A Convenient Synthesis of Pyrazolidine and 3-Amino-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one

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A convenient four-step synthesis of the aminobicyclopyrazolone hydrochloride **1**•HCl was achieved starting from di-*tert*-butyl hydrazodiformate (**8**). The route entails cyclization of **8** with 1,3-dibromopropane under phase transfer conditions followed by deprotection of 1,2-di-*tert*-butoxycarbonylpyrazolidine (**9**) to give pyrazolidine hydrochloride (**2**•HCl). Cyanoacetylation of the latter and ring closure of the resulting cyanoacetyl pyrazolidine (**7**) gave **1**•HCl. This novel synthesis circumvents distillation of pyrazolidine (**2**) and flash chromatography to provide the hydrochloride of **1** in 35-46% overall yields compared to 6% yield for the patent procedure.

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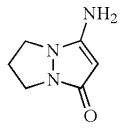
Introduction.

Aminobicyclopyrazolone **1** is described in the patent literature as a synthetic intermediate *en route* to photographic developing agents [1]. This densely functionalized enaminone is a versatile synthon, reacting with a variety of electrophiles in its enamine form [2] or through the corresponding 1,3-dicarbonyl compound which is accessible by acid hydrolysis [1]. Selective syntheses of pyrazolo[1,2-*a*]pyrazoles have recently been described [3] and a number of aminopyrazolone congeners possess biological activity including cardiovascular [4], antifungal [5], antiinflammatory [6], angiotensin II antagonism [7], platelet aggregation inhibition [8] and corticotropin releasing factor antagonism [9]. For these reasons, alternative aminodihydropyrazolone syntheses are of interest to researchers in the fields of organic and medicinal chemistry.



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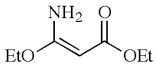

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The patent synthesis of **1** [1] involves preparation of pyrazolidine (**2**) from hydrazine hydrate and 1,3-dibromopropane as described by Buhle *et al.* [10]. Fractional distillation of **2** and reaction with ethyl aminoethoxyacrylate (**3**) gave **1** in *ca.* 6% overall yield. We required multigram quantities of **1** for analog synthesis [2] and wished to develop an improved synthetic route to this compound that provided pure material in reasonable overall yields. In this paper, we describe a convenient four-step synthesis of **1** that affords a tractable hydrochloride salt of the product in 35-46% overall yields and avoids tedious distillation of **2** and chromatography.

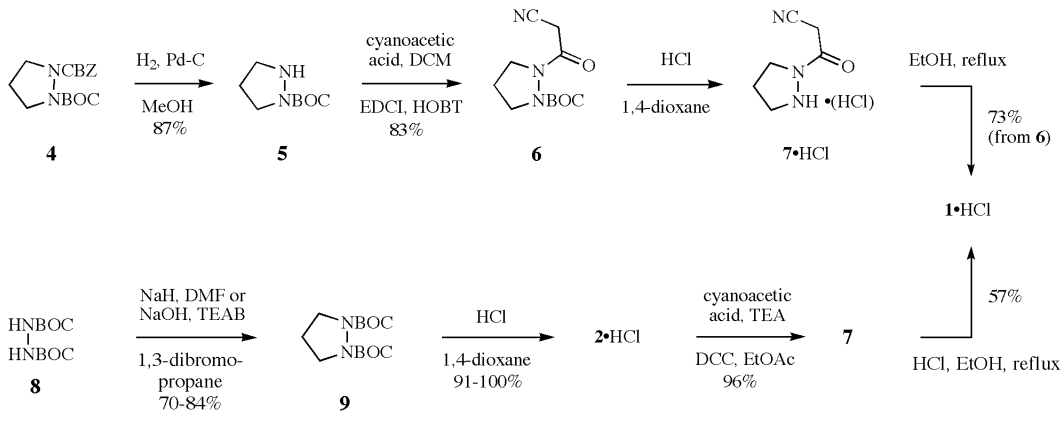
Results and Discussion.

Our initial approach to **1** utilized an orthogonally protected pyrazolidine (**4**) which was prepared in two steps and 69% yield from *tert*-butylcarbazate employing published procedures [11]. Hydrogenolysis of **4** and coupling of the mono-protected pyrazolidine product **5** [11a] with cyanoacetic acid gave the novel cyanoacetyl pyrazolidine **6** in 72% overall yield from **4**. Removal of the *tert*-butoxycarbonyl group in **6** with hydrogen chloride in 1,4-dioxane gave the hydrochloride of **7** and effected partial ring closure to **1** based on proton nmr spectroscopy (*ca.* 25% cyclized). Heating a solution of **7**•HCl in ethanol at reflux completed cyclization to **1** within 30 minutes. Cooling the reaction mixture and dropwise addition of ethyl acetate precipitated the hydrochloride of **1** as a white solid (73% yield from **6**).

The synthesis of **1** from **4** supplied multigram quantities of product in 36% overall yield; however, the route is lengthy (six steps from *tert*-butylcarbazate) and necessitates one protection and two deprotection steps. For this reason, a revised synthesis of **1** from di-*tert*-butyl hydrazodiformate (**8**) was explored (Scheme 1). Accordingly, **8** was reacted with sodium hydride in dimethylformamide followed by addition of 1,3-dibromopropane. This cyclization technique produced the desired pyrazolidine (**9**) in good yield; however, in view of the hazards associated with sodium hydride/dimethylformamide mixtures [12,13], we explored alternative conditions for this transformation. We soon discovered that this reaction could be readily accomplished with 50% sodium hydroxide and toluene at 100 °C in the presence of 10 mol% tetraethyl ammonium bromide (TEAB) (Scheme 1). These phase-transfer catalysis (PTC) conditions [14] are a safer alternative to the sodium hydride method and facilitate practical access to the medicinally interesting [11] pyrazolidine ring system.

Pyrazolidine hydrochloride (**2**•HCl) [15,16] was obtained as a hygroscopic white solid by treatment of **9** with hydrogen chloride in 1,4-dioxane. Our efforts to convert **2** to **1** with the hydrochloride of **3** in a refluxing solution of sodium ethoxide in ethanol were unsuccessful. Alternatively, cyanoacetylation of the hydrochloride of **2** with cyanoacetic acid and dicyclohexylcarbodiimide in the

Scheme 1



presence of triethyl amine (TEA) gave the cyanoacetyl pyrazolidine **7**. Cyclization of **7** in a refluxing solution of hydrogen chloride in ethanol afforded **1**•HCl in 35-46% overall yield from **8**. This revised synthesis of **1** reduced the number of synthetic transformations by two and increased the overall yield of product by up to ten percent.

It is important to note that melting point analysis of **1**•HCl revealed vigorous decomposition with gas evolution above 174 °C. Furthermore, the energy of exothermic decomposition of **1**•HCl as measured by differential scanning calorimetry (DSC) was 0.82 kJ/g over the 153-325 °C range. For these reasons, synthetic operations involving **1**•HCl should be kept well below 150 °C.

In summary, convenient syntheses of the hydrochlorides of pyrazolidine (**2**) and bicyclopyrazolone **1** were accomplished starting from di-*tert*-butyl hydrazodiformate (**8**). The route entails cyclization of **8** with 1,3-dibromopropane under phase transfer conditions followed by removal of the *tert*-butoxycarbonyl protecting groups in **9** to give pyrazolidine hydrochloride (**2**•HCl). Cyanoacetylation of the latter and ring closure of the resulting cyanoacetyl pyrazolidine (**7**) gave the desired bicyclopyrazolone (**1**•HCl). The title synthesis avoids fractional distillation of pyrazolidine (**2**) and preparative chromatography to provide a tractable hydrochloride salt of **1** in 35-46% overall yields. Pyrazolidine **2** and aminobicyclopyrazolone **1** are versatile intermediates in organic synthesis and medicinal chemistry [1,2].

EXPERIMENTAL

General.

All reagent chemicals were used without purification. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia. Proton nmr spectra were recorded at 300 or 400 MHz and chemical shifts are reported in ppm relative to the residual protonated solvent resonance of deuteriochloroform (δ 7.24) or d_6-dimethylsulfoxide (δ 2.49). Coupling constants are reported in hertz. Carbon-13 nmr spectra were recorded at 74 MHz and chemical shifts are reported in ppm relative to the multiplet for dimethylsulfoxide (δ 40.2). Mass spectra (ms) are reported in the form *m/z* (positive ion, relative intensity).

1-*tert*-Butoxycarbonylpyrazolidine (**5**).

A solution of **4** [11a] (83 g, 271 mmol) in 85% methanol/water (600 mL) was hydrogenolyzed at atmospheric pressure over 5% palladium on carbon (Degussa type, 16 g) for 3 days. The catalyst was removed by filtration, and the filtrate was resubjected to the same hydrogenolysis conditions overnight. The catalyst was removed by filtration, and the filtrate was concentrated at reduced pressure to yield **5** [11a] (40.6 g, 235 mmol, 87% yield) as a colorless oil: ^{1}H nmr (d_6-dimethylsulfoxide): δ 5.05 (1H, br), 3.23 (2H, t, J = 7.2), 2.74 (2H, t, J = 6.4), 1.85 (2H, m), 1.35 (9H, br s). This material was used without further purification.

1-*tert*-Butoxycarbonyl-2-cyanoacetylpyrazolidine (**6**).

To a stirring solution of **5** (35.5 g, 206 mmol), cyanoacetic acid (17.5 g, 206 mmol) and 1-hydroxybenzotriazole (HOBT) (2.78 g, 20.6 mmol) in dichloromethane (500 mL) at 0 °C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (49.4 g, 258 mmol). The reaction mixture was stirred at room temperature overnight and then washed with water, 10% citric acid solution and brine. The organic layer was dried and concentrated at reduced pressure to afford **6** as an oil (41.0 g, 0.171 mmol, 83% yield). This material was used without further purification. An analytical sample of **6** was obtained by flash chromatography on silica gel eluting with 1.5% methanol/dichloromethane: ^{1}H nmr (deuteriochloroform): δ 4.11 (1H, m), 4.04 (1H, m), 3.69 (1H, d, J = 18.3), 3.54 (1H, d, J = 18.3), 3.27 (1H, m), 3.13 (1H, m), 2.13 (1H, m), 2.07 (1H, m), 1.50 (9H, s); ms *m/z* 140 (100), 262 (M+Na$^+$, 5).

Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 54.98; H, 7.16; N, 17.35.

1-Cyanoacetylpyrazolidine Hydrochloride (**7**•HCl) from **6**.

A solution of **6** (41 g, 171 mmol) in 4 *M* hydrogen chloride/1,4-dioxane (400 mL) was stirred at room temperature for 4 hours. The reaction mixture was diluted with diethyl ether (1 L) and the supernatant was decanted. The remaining hygroscopic solid was dried under high vacuum to yield the crude hydrochloride of **7** as a white

solid (30 g, 100% crude yield). This material was used in the next step without further purification. An analytical sample of the free base was obtained by washing a dichloromethane solution of **7**•HCl with aqueous sodium bicarbonate solution. The organic layer was dried and concentrated *in vacuo* to afford **7** as an oil that crystallized on standing: ^{1}H nmr (deuteriochloroform): δ 4.08 (1H, t, J = 8.7), 3.63 (2H, s), 3.58 (2H, t, J = 7.3), 3.04 (2H, m), 2.14 (2H, m).

Anal. Calcd for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.73; H, 6.56; N, 30.06.

3-Amino-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one Hydrochloride (**1**•HCl) from **7**•HCl.

A solution of **7**•HCl (30 g, 171 mmol) in ethanol (400 mL) was heated at reflux for 20 minutes and cooled to room temperature. Diethyl ether (1 L) was added dropwise and the resulting precipitate (**1**•HCl) was collected by filtration as a white solid (22 g, 125 mmol, 73% yield): mp 174-176 °C (decomposition); Differential scanning calorimetry (DSC): energy of exothermic decomposition = 0.82 kJ/g from 153-325 °C; ir: 3289, 3143, 2587, 1582 (C=O) cm^{-1}; ^{1}H nmr (d_6-dimethylsulfoxide): δ 7.06 (2H, br), 4.96 (1H, s), 3.79 (4H, m), 2.55 (2H, m); ^{13}C nmr (d_6-dimethylsulfoxide): δ 158.13 (C), 152.70 (C), 77.76 (C), 45.20 (CH_2), 44.23 (CH_2), 28.09 (CH_2); ms *m/z* 140 (M+1, 100).

Anal. Calcd for $C_6H_{10}ClN_3O$•(0.4 H_2O): C, 39.42; H, 5.95; N, 22.98. Found: C, 39.42; H, 6.16; N, 22.80.

1,2-Bis-*tert*-butoxycarbonylpyrazolidine (**9**) (Sodium Hydride Method).

A solution of **8** (10.2 g, 43.7 mmol) in dimethylformamide (100 mL) was added dropwise to a stirred suspension of sodium hydride (2.20 g, 91.67 mmol) in dimethylformamide (50 mL) (caution!) [12,13] at room temperature. After stirring 30 minutes, neat 1,3-dibromopropane (4.43 ml, 43.69 mmol) was added dropwise and the reaction mixture was stirred overnight. The reaction was quenched with water and the dimethylformamide was removed by distillation at reduced pressure. The crude material was dissolved in ethyl acetate, washed with water, dried, filtered and concentrated to afford **9** [17] as a colorless oil (10.0 g, 36.7 mmol, 84% yield): ^{1}H nmr (deuteriochloroform): δ 3.85 (2H, m), 3.18 (2H, m), 1.98 (2H, quint, J = 7.2), 1.45 (18H, br s). This material was used without further purification.

1,2-Bis-*tert*-butoxycarbonylpyrazolidine (**9**) (Phase Transfer Method).

A mixture of **8** (5.00 g, 21.5 mmol), 1,3-dibromopropane (6.5 g, 32.3 mmol), tetraethyl ammonium bromide (680 mg, 3.23 mmol), 50% sodium hydroxide (25 mL) and toluene (50 mL) was stirred vigorously at 100 °C for two hours. The reaction mixture was diluted with ethyl acetate and washed with aqueous sodium bicarbonate, water and brine. The organic phase was dried, filtered and concentrated to give **9** [17] (6 g) as an oil. Spectral data were identical to that described for **9** above and showed the presence of excess 1,3-dibromopropane (70% crude yield based on proton nmr). This material was used without further purification.

Pyrazolidine Hydrochloride (**2**•HCl).

In a typical procedure, a 0.4 *M* solution of **9** (prepared by the sodium hydride or phase transfer method) in 4 *M* hydrogen chloride/1,4-dioxane was stirred 3 hours at room temperature. The mixture was diluted with diethyl ether and the hydrochloride of **2** [15,16] was collected by filtration under nitrogen as a white, hygroscopic solid (91-100% yield): mp 54-56 °C; ^{1}H nmr (d_6-dimethylsulfoxide): δ 8.25 (4H, br), 3.01 (4H, t, J = 7.2), 1.93 (2H, quint, J = 7.2); ^{13}C nmr (d_6-dimethylsulfoxide): δ 46.58 ($2CH_2$), 26.18 (CH_2); ms *m/z* 73 (M+1, 100).

Anal. Calcd for $C_3H_8N_2$•(1.31 HCl): C, 30.06; H, 7.83; N, 23.37. Found: C, 30.10; H, 8.05; N, 23.01.

1-Cyanoacetylpyrazolidine (**7**) from **2**•HCl.

Neat triethyl amine (6.26 mL, 44.9 mmol) was added dropwise to a stirred mixture of **2**•HCl and cyanoacetic acid (1.91 g, 22.46 mmol) in ethyl acetate (65 mL) at room temperature. Dicyclohexylcarbodiimide (DCC) (4.64 g, 22.50 mmol) was added portionwise, and the reaction mixture was heated gently to aid dissolution and then stirred at room temperature overnight. The precipitated dicyclohexyl urea was removed by filtration and the filtrate was diluted with diethyl ether and refiltered. The filtrate was concentrated at reduced pressure to provide **7** as a colorless oil that partially crystallized on standing (3 g, 21.6 mmol, 96% yield). Spectral data were identical to that described for **7** above. This material was used without further purification.

3-Amino-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one Hydrochloride (**1**•HCl) from **7**.

A solution of **7** (3 g, 21.6 mmol) in 0.75 *M* hydrogen chloride/ethanol (33 mL) (prepared from ethanol and acetyl chloride at 0 °C) was heated at reflux for 30 minutes. The solution was diluted with ethyl acetate and allowed to cool to room temperature. The title compound (**1**•HCl) was collected by filtration as a white solid (2.2 g, 12.2 mmol, 57% yield). Spectral data were identical to that described for **1**•HCl above.

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