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Efficient syntheses of ethyl 4-cyano-5-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate and ethyl (2*Z*)-(4-cyano-5-oxopyrrolidin-2-ylidene)ethanoate

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ABSTRACT

Ethyl 2-chloroacetoacetate and its 4-chloro isomer react with cyanoacetamide in the presence of the mild, nonnucleophilic base, triethylamine under stoichiometric conditions to give high yields of ethyl 4-cyano-2-hydroxy-2-methyl-5-oxopyrrolidine-3-carboxylate and ethyl (4-cyano-2-hydroxy-5-oxopyrrolidin-2-yl)acetate, respectively. These, under acid-catalyzed dehydration conditions, afforded ethyl 4-cyano-5-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate and ethyl (2*Z*)-(4-cyano-5-oxopyrrolidin-2-ylidene)ethanoate, respectively. Similarly, the 4-chloro isomer reacted with ethyl cyanoacetate to give the novel product, diethyl 2-cyano-4-oxohexanedioate. The use of triethylamine enables access to a whole new library of pyrrole derivatives from easily accessible, commercially available starting materials. The reactions described in this Letter enable access to libraries of important pyrrole systems in any of the isotopically enriched forms.

The substituted pyrrole ring system is the basic building block of a number of important biological compounds including vitamin B_{12}, chlorophyll, heme, etc.[1–3] Similarly, substituted pyrrolidinones are important components in the preparation of bile pigments,[4] and of several classes of bioactive natural compounds with a wide range of activity. They are useful intermediates for the synthesis of (+)-lactacystin,[5–7] (−)-rolipram,[8] etc. 4-(Aminomethyl)-1-aryl-2-pyrrolidinones are a new class of monoamine oxidase B inactivators.[9] In addition, the ability to functionalize and modify the pyrrole or pyrrolidinone moieties could allow the preparation of some types of natural products as well as the synthesis of biologically active molecules.

We have a programme to make libraries of stable isotope-enriched pyrrole systems accessible.[10] We reasoned that the reaction of a simple functionalized halogen compound with an activated amide may give, in one step, a product with all the required functional groups to form the required pyrrole or pyrrolidinone system. The key step requires the presence of the mild nonnucleophilic base, trimethylamine ($pK_a \sim 10$) to deprotonate the active methylene group ($pK_a \sim 10$), without appreciably deprotonating the amide function ($pK_a \sim 16$).[11]

We now report a triethylamine-catalyzed reaction of ethyl 2-chloroacetoacetate and its isomer, ethyl 4-chloroacetoacetate with cyanoacetamide to afford C-alkylation products, followed by an intramolecular cyclization and acid-catalyzed dehydration for the preparation of ethyl 4-cyano-5-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (**1**) and ethyl (2*Z*)-(4-cyano-5-oxopyrrolidin-2-ylidene)ethanoate (**2**), respectively.

A solution of ethyl 2-chloroacetoacetate (**4**) (1.64 g, 10 mmol), cyanoacetamide (**3**) (0.84 g, 10 mmol), and triethylamine (1.01 g, 10 mmol) in acetonitrile was refluxed for 2 h. After work-up, the product, ethyl 4-cyano-2-hydroxy-2-methyl-5-oxopyrrolidine-3-carboxylate (**5**) (1.85 g, 87%) was obtained as a mixture of isomers (Scheme 1). Subsequently, product **5** was refluxed in toluene in the presence of *p*-toluenesulfonic acid to afford, after work-up, the novel product ethyl 4-cyano-5-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (**1**) in high yield (1.25 g, 81%).

As shown in Scheme 1, following alkylation of cyanoacetamide (**3**) by ethyl 2-chloroacetoacetate (**4**), nucleophilic attack of the amide function led to a stable isomeric mixture of product **5** which easily underwent acid-catalyzed elimination of water followed by a proton shift to give the product, ethyl 4-cyano-5-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylate (**1**). The analytical data were in agreement with the structures of products **5** and **1**.

Similarly, reaction of ethyl 4-chloroacetoacetate (**6**) and cyanoacetamide (**3**) afforded a novel product **7** (1.90 g, 89%) as a mixture of diastereoisomers. Mass spectrometry and other spectroscopic data indicated that this product was ethyl (4-cyano-2-hydroxy-5-oxopyrrolidin-2-yl)acetate (**7**). The product **7** was heated at reflux in the presence of *p*-toluenesulfonic acid in toluene for 4 h and the elimination of water resulted in pyrrolidone **2** as a colorless solid in a yield of 1.35 g, (87%).

Analytical data confirmed the product as ethyl (2*Z*)-(4-cyano-5-oxopyrrolidin-2-ylidene)ethanoate (**2**). Also, the ^{1}H NMR assignments were further confirmed by ^{1}H–13C and ^{1}H-correlation

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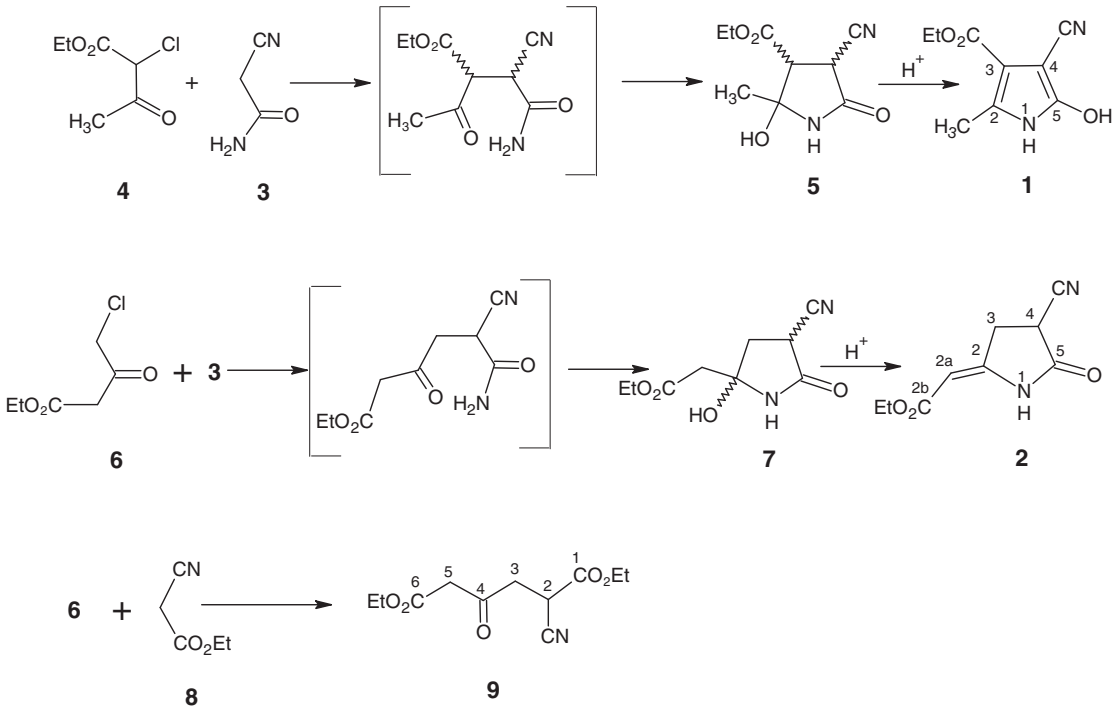

Scheme 1.

spectroscopy methods. The pyrrolidinone structure of product **2** was established by comparing its analytical data with those of ethyl (2*Z*)-(5-oxopyrrolidin-2-ylidene)ethanoate (obtained as an intermediate in a stepwise synthesis of levulinic acid).[12]

Based on the effectiveness of triethylamine in this process, we searched the literature for possible precedents. The reactions of ethyl 2-chloroacetoacetate (**4**) with ethyl cyanoacetate (**8**) using triethylamine and diisopropylethylamine have been described.[13,14] Recently, the reaction of ethyl acetoacetate with chloroacetaldehyde in the presence of ammonium hydroxide was reported, the product of which was ethyl 2-methyl-1*H*-pyrrole-3-carboxylate. The reaction proceeds via initial alkylation followed by a subsequent Paal–Knorr reaction.[15]

These results motivated us to use ethyl 4-chloroacetoacetate (**6**) as the alkylating agent in the reaction with ethyl cyanoacetate (**8**). In this case, the new product, diethyl 2-cyano-4-oxohexanedioate (**9**) was obtained in high yield (2.15 g, 89%).

Access to any isotopomer of cyanoacetamide and ethyl cyanoacetate has been previously reported by us.[16] Similarly, access to any isotopomer of ethyl acetoacetate and its 2-chloro derivative has been described.[17] The reagents we used in this work are commercially available materials, which can easily be obtained in any stable isotope enriched form. Thus, using the chemistry described in this Letter, many biologically important pyrrole systems are accessible in any stable isotope labeled form.

Ethyl 4-cyano-2-hydroxy-2-methyl-5-oxopyrrolidine-3-carboxylate (**5**): To a solution of ethyl 2-chloroacetoacetate (**4**) (1.64 g, 10 mmol), cyanoacetamide (**3**) (0.84 g, 10 mmol) in MeCN (50 mL) was added Et_3N (1.01 g, 10 mmol). The solution was refluxed for 2 h and the precipitated solid filtered and the filtrate evaporated in vacuo to yield 1.85 g, (87%) of compound **5** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.33 (t, $^3J_{H-H}$ = 7.1 Hz, 3H, CH_3), 1.78 (s, 3H, CH_3), 3.52 (d, $^3J_{H-H}$ = 10.6 Hz, 1H, CH), 4.14 (q, $^3J_{H-H}$ = 7.1 Hz, 2H, CH_2), 4.44 (d, $^3J_{H-H}$ = 10.6 Hz, 1H, CH), 7.28 (s, 1H, NH), 7.82 (s, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 14.1 (CH_3), 26.6 (CH_3), 35.3 (CH), 55.2 (CH), 62.5 (CH_2), 85.6 (C), 115.8 (CN), 167.2 (C=O), 167.8 (C=O) ppm. FT-IR (neat): 3430, 3320, 3234, 3176, 2986, 2243, 1699, 1668, 1652, 1615, 1575, 1557 cm^{-1}. HRMS (calculated for $C_9H_{12}N_2O_4$) *m/z* 212.2026, (obtained) 212.2013.

Ethyl 4-cyano-5-hydroxy-2-methyl-1H-pyrrole-3-carboxylate (**1**): To a solution of **5** (1.70 g, 8 mmol) in toluene (50 mL) was added *p*TsOH (0.20 g, 1 mmol) and the mixture refluxed for 2 h. The solvent was evaporated and the residue was dissolved in $CHCl_3$ (50 mL)/EtOAc (25 mL). The precipitated solid was filtered and dried under vacuum to yield **1**, 1.25 g, (81%) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.21 (t, $^3J_{H-H}$ = 7.1 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.14 (q, $^3J_{H-H}$ = 7.0 Hz, 2H, CH_2), 11.52 (s, 1H, NH), 11.65 (s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.5 (CH_3), 15.3 (CH_3), 60.4 (CH_2), 72.1 (C–CN), 108.5 (C-CO_2Et), 117.3 (CN), 129.3 (C–CH_3), 153.2 (C–OH), 164.2 (C=O) ppm. FT-IR (neat): 3329, 3168, 2987, 2244, 1668, 1652, 1575 cm^{-1}. HRMS (calculated for $C_9H_{10}N_2O_3$) *m/z* 194.1873, (obtained) 194.1864.

Ethyl (4-cyano-2-hydroxy-5-oxopyrrolidin-2-yl)acetate (**7**): To a solution of ethyl 4-chloroacetoacetate (**6**) (1.64 g, 10 mmol) and cyanoacetamide (**3**) (0.84 g, 10 mmol) in MeCN (50 mL) was added Et_3N (1.01 g, 10 mmol). The solution was stirred for 16 h at room temperature. The precipitated solid was filtered and the filtrate evaporated under reduced pressure to give crude **7**. Further purification by column chromatography (EtOAc/*n*-hexane, 8:2) afforded **7** as a colorless solid (1.90 g, 89%). ^{1}H NMR (300 MHz, CD_3CN/TMS) δ = 1.23 (t, $^3J_{H-H}$ = 7.2 Hz, 3H, CH_3), 2.54–2.58 (m, 2H, CH_2), 2.75 (m, 2H, CH_2), 3.92 (t, $^3J_{H-H}$ = 9.5 Hz, 1H, CH), 4.16 (q, $^3J_{H-H}$ = 7.1 Hz, 2H, CH_2), 4.51 (br s, 1H, NH), 7.30 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.2 (CH_3), 33.1 (CH), 39.8 (CH_2), 44.8 (CH_2), 61.2 (CH_2), 85.2 (C–OH), 119.5 (CN), 169.1 (C=O), 170.1 (C=O) ppm. FT-IR (neat): 3470, 3314, 2974, 2932, 2254, 1714, 1702, 1438 cm^{-1}. HRMS (calculated for $C_9H_{12}N_2O_4$) *m/z* 212.2026, (obtained) 212.2010.

Ethyl (2Z)-(4-cyano-5-oxopyrrolidin-2-ylidene)ethanoate (**2**): To a solution of **7** (1.70 g, 8 mmol) in toluene (50 mL) was added *p*TsOH (0.20 g, 1 mmol) and the mixture refluxed for 4 h. The mixture was filtered and the filtrate evaporated under reduced pressure to yield a viscous substance which crystallized at room temperature to

yield 1.35 g, (87%) of product **2**. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ = 1.28 (t, $^3J_{H-H}$ = 7.2 Hz, 3H, CH_3), 3.14 (dd, $^2J_{H-H}$ = 17.5 Hz, $^3J_{H-H}$ = 7.3 Hz, 1H of CH_2), 3.26 (dd, $^2J_{H-H}$ = 17.5 Hz, $^3J_{H-H}$ = 9.9 Hz, 1H of CH_2), 3.76 (dd, $^3J_{H-H}$ = 9.8 Hz, $^3J_{H-H}$ = 7.3 Hz, 1H, CH), 4.20 (q, $^3J_{H-H}$ = 7.3 Hz, 2H, CH_2), 5.14 (s, 1H, CH), 10.16 (br s, 1H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 14.1 (CH_3), 30.5 (CH), 30.7 (CH_2), 60.4 (CH_2), 92.9 (CH), 115.5 (CN), 151.7 (=C), 167.4 (C=O), 167.9 (C=O) ppm. FT-IR (neat): 3326, 2984, 2913, 2257, 1752, 1679, 1641, 1471 cm^{-1}. HRMS (calculated for $C_9H_{10}N_2O_3$) *m/z* 194.1873, (obtained) 194.1864.

Diethyl 2-cyano-4-oxohexanedioate (**9**): To a solution of ethyl 4-chloroacetoacetate (**6**) (1.64 g, 10 mmol) and ethyl cyanoacetate (**8**) (1.13 g, 10 mmol) in MeCN (50 mL) was added Et_3N (1.01 g, 10 mmol). The solution was refluxed for 1 h. The precipitated solid was filtered and the filtrate evaporated under reduced pressure to give the product. Further purification by column chromatography (EtOAc/*n*-hexane, 8:2) afforded **9** as a yellow oil (2.15 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ = 1.24 (t, $^3J_{H-H}$ = 7.3 Hz, 3H, CH_3), 1.34 (t, $^3J_{H-H}$ = 7.3 Hz, 3H, CH_3), 3.18 (dd, $^2J_{H-H}$ = 18.5 Hz, $^3J_{H-H}$ = 5.7 Hz, 1H of CH_2), 3.31 (dd, $^2J_{H-H}$ = 18.5 Hz, $^3J_{H-H}$ = 6.5 Hz, 1H of CH_2), 3.56 (s, 2H, CH_2), 4.01 (t, $^3J_{H-H}$ = 6.2 Hz, 1H, CH), 4.23 (q, $^3J_{H-H}$ = 7.3 Hz, 2H, CH_2), 4.28 (q, $^3J_{H-H}$ = 7.3 Hz, 2H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.5 (CH_3), 13.6 (CH_3), 31.3 (CH), 41.1 (CH_2), 48.3 (CH_2), 61.3 (CH_2), 62.9 (CH_2), 115.7 (CN), 164.8 (C=O), 166.1 (C=O), 197.7 (C=O) ppm. FT-IR (neat): 2259, 1738, 1721 cm^{-1}. HRMS (calculated for $C_{11}H_{15}NO_5$) *m/z* 241.2405, (obtained) 241.2395.

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