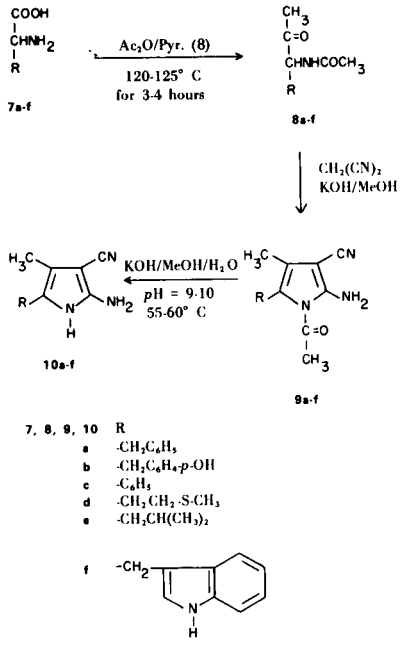
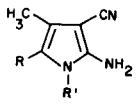
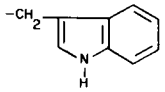
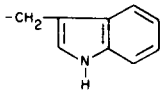


Table I

Substituted 2-Amino-3-cyano-4-methylpyrroles



Compound	R	R′	Empirical Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
10a	$-CH_2C_6H_5$	-H	$C_{13}H_{13}N_3$	73.91	6.20	19.89		73.73	6.23	19.81	
10b	$-CH_2-C_6H_4$-*p*-OH	-H	$C_{13}H_{13}N_3O$	68.70	5.76	18.49		68.95	5.86	18.34	
10c	$-C_6H_5$	-H	$C_{12}H_{11}N_3$	73.07	5.62	21.30		73.04	5.64	21.26	
10d	$-CH_2CH_2-S-CH_3$	-H	$C_9H_{13}N_3S$	55.35	6.71	21.52	16.42	55.17	6.74	21.45	16.34
10e	$-CH_2-CH(CH_3)_2$	-H	$C_{12}H_{17}N_3O$ (a)	65.67	7.81	19.23		65.72	7.81	19.22	
10f		-H	$C_{15}H_{14}N_4$	71.98	5.64	22.38		71.72	5.66	22.33	
9f		$-\overset{O}{\overset{\|}{C}}-CH_3$	$C_{17}H_{16}N_4O$	69.85	5.52	19.17		69.71	5.59	19.08	

(a) 2-Amino-3-cyano-4-methyl-5-isobutylpyrrole (**10e**) ($C_{10}H_{15}N_3$) was a gummy semi-solid. The compound was characterized as 2-acetamido-3-cyano-4-methyl-5-isobutylpyrrole (**11e**): $C_{12}H_{17}N_3O$.

to yield the corresponding N_1-deacetylated pyrroles (**10a-e**). The hydrolysis proceeds smoothly by heating the reaction mixture at 55 to 60° as the *p*H is maintained between 9 and 10 by adding 50% aqueous potassium hydroxide solution. Compound **9f** was isolated after condensing **8f** with malononitrile and subsequently hydrolyzed to yield **10f**.

The structural assignments of these pyrroles were made on the basis of elemental analysis (Table I), infrared spectra, nmr spectra, and thin-layer chromatography. This data is presented in the Experimental.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Hitachi Perkin-Elmer R24 High Resolution nmr spectrometer using tetramethylsilance as internal reference. Infrared spectra were determined on a Beckman IR-20A Grating Spectrophotometer using the potassium bromide technique. Elemental analysis were performed by Atlantic Microlab, Inc., Atlanta, Georgia. Tlc were performed on Eastman Chromatogram sheets, type 6060 (silica gel).

2-Amino-3-cyano-4-methyl-5-benzylpyrrole (**10a**).

A solution of 1-phenyl-2-acetamido-3-butanone (41.05 g., 0.2 mole) (**8a**) (8,9) and malononitrile (19.8 g., 0.3 mole) in 100 ml. of absolute methanol was stirred in an ice bath while the *p*H of the solution was adjusted to 10 by the addition of 50% aqueous potassium hydroxide solution. The solution was stirred for 15 minutes in the ice bath, then heated at 60° for 30 minutes as the *p*H was maintained between 9 and 10. The hot amber colored solution was poured over 400 g. crushed ice. After the ice had melted, the precipitate was collected, washed with distilled water and air dried. The crude pyrrole (33.1 g., 78.4%) was recrystallized three times from methanol-water to yield pink cyrstals (homogenous on tlc - ethyl acetate, R_f = 0.52): m.p. 119-120°; ir (potassium bromide): 3440, 3340, 3280, 2200, 1625, 1580, 1500, 760, 700 cm^{-1}; nmr (deuteriochloroform): δ 2.00 (s, 3H, CH_3 at C_4), 3.67 (s, 2H, methylene of benzyl), 3.80 (broad s, 2H, NH_2), 7.10 (s, 5H, aromatic H's), 7.50 (broad s, 1H, N_1H).

2-Amino-3-cyano-4-methyl-5-*p*-hydroxybenzylpyrrole (**10b**).

A suspension of 1-*p*-hydroxyphenyl-2-acetamido-3-butanone (66.4 g., 0.3 mole) (**8b**) (8) and malononitrile (29.7 g., 0.45 mole) in 200 ml. of absolute methanol was stirred at room temperature as the *p*H was adjusted to 10 by the addition of 50% aqueous potassium hydroxide. Shortly after the *p*H was achieved, an exothermic reaction occurred and a dark solution was obtained. This solution was heated at 50-55° for 30 minutes while the *p*H was maintained between 9 and 10. The warm solution was poured over 500 g. crushed ice, the *p*H adjusted to 6 with glacial acetic acid, and the insoluble pyrrole was collected by filtration. The crude product was resuspended in distilled water, collected, and air dried. The product (54.0 g., 79.2%) was recrystallized several times from methanol-water (3:1) to yield tan crystals (homogenous on tlc - acetone, R_f = 0.49; ethyl acetate, R_f = 0.46): m.p. 208.5-211.5°; ir (potassium bromide): 3380, 3275 (broad), 2200, 1615, 1560, 1490, 1370, 1270, 1240, 1170, 820, 770 cm^{-1}; nmr (DMSO-d_6): δ 1.86 (s, 3H, CH_3 at C_4), 3.45 (s, 2H, methylene of *p*-hydroxybenzyl), 5.16 (s, 2H, NH_2), 6.66 (q, 4H, aromatic H's), 8.95 (s, 1H, N_1H), 9.56 (s, 1H, phenolic OH).

2-Amino-3-cyano-4-methyl-5-phenylpyrrole (**10c**).

A solution of 1-acetamido-1-phenyl-2-propanone (57.4 g., 0.3 mole) (**8c**) (8) and malononitrile (29.7 g., 0.45 (mole) in

250 ml. of absolute methanol was stirred in an ice bath as the *p*H was adjusted to 10 with the addition of 50% aqueous potassium hydroxide solution. After the *p*H was achieved, the contents of the vessel were heated to 55 to 60°. Shortly after the heating process was started, a heavy precipitate was formed. (This precipitate was characterized as the N_1-acetyl derivative (**9c**) by infrared and nmr spectra). The suspension was heated at 55 to 60°with continuous stirring until a clear dark solution was achieved. The addition of another 100 ml. of methanol while maintaining the *p*H 9-10 facilitated the deacetylation. Once a clear solution was achieved, it was poured over 700 g. of crushed ice, the insoluble pyrrole was collected by filtration, washed with distilled water and air dried. The crude product (49.8 g., 84.2%) was recrystallized twice from methanol-water (3:1). Two g. of this product were recrystallized from benzene to yield fluffy white flakes (homogenous on tlc - acetone, R_f = 0.66): m.p. 134-135.5°; ir (potassium bromide): 3330, 3275, 2200, 1600, 1545, 1490, 750, 690 cm^{-1}; nmr (deuteriochloroform): δ 2.18 (s, 3H, CH_3 at C_4), 5.16 (broad s, 2H, NH_2), 7.28 (m, 5H, aromatic H's of phenyl), 9.65 (broad s, 1H, N_1H).

2-Amino-3-cyano-4-methyl-5-[2-(methylthio)ethyl]pyrrole (**10d**).

A solution of 1-methylthio-3-acetamido-4-pentanone (50.2 g., 0.266 mole) (**8d**) (8) and malononitrile (26.4 g., 0.4 mole) in 100 ml. of absolute methanol was condensed according to the procedure described for the synthesis of **10a**. The crude pyrrole (29.4 g., 56.6%) was recrystallized several times from methanol-water (1:1) to yield cream colored platelets (homogenous on tlc - ethyl acetate, R_f = 0.48): m.p. 82-83°; ir (potassium bromide): 3420, 3340, 2910, 2180, 1625, 1575, 1490, 1440 cm^{-1}; nmr (DMSO-d_6): δ 1.77 (s, 3H, CH_3 of *CH*$_3$-S-CH_2-CH_2-), 1.96 (s, 3H, CH_3 at C_4), 2.46 (s, 4H, ethylene of CH_3-S-*CH*$_2$-*CH*$_2$-); 5.18 (s, 2H, -NH_2), 9.67 (broad s, 1H, N_1H).

2-Amino-3-cyano-4-methyl-5-isobutylpyrrole (**10e**).

A solution of 3-acetamido-5-methyl-2-hexanone (34.25 g., 0.2 mole) (**8e**) (8) and malononitrile (19.8 g., 0.3 mole) in 100 ml. of absolute methanol was condensed according to the procedure described for **10a**. The crude gummy orange semi-solid (29.0 g., 81.7%) would not solidify with a variety of techniques employed. This product was characterized as the acetamide derivative (**11e**).

2-Acetamido-3-cyano-4-methyl-5-isobutylpyrrole (**11e**).

A solution of the crude gummy **10e** (5.0 g., 0.028 mole) in 50 ml. of boiling methanol was treated with 10 ml. of acetic anhydride. This hot solution was stirred for 5 minutes, cooled to room temperature, and the crystals collected. The acetamide (4.75 g., 76.8%) was recrystallized twice from absolute ethanol to yield white needles (homogenous on tlc - ethyl acetate, R_f = 0.56): m.p. 208-209°; ir (potassium bromide): 3280, 3250, 3180, 3250, 2960, 2220, 1670, 1620, 1600, 1510, 1470, 1270, 1210 cm^{-1}; nmr (DMSO-d_6): δ 0.8 (d, 6H, gem dimethyls of isobutyl group), 1.2-1.7 (complex m, 1H, methine proton of isobutyl group), 1.9 (s, 3H, CH_3 at C_4), 2.0 (s, 3H, CH_3 of acetyl), 2.3 (d, 2H, methylene of isobutyl group at C_5), 10.1 (broad s, 1H, NH of amide at C_2), 10.9 (broad s, 1H, N_1H).

1-Acetyl-2-amino-3-cyano-4-methyl-5-(3-indolylmethyl)pyrrole (**9f**).

A solution of 1-(3-indolyl)-2-acetamido-3-butanone (56.2 g., 0.23 mole) (**8f**) (8) and malononitrile (23.1 g., 0.35 mole) in 250 ml. of absolute methanol was condensed according to the procedure described for **10c**. After 15 minutes of heating at 60° at a *p*H of 9 to 10, a small amount of precipitate was formed. The contents of the vessel were cooled by submerging the reaction flask in an ice bath. The insoluble pyrrole was removed by filtration, washed with hot 80% methanol and air dried. The pale yellow powder (8.2 g., 12.2%) was analytically pure (homogenous on tlc - ethyl acetate, R_f = 0.41): m.p. 261-262° dec; ir (potassium bromide): 3460, 3340, 3240, 3120, 2195, 1680, 1630, 1610, 1580, 1500, 1455, 1400, 1360, 1310, 1255, 1225, 1145, 1020, 940, 760, 750, 650 cm^{-1}; nmr (DMSO-d_6): δ 1.85 (s, 3H, CH_3 at C_4 of pyrrole), 2.46 (s, 3H, CH_3 of acetyl at N_1 of pyrrole), 3.58 (s, 2H, methylene at C_5 of pyrrole), 5.09 (s, 2H, -NH_2 at C_2 of pyrrole), 6.9-7.35 (complex m, 4H, protons on the 4,5,6,7 position of indole ring), 7.95-8.15 (broad m, 1H, proton on the 2 position of indole ring), 9.45 (broad s, 1H, indole N_1H).

2-Amino-3-cyano-4-methyl-5-(3-indolylmethyl)pyrrole (**10f**).

A suspension of **9f** (6.0 g., 0.02 mole) in 75 ml. of methanol and 5 ml. of water was alkalinized to a *p*H of 10 by the addition of 50% aqueous potassium hydroxide. This suspension was heated at 60° with stirring until a clear solution was achieved. The solution was stirred for an additional 5 minutes, poured over 300 g. of crushed ice, the insoluble pyrrole collected by filtration, and air dried. The pale yellow product (5.0 g., 97.3%) was recrystallized twice from benzene-cyclohexane to yield pale yellow crystals (homogenous on tlc - ethyl acetate, R_f = 0.43): m.p. 163-164° dec.; ir (potassium bromide): 3420, 3360, 3320, 3250, 2190, 1620, 1580, 1500, 1455, 1345, 1095, 740 cm^{-1}; nmr (DMSO-d_6): δ 1.9 (s, 3H, CH_3 at C_4 of pyrrole), 3.65 (s, 2H, methylene at C_5 of pyrrole), 5.1 (s, 2H, -NH_2 at C_2 of pyrrole), 6.7-7.3 (m, 5H, aromatic protons on indole ring), 9.4 (broad s, 1H, indole N_1H), 10.6 (broad s, 1H, N_1H of pyrrole).

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