The Synthesis of 1-Substituted 6-Amino-1*H*-pyrrolo-[3,2-*c*]pyridin-4(5*H*)-ones

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The synthesis of 1-methyl- (**1a**) and 1-benzyl-6-amino-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (**1b**) from the appropriate *N*-alkylaminoacetaldehyde is described. These provide examples of a synthetic procedure that can be used to prepare 1-substituted 6-amino-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-ones wherein the N-1 substituent is regiospecifically placed.

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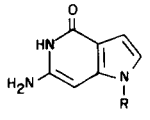
It has recently become necessary in this laboratory to have available a convenient regiospecific synthesis of N-1 substituted derivatives of 6-amino-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one. This paper describes two examples (**1a** and **1b**) of the method developed for preparing such compounds.

Thus, employing an adaptation of a previously reported procedure [1], treatment of *N*-methylaminoacetaldehyde with diethyl acetonedicarboxylate in base produced ethyl 3-(ethoxycarbonyl)-1-methylpyrrole-2-acetate (**2**) and a compound believed to be 3-(ethoxycarbonyl)-1-methylpyrrole-2-acetic acid (**3**). Compound **2** was then transformed into the amide **4** with anhydrous ammonia. Dehydration of **4** to **5** followed by ring closure of **5** with anhydrous ammonia in a sealed reaction vessel produced 6-amino-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (**1a**).



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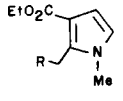
a, R = Me

b, R = $CH_2C_6H_5$

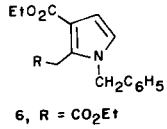


2, R = CO_2Et

3, R = CO_2H

4, R = $CONH_2$

5, R = CN



6, R = CO_2Et

7, R = $CONH_2$

8, R = CN

9, R = CO_2H

10, R = CO_2Me

The 1-benzyl derivative **1b** was prepared from *N*-benzylaminoacetaldehyde and diethyl acetonedicarboxylate by a similar sequence of reactions involving **6**→**7**→**8**→**1b**. In this case, the by-product in the formation of **6** (that is, 1-benzyl-3-(ethoxycarbonyl)pyrrole-2-acetic acid, **9**) was converted into **10** with diazomethane. Compound **10** was then used to prepare additional amounts of **7**.

It should be noted that numerous attempts to debenzylate **1b** led to recovery of starting material or to total destruction of the heterocyclic unit [2].

EXPERIMENTAL

General Methods.

All melting points were obtained on a Thomas-Hoover or a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman AccuLab 3 spectrophotometer using potassium bromide disks. The pmr spectra were determined in methyl sulfoxide-d_6 at 60 MHz with a Varian EM-360 spectrometer and are reported in parts per million downfield from tetramethylsilane as an internal standard. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

Ethyl 3-(Ethoxycarbonyl)-1-methylpyrrole-2-acetate (**2**).

A mixture of 15.2 g (75.2 mmoles) of diethyl acetonedicarboxylate and 90 ml of water was stirred while *N*-methylaminoacetaldehyde hydrochloride (prepared from 11 g (75 mmoles) of *N*-methylaminoacetaldehyde diethyl acetal [3]) and, simultaneously, 300 ml of 2.5 *N* aqueous sodium hydroxide were added at such a rate to maintain the *p*H of the mixture between 9 and 10. The mixture was then stirred at 35° for 24 hours, cooled to room temperature and extracted with diethyl ether (4 × 60 ml). The combined extracts were dried over anhydrous magnesium sulfate and evaporated to a red oil on a rotary evaporator. Trituration of the red oil with benzene gave yellow crystals which were isolated by filtration (3.45 g, 14.4 mmoles, 19%) and recrystallized from benzene-petroleum ether as white crystals of **2**, mp 58-59°; ir 1730 cm^{-1} and 1680 cm^{-1} (C=O); pmr: δ 1.2 (m, 6 H, Me of esters), 3.5 (s, 2 H, CH_2 of acetate), 3.65 (s, 3 H, N-Me), 4.04 (m, 4 H, CH_2 of esters), 6.35 (d, 1 H, J = 3 Hz, H-4 or H-5), 6.7 (d, 1 H, J = 3 Hz, H-4 or H-5).

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.35; H, 7.30; N, 5.85.

Neutralization of the aqueous phase following the ether extraction to obtain **2** led to isolation of what was believed to be 3-(ethoxycarbonyl)-1-methylpyrrole-2-acetic acid (**3**) upon further extraction with diethyl ether. This product (obtained in 23% yield) was not fully characterized due to its amorphous nature.

3-(Ethoxycarbonyl)-1-methylpyrrole-2-acetamide (**4**).

A mixture of 4 g (16.7 mmoles) of **2** and 80 ml of liquid ammonia was heated in a sealed stainless steel reaction vessel for 8 days at 120°. After cooling the vessel to room temperature, the ammonia was allowed to evaporate in the fume hood and the remaining gray residue was recrystallized from benzene-petroleum ether to give **4** (2 g, 9.51 mmoles, 57%) as colorless needles, mp 119-120°; ir: 3410 cm^{-1} (NH), 1670 cm^{-1} and 1660 cm^{-1} (C=O); pmr: δ 1.5 (t, 3 H, J = 7 Hz, Me of ester), 3.7 (s, 3 H, N-Me), 3.89 (s, 2 H, CH_2 of acetamide), 4.42 (q, 2 H, J = 7 Hz, CH_2 of ester), 6.6 (d, 1 H, J = 3 Hz, H-4 or H-5), 6.98 (d, 1 H, J = 3 Hz, H-4 or H-5), 7.21 (broad s, 1 H, NH, exchangeable with deuterium oxide), 7.58 (broad s, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.22; H, 6.65; N, 13.28.

3-(Ethoxycarbonyl)-1-methylpyrrole-2-acetonitrile (**5**).

A mixture of 2 g (9.5 mmoles) of **4** in 5 ml (8.3 g, 54 mmoles) of phosphorus oxychloride was refluxed for 20 minutes. The red solution was cooled to room temperature and poured onto ice. Following adjustment of the *p*H of the aqueous mixture to 6 with concentrated ammonium hydroxide at 10°, it was extracted with hot ethyl acetate (3 × 30 ml) after which the combined extracts were dried over anhydrous magnesium sulfate and evaporated to a reddish oil by means of a rotary evaporator. This oil was purified by distillation (92-95°/5 mm Hg) to give a yellow oil which crystallized upon cooling and was recrystallized from petroleum ether to give 0.46 g (2.39 mmoles, 25%) of white, cotton-like crystals of **5**, mp 54°; ir 2280 cm^{-1} (CN), 1680 cm^{-1} (C=O); pmr: δ 1.25 (t, 3 H, J = 7 Hz, Me of ester), 3.65 (s, 3 H, N-Me), 4.2 (m, 4 H, CH_2 of ester and CH_2 of acetonitrile), 6.35 (d, 1 H, J = 3 Hz, H-4 or H-5), 6.85 (d, 1 H, J = 3 Hz, H-4 or H-5).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.67; H, 6.37; N, 14.76.

6-Amino-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (**1a**) [4].

Compound **5** (0.3 g, 1.56 mmoles) was placed in 30 ml of liquid ammonia and heated in a sealed stainless steel reaction vessel at 160°C for 4 days. After cooling to room temperature, the ammonia was allowed to evaporate in a fume hood and the residue crystallized from 15 ml of 95% ethanol to give 0.045 g (0.27 mmole, 17%) of **1a** as white needles: decomposes beginning at 250°; ir 3420 cm^{-1} (NH), 3180-2890 cm^{-1} (broad, OH), 1640 cm^{-1} (C=O); pmr: δ 3.51 (s, 3 H, N-Me), 5.3 (broad s, 3 H, H-7 and NH_2 exchangeable with deuterium oxide), 6.16 (d, 1 H, J = 3 Hz, H-2 or H-3), 6.58 (d, 1 H, J = 3 Hz, H-2 or H-3), 9.9 (broad s, 1 H, NH or OH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.68; H, 5.66; N, 25.70.

N-Benzylaminoacetaldehyde Hydrochloride.

N-Benzylaminoacetaldehyde diethyl acetal [5] (3 g, 13.4 mmoles) was diluted with 1 ml of water. This mixture was cooled to 0° and then added dropwise into 18 ml of cooled (-5°) hydrochloric acid (sp. gr. 1.19). The resultant yellow solution was stirred at room temperature for 4-5 hours at which time the excess hydrochloric acid was evaporated with the aid of an aspirator in a bath of temperature not exceeding 40° (*ca.* 7 hours). The resulting *N*-benzylaminoacetaldehyde hydrochloride was used directly in the next step.

Ethyl 1-Benzyl-3-(ethoxycarbonyl)pyrrole-2-acetate (**6**) and 1-Benzyl-3-(ethoxycarbonyl)pyrrole-2-acetic Acid (**9**).

A mixture of 2.74 g (13.5 mmoles) of diethyl acetonedicarboxylate and 21 ml of water was stirred. During this time, a 5 ml aqueous solution of *N*-benzylaminoacetaldehyde hydrochloride (obtained by hydrolysis of 3 g (13.5 mmoles) of *N*-benzylaminoacetaldehyde diethyl acetal as desribed above) and, simultaneously, 20% aqueous sodium hydroxide solution were added at such a rate as to maintain the *p*H of the mixture between 9 and 10. The mixture was then stirred for 24 hours at 50°, cooled to room temperature and extracted with ethyl acetate (3 × 25 ml). The combined extracts were dried over anhydrous magnesium sulfate and the solvent evaporated on a rotary evaporator to give a reddish oil which, following distillation (74-80°/0.2 mm Hg) into a yellow oil, solidified to give 1.21 g (3.8 mmoles, 28%) of **6**; mp 44-45°; ir: 1715 cm^{-1} and 1680 cm^{-1} (C=O); pmr: δ 1.15 (m, 6 H, 2 Me of esters), 3.95 (m, 6 H, 2 CH_2 of esters and CH_2 of acetate), 5.12 (s, 2 H, CH_2 of benzyl), 6.42 (d, 1 H, J = 3 Hz, H-4 or H-5), 6.75 (d, 1 H, J = 3 Hz, H-4 or H-5), 7.20 (m, 5 H, phenyl).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.45; H, 6.66; N, 4.42.

Following the ethyl acetate extraction to obtain **6** as just described, the residual aqueous mixture was neutralized (litmus) with 2.4 *N* hydrochloric acid and extracted again with ethyl acetate (3 × 25 ml). The combined extracts were dried over anhydrous magnesium sulfate and evaporated on a rotary evaporator to a yellow oil which, upon trituration with 20 ml of ligroin, gave 800 mg (2.78 mmoles, 21%) of **9**, mp 102-103°; ir: 3100-2540 cm^{-1} (broad, OH), 1715 cm^{-1} and 1680 cm^{-1} (C=O); pmr: δ 1.23 (t, 3 H, J = 7 Hz, Me), 3.95 (s, 2 H, CH_2 of acetic acid), 4.05 (q, 2 H, J = 7 Hz, CH_2 of ester), 5.15 (s, 2 H, CH_2 of benzyl), 6.47 (d, 1 H, J = 3 Hz, H-4 or H-5), 6.75 (d, 1 H, J = 3 Hz, H-4 or H-5), 7.25 (m, 5 H, phenyl).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.88. Found: C, 66.63; H, 5.97; N, 4.93.

Methyl 1-Benzyl-3-(ethoxycarbonyl)pyrrole-2-acetate (**10**).

Two grams (6.96 mmoles) of **9** was mixed with 40 ml of anhydrous diethyl ether and stirred on a magnetic stirrer for 30 minutes. To this, a cold ethereal solution of diazomethane [6] (10 mmoles) was added portionwise over a period of 5 minutes. This mixture was then stirred for 6 hours at which time the excess diazomethane was decomposed with a few drops of glacial acetic acid and the mixture filtered. The filtrate was evaporated on a rotary evaporator to an oil which, upon distillation, gave 2 g (6.64 mmoles, 95%) of **10** as a yellow oil, bp 87°/0.2 mm Hg; ir: 1730 cm^{-1} and 1690 cm^{-1} (C=O); pmr: δ 1.2 (t, 3 H, J = 7 Hz, Me of ethyl ester), 3.5 (s, 3 H, Me of methyl ester), 3.68 (s, 2 H, CH_2 of acetate), 4.0 (q, 2 H, J = 7 Hz, CH_2 of ethyl ester), 5.18 (s, 2 H, CH_2 of benzyl), 6.43 (d, 1 H, J = 3 Hz, H-4 or H-5), 6.8 (d, 1 H, J = 3 Hz, H-4 or H-5), 7.2 (m, 5 H, phenyl).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.56; H, 6.59; N, 4.42.

1-Benzyl-3-(ethoxycarbonyl)pyrrole-2-acetamide (**7**).

A mixture of 10 g (32 mmoles) of **6** in 50 ml of liquid ammonia was heated in a sealed stainless steel reaction vessel at 120° for 24 hours. After cooling to room temperature, the ammonia was allowed to evaporate in the fume hood and the remaining solid residue recrystallized from ethyl acetate-ligroin to give 6 g (21 mmoles, 66%) of **7** as white needles, mp 118-119°; ir: 3430 cm^{-1} (NH), 1700 cm^{-1} and 1660 cm^{-1} (C=O); pmr: δ 1.2 (t, 3 H, J = 7 Hz, Me), 3.72 (s, 2 H, CH_2 of acetamide), 4.1 (q, 2 H, J = 7 Hz, CH_2 of ester), 5.1 (s, 2 H, CH_2 of benzyl), 6.35 (d, 1 H, J = 3 Hz, H-4 or H-5), 6.72 (d, 1 H, J = 3 Hz, H-4 or H-5), 7.2 (m, 7 H, phenyl and amide NH_2).

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.79. Found: C, 67.05; H, 6.46; N, 9.64.

A 70% (3.32 g, 11.6 mmoles) yield of **7** was also obtained from 5 g (16.6 mmoles) of **10** and 50 ml of liquid ammonia under the same conditions as employed with **6**.

1-Benzyl-3-(ethoxycarbonyl)pyrrole-2-acetonitrile (**8**).

1-Benzyl-3-(ethoxycarbonyl)pyrrole-2-acetamide (**7**) (0.33 g, 1.15 mmoles) was heated under reflux with 4 ml (42.91 mmoles) of phosphorus oxychloride for 1.5 hours. After this, the solution was cooled to room temperature, poured into ice (30 g) and the *p*H of the resulting solution adjusted to 6 (*p*H paper) by adding concentrated ammonium hydroxide slowly with stirring and cooling in an ice water bath. The aqueous mixture was then extracted with ethyl acetate (3 × 75 ml) and the extracts combined, dried over anhydrous sodium sulfate, and the ethyl acetate evaporated to leave a dark brown oil. Distillation [7] of this oil (106°/0.2 mm Hg) produced a colorless oil which solidified into white stars of **8** (0.25 g, 0.93 mmoles, 81%), mp 84-86°; ir: 2260 cm^{-1} (CN), 1685 cm^{-1} (C=O); pmr: δ 1.28 (t, 3 H, J = 7 Hz, Me), 4.23 (q, 2 H, J = 7 Hz, CH_2 of ester), 4.25 (s, 2 H, CH_2 of acetonitrile), 5.3 (s, 2 H, CH_2 of benzyl), 6.5 (d, 1 H, J = 3 Hz, H-4 or H-5), 6.93 (d, 1 H, J = 3 Hz, H-4 or H-5), 7.25 (m, 5 H, phenyl).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.84; H, 6.02; N, 10.44.

1-Benzyl-6-amino-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (**1b**) [4].

Compound **8** (0.8, 2.98 mmoles) was mixed with 50 ml of liquid ammonia and heated in a sealed stainless steel reaction vessel at 160° for 90 hours. The mixture was cooled to room temperature and the ammonia allowed to evaporate in the fume hood. The resulting solid was recrystallized from 95% ethanol (with decolorizing charcoal) as light tan platelets of **1b** (0.3 g, 1.25 mmoles, 42%), mp 263-264°; ir 3410 cm^{-1} (NH), 3200-2800 cm^{-1} (broad, OH); pmr: δ 5.11 (s, 2 H, CH_2 of benzyl), 5.37 (s, 3 H, H-7 and

NH_2), 6.32 (d, 1 H, J = 3 Hz, H-2 or H-3), 6.85 (d, 1 H, J = 3 Hz, H-2 or H-3), 7.25 (m, 5 H, phenyl), 10.0 (s, 1 H, NH or OH).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.52; H, 5.50; N, 17.38.

Acknowledgement.

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REFERENCES AND NOTES

[1] S. W. Schneller, R. S. Hosmane, L. B. MacCartney, and D. A. Hessinger, *J. Med. Chem.*, **21**, 990 (1978) and S. W. Schneller and R. S. Hosmane, *J. Org. Chem.*, **43**, 4487 (1978).

[2] Other reports on the difficulty of debenzylating *N*-benzylpyrroles exist (for example, [a] H. J. Anderson and J. K. Groves, *Tetrahedron Letters*, 3165 (1971), and [b] M.-I. Lim, R. S. Klein, and J. J. Fox, *J. Org. Chem.*, **44**, 3826 (1979)).

[3] For the synthesis of *N*-methylaminoacetaldehyde diethyl acetal see M. Chastrette, *Ann. Chim.*, **7**, 643 (1962). For the conditions used to hydrolyze the acetal see E. Fischer, *Ber.*, **26**, 92 (1893).

[4] For the sake of analogy to guanine, the keto tautomer of **1a** and **1b** has been used herein for naming and drawing these compounds. However, the ir data suggests that **1a** exists as a mixture of the keto and enol tautomers whereas **1b** prefers the enolic form under these spectral measurement conditions.

[5] E. Fischer, *Ber.*, **26**, 464 (1893).

[6] F. Arndt, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, ed, John Wiley and Sons, Inc., New York, 1943, pp 165-167.

[7] In order to avoid extensive decomposition of this oil during distillation an alternative procedure for its purification as **8** was devised using silica gel column chromatography with chloroform-ethyl acetate (8:1, v/v) as the eluant. Compound **8** moved as a pink-to-tan band and required 50% of the solvent before it appeared off the column. The **8** obtained in this manner was recrystallized from methanol.