Isolation of 5-Hydroxy-γ-lactams from a Classical 2-Aminopyrrole Synthesis

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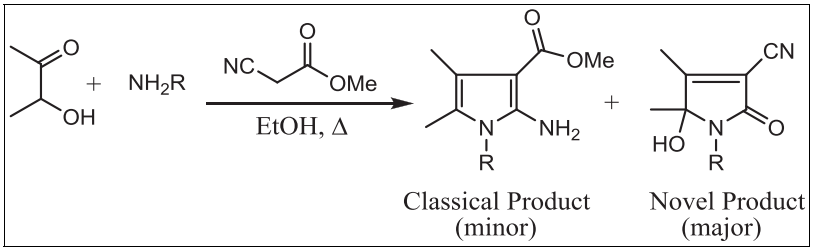
Dedicated to Dr. J. Walter Sowell (mentor to CES) on occasion of his retirement from academia.



5-hydroxy-γ-lactams have been isolated as major byproducts from a classical 2-aminopyrrole synthesis involving condensation of an *in situ* prepared α-aminoketone with methyl cyanoacetate. The classical 2-aminopyrrole was obtained in very low yield, or not at all. One 5-hydroxy-γ-lactam was dehydrated to the known 5-methylene-γ-lactam in good yield using thionyl chloride.

INTRODUCTION

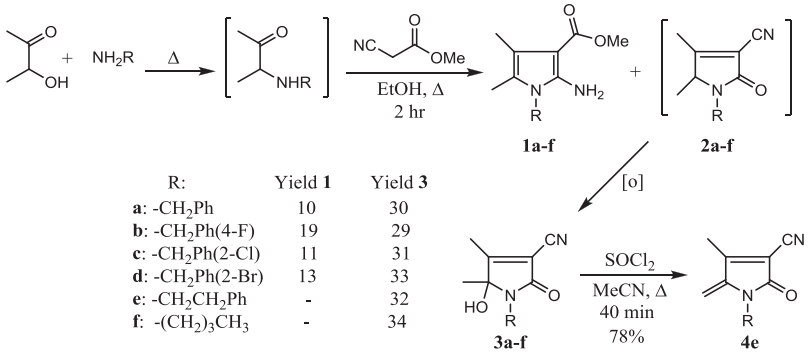
In 1975, Roth and Eger first described the now classical synthesis of *N*-1-substituted-2-aminopyrroles containing a cyano group at the 3-position [1]. Later, Sowell and coworkers extended this reaction to synthesis of similar 2-aminopyrroles with esters [2] or sulfones [3] at the 3-position. This multicomponent reaction typically involves condensation of an *in situ* formed α-aminoketone (prepared by reaction of an α-hydroxyketone with a primary amine) with an activated CH_2CN compound, such as malononitrile, an alkyl cyanoacetate, or a (cyanomethyl) sulfonyl derivative. Although the 4,5-dimethylpyrrole analogues are most commonly prepared (using acetoin as a starting material), other substituent patterns can also be obtained, such as the 4,5-diphenyl analogues (using benzoin) [1,4]. These functionalized 2-aminopyrroles have since served as starting point for synthesis of a variety of pyrrole-containing derivatives, including annulated bicyclic and tricyclic ring systems [4–12].

Yields for the 2-aminopyrroles by this classical synthesis are generally moderate to good, including for the tert-butyl esters (prepared using tert-butyl cyanoacetate). However, yields for the methyl esters (prepared using methyl cyanoacetate) are generally lower [2]. To our knowledge, there has been no report of the formation of byproducts from this classical pyrrole synthesis, nor has an explanation for the lower yield for the methyl esters been offered. Herein, we describe the isolation of a unique 5-hydroxy-γ-lactam product from this pyrrole synthesis when using methyl cyanoacetate as the CH_2CN compound. The formation of this previously unreported byproduct helps explain why yields for these 2-aminopyrroles are relatively low compared with yields for the analogous pyrroles containing tert-butyl esters or other functional groups.

RESULTS AND DISCUSSION

The 2-aminopyrrole **1a** (Scheme 1) was recently needed in our laboratory for an ongoing project. We were able to prepare this known pyrrole [2] in ~15% purified yield using our modified version of the classical synthesis and following standard recrystallization of the crude product. Our modified version involves heating the acetoin and primary amine briefly without solvent to produce the α-aminoketone, followed by reaction of this intermediate with the CH_2CN compound in refluxing EtOH. This procedure, which eliminates the use of an organic solvent in the first step and also allows for performing this step in just 1–2 min, has given good yields of the pyrroles containing sulfones at the 3-position [13]. However, our yield for pyrrole **1a** using this procedure was lower than that originally reported by Sowell and coworkers (33%, using Dean-Stark conditions and cyclohexane as solvent for each step). Interestingly, TLC analysis of our crude product mixture showed that a second major product was formed in our reaction in addition to pyrrole **1a**. This other major product was thus being removed during the recrystallization process to give pure samples of the more crystalline 2-aminopyrrole, which is perhaps why the byproduct has not been detected previously. To isolate

Scheme 1. Synthesis of 2-aminopyrroles (**1a–f**), 5-hydroxy-γ-lactams (**3a–f**), and 5-methylene-γ-lactam (**4e**).



R:	Yield **1**	Yield **3**
a: -CH_2Ph	10	30
b: -CH_2Ph(4-F)	19	29
c: -CH_2Ph(2-Cl)	11	31
d: -CH_2Ph(2-Br)	13	33
e: -CH_2CH_2Ph	-	32
f: -$(CH_2)_3CH_3$	-	34

both products, we instead purified a crude product mixture by column chromatography. This gave 2-aminopyrrole **1a**, eluting from the column first, in 10% yield, followed by the second more polar product in a higher 30% yield. As discussed in the succeeding text, this second/major product was eventually determined to be 5-hydroxylactam **3a**. We next repeated the reaction with other primary amines, and these reactions also gave the corresponding 5-hydroxylactam (**3b–f**) as the major product (29–34% yield), with the classical 2-aminopyrroles (**1b–d**) also obtained in lower 10–19% yield. Curiously, we were only able to obtain pure 2-aminopyrrole when using benzylamines in the synthesis. When phenethylamine or butylamine was used, the 2-aminopyrrole (**1e–f**) was formed in even lower amounts and we were unable to obtain pure samples via chromatography (as pronounced darkening of the silica gel column typically occurred during the chromatography, it is possible that some decomposition of these 2-aminopyrroles may have taken place during the purification process).

The 5-hydroxylactams (**3a–f**) were identified by IR and NMR spectroscopy and combustion analysis. A key indicator of structure was the presence of both a carbonyl and OH absorbance in the IR spectrum. Also, hydroxylactam **3e** is a known compound, having been previously prepared by a different cyclization route [14]. Our product assignment for hydroxylactams **3** is thus confirmed by comparison with literature data for **3e**. The other hydroxylactams (**3a–d, 3f**) and 2-aminopyrroles (**1b–e**) prepared here are each novel.

Hydroxylactam **3** is apparently formed by air oxidation of intermediate lactam **2**, which, in turn, is most likely formed by cyclization of the amino group of the α-aminoketone onto the ester of methyl cyanoacetate (instead of cyclization onto the cyano group to give aminopyrrole **1**). Although we have not observed lactam **2** by any means, such by TLC, its formation is mechanistically sound and the air oxidation of such an intermediate to give **3** is consistent with the oxidation of other pyrrole type compounds at the 5-position to give 5-hydroxy-γ-lactams [15], with oxidation to similar hydroxylated pyrroles by air also known [16,17].

As might be expected, hydroxylactam **3a** was formed in only negligible/trace amounts when tert-butyl cyanoacetate was used in our synthesis instead of the methyl ester (using our modified conditions). In this case, the known 2-aminopyrrole [2] with the tert-butyl ester at the 3-position was the only significant product formed based on our TLC analysis of the crude reaction mixture (benzylamine was used as the amine), with that product being isolated in 42% yield following chromatography (pronounced darkening also occurred during the chromatography, again suggesting some decomposition of the 2-aminopyrrole on the column). The lack of formation of the 5-hydroxylactam product **3a** in this reaction indicates that the cyclization predominantly occurred via attack of the cyano group by the amine, with very little to no attack of the tert-butyl ester. The greater selectivity for the cyclization step when using tert-butyl cyanoacetate (or malononitrile, cyanomethylsulfonyls, etc) helps explain why yields for those 2-aminopyrroles are usually higher than for those containing a methyl ester.

Finally, as the known 5-hydroxylactam **3e** has previously been dehydrated to the 5-methylene-γ-lactam using formic acid [14], we attempted this reaction in order to further confirm our structure assignment for lactams **3**. However, we used thionyl chloride as reagent (in refluxing acetonitrile) instead of formic acid. This reaction readily gave the dehydrated 5-methylene-γ-lactam product **4e** in 78% yield (Scheme 1).

CONCLUSION

In conclusion, we have shown that a classical, multicomponent 2-aminopyrrole synthesis yields 5-hydroxy-γ-lactams as the major product when methyl cyanoacetate is used as the activated CH_2CN compound. The classical 2-aminopyrrole is also formed, but as a minor product (in negligible amount in some cases). One 5-hydroxy-γ-lactam was subsequently dehydrated to the known 5-methylene-γ-lactam using thionyl chloride in good yield.

EXPERIMENTAL

General. Melting points were obtained using a digital Mel-Temp apparatus and are uncorrected. IR spectra were obtained using attenuated total reflection. NMR were recorded on a Bruker 300 Avance instrument using DMSO-d_6 as solvent, with signals referenced to the residual DMSO-d_6 peaks (2.49 ppm for ^{1}H NMR, 39.5 ppm for ^{13}C NMR). Elemental analyses were performed by Atlantic Microlab in Norcross, GA. Distilled hexanes was used for chromatography.

General procedure for synthesis of pyrroles (1a–d) and 5-hydroxylactams (3a–f). Acetoin (3-hydroxy-2-butanone, finely ground) (20 mmol) and the primary amine (20 mmol) were combined in a 50 mL round-bottom flask and heated on a hotplate until the mixture dissolved and a homogenous yellow liquid was obtained (~1–2 min of heating; the water vapor that condensed in the neck of the flask was removed using a chemwipe). Absolute EtOH (7–8 mL) was then added followed by methyl cyanoacetate (20 mmol) and the solution was heated at reflux (open condenser) for 2 h. The darkened solution was then diluted with water and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and then evaporated onto silica gel (high vacuum). Column chromatography (SiO_2) of the mixture eluting with a gradient of hexanes:EtOAc (~10:1 to 1:1) gave, after concentration of pure fractions *in vacuo*, the 2-aminopyrrole (usually as a solid) followed by the 5-hydroxylactam (usually as an oil), with yields given in Scheme 1 (yields for pyrroles **1e–f** were negligible and these could not be obtained in pure form). Analytical samples of the isolated pyrroles **1a–d** were obtained by recrystallization from MeOH. Crystalline samples of the 5-hydroxylactams **3a–f** were generally obtained by slow evaporation from diethyl ether, diethyl ether/hexanes, or toluene/cyclohexane.

DATA FOR PYRROLES (1A–D):

2-Amino-1-benzyl-3-methoxycarbonyl-4,5-dimethylpyrrole (1a). This compound was obtained as a tan fluffy solid, mp 138–140°C (Lit mp: 138–139°C) [2].

2-Amino-1-(4-fluorobenzyl)-3-methoxycarbonyl-4,5-dimethylpyrrole (1b). This compound was obtained as a colorless fine crystalline solid, mp 138–139°C; IR (cm^{-1}): 3428, 3322, 2919, 1641, 1606, 1501, 1447, 1359, 1306, 1255, 1227, 1108, 1094, 810, 781; ^{1}H NMR: 1.84 (s, 3H), 1.99 (s, 3H), 3.62 (s, 3H), 4.96 (s, 2H), 6.00 (s, 2H), 6.99–7.04 (m, 2H), 7.10–7.17 (m, 2H); ^{13}C NMR: 9.4, 11.8, 44.3, 50.1, 91.4, 111.4, 115.7 (d, J = 21 Hz), 117.7, 128.6 (d, J = 8.3 Hz), 134.5 (d, J = 3.0 Hz), 147.3, 161.7 (d, J = 240 Hz), 166.6. *Anal*. Calcd. for $C_{15}H_{17}FN_2O_2$ (276.31): C, 65.20; H, 6.20; N, 10.14. Found: C, 65.20; H, 6.32; N, 10.09.

2-Amino-1-(2-chlorobenzyl)-3-methoxycarbonyl-4,5-dimethylpyrrole (1c). This compound was obtained as a pale yellow fluffy solid, mp 159–161°C; IR (cm^{-1}): 3421, 3321, 2926, 1645, 1611, 1523, 1499, 1439, 1300, 1250, 1106, 1070, 781, 749; ^{1}H NMR: 1.80 (s, 3H), 2.03 (s, 3H), 3.64 (s, 3H), 5.01 (s, 2H), 6.02 (s, 2H), 6.33–6.36 (m, 1H), 7.25–7.29 (m, 2H), 7.46–7.49 (m, 1H); ^{13}C NMR: 8.6, 11.4, 42.7, 49.6, 90.9, 111.1, 117.1, 126.4, 127.5, 128.6, 129.2, 131.0, 135.0, 147.1, 166.1. *Anal*. Calcd. for $C_{15}H_{17}ClN_2O_2$ (292.76): C, 61.54; H, 5.85; N, 9.57. Found: C, 61.37; H, 5.87; N, 9.42.

2-Amino-1-(2-bromobenzyl)-3-methoxycarbonyl-4,5-dimethylpyrrole (1d). This compound was obtained as a pale yellow fluffy solid, mp 159–160°C; IR (cm^{-1}): 3424, 3326, 2926, 1646, 1607, 1501, 1438, 1300, 1251, 1105, 1028, 781, 748; ^{1}H NMR: 1.79 (s, 3H), 2.03 (s, 3H), 3.64 (s, 3H), 4.95 (s, 2H), 6.00 (s, 2H), 6.31 (d, J = 8.0 Hz, 1H), 7.18–7.21 (t, 1H), 7.28–7.31 (t, 1H), 7.63 (d, J = 7.5 Hz, 1H); ^{13}C NMR: 8.6, 11.4, 45.2, 49.7, 90.9, 111.2, 117.0, 121.1, 126.5, 128.1, 129.0, 132.4, 136.4, 147.1, 166.1. *Anal*. Calcd. for $C_{15}H_{17}BrN_2O_2$ (337.21): C, 53.43; H, 5.08; N, 8.31. Found: C, 53.40; H, 5.11; N, 8.18.

DATA FOR 5-HYDROXY-γ-LACTAMS (3A–F)

1-Benzyl-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile (3a). This compound was obtained as pale pink/colorless crystals, mp 96–97°C (toluene/cyclohexane); IR (cm^{-1}): 3397, 3063, 3036, 2985, 2933, 2235, 1684, 1414, 1154, 737, 698; ^{1}H NMR: 1.27 (s, 3H), 2.20 (s, 3H), 4.35 (d, J = 16 Hz, 1H), 4.59 (d, J = 16 Hz, 1H), 6.62 (s, 1H), 7.21–7.31 (m, 5H); ^{13}C NMR: 12.7, 22.3, 41.6, 89.8, 107.0, 112.4, 126.9, 127.3, 128.2, 138.1, 162.8, 175.9. *Anal*. Calcd. for $C_{14}H_{14}N_2O_2$ (242.27): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.51; H, 5.83; N, 11.67.

1-(4-Fluorobenzyl)-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile (3b). This compound was obtained as colorless crystals (diethyl ether), mp 100–101°C; IR (cm^{-1}): 3352, 3007, 2991, 2940, 2933, 2231, 1687, 1672, 1604, 1509, 1404, 1225, 1151, 1096, 856, 775, 760; ^{1}H NMR: 1.26 (s, 3H), 2.17 (s, 3H), 4.32 (d, J = 16 Hz, 1H), 4.52 (d, J = 16 Hz, 1H), 6.63 (s, 1H), 7.08–7.13 (m, 2H), 7.30–7.34 (m, 2H); ^{13}C NMR: 12.7, 22.3, 41.0, 89.9, 107.0, 112.5, 115.0 (d, J = 22 Hz), 129.5 (d, J = 8.3 Hz), 134.3 (d, J = 2.3 Hz), 161.3 (d, J = 241 Hz), 162.8, 176.0. *Anal*. Calcd. for $C_{14}H_{13}FN_2O_2$ (260.27): C, 64.61; H, 5.03; N, 10.76. Found: C, 64.50; H, 5.06; N, 10.72.

1-(2-Chlorobenzyl)-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile (3c). This compound was obtained as pale golden crystals, mp 143–144°C (diethyl ether); IR (cm^{-1}): 3235, 2988, 2232, 1678, 1432, 1394, 1163, 1050, 1038, 949, 746; ^1H NMR: 1.30 (s, 3H), 2.22 (s, 3H), 4.51 (s, 2H), 6.65 (s, 1H), 7.23–7.30 (m, 3H), 7.41–7.45 (m, 1H); ^{13}C NMR: 12.7, 21.9, 39.3, 89.8, 107.0, 112.4, 127.2, 128.5, 128.7, 129.1, 131.4, 134.7, 162.9, 176.0. *Anal*. Calcd. for $C_{14}H_{13}ClN_2O_2$ (276.72): C, 60.77; H, 4.74; N, 10.12. Found: C, 60.60; H, 4.87; N, 10.04.

1-(2-Bromobenzyl)-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile (3d). This compound was obtained as a fine golden crystalline solid, mp 154–156°C (diethyl ether); IR (cm^{-1}): 3253, 2988, 2232, 1674, 1436, 1393, 1162, 1028, 950, 744; ^1H NMR: 1.31 (s, 3H), 2.24 (s, 3H), 4.49 (s, 2H), 6.68 (s, 1H), 7.19–7.25 (m, 2H), 7.32–7.37 (m, 1H), 7.61 (d, J = 7.8 Hz, 1H); ^{13}C NMR: 12.7, 21.9, 41.9, 89.7, 106.9, 112.4, 121.6, 127.7, 128.4, 128.9, 132.3, 136.2, 162.9, 176.0. *Anal*. Calcd. for $C_{14}H_{13}BrN_2O_2$ (321.17): C, 52.36; H, 4.08; N, 8.72. Found: C, 52.34; H, 4.05; N, 8.62.

5-Hydroxy-4,5-dimethyl-2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonitrile (3e). This compound was obtained as a pale orange crystalline solid, mp 136–137°C (diethyl ether); IR (cm^{-1}): 3262, 3020, 2996, 2940, 2232, 1681, 1416, 1158, 1103, 753, 701; ^1H NMR: 1.32 (s, 3H), 2.17 (s, 3H), 2.88 (t, 2H), 3.49 (t, 2H), 6.53 (s, 1H), 7.17–7.33 (m, 5H); ^{13}C NMR: 12.6, 21.7, 34.5, 89.7, 106.9, 112.4, 126.2, 128.4, 128.6, 139.0, 162.3, 175.6 (one signal obscured by DMSO peaks). *Anal*. Calcd. for $C_{15}H_{16}N_2O_2$ (256.30): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.36; H, 6.19; N, 10.94.

1-Butyl-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile (3f). This compound was obtained as golden micro-needles, mp 76–78°C (diethyl ether/hexanes); IR (cm^{-1}): 3324, 2961 2875, 2231, 1688, 1449, 1409, 1375, 1153, 1095, 766; ^1H NMR: 0.87 (t, 3H), 1.27 (m, 2H), 1.39 (s, 3H), 1.52 (m, 2H), 3.14 (m, 1H), 3.26 (m, 1H), 6.44 (s, 1H); ^{13}C NMR: 12.6, 13.7, 19.8, 21.9, 30.7, 38.3, 89.8, 107.0, 112.6, 162.2, 175.4. *Anal*. Calcd. for $C_{11}H_{16}N_2O_2$ (208.26): C, 63.44; H, 7.74; N, 13.45. Found: C, 63.28; H, 7.61; N, 13.18.

DEHYDRATION OF LACTAM 3E TO 5-METHYLENE-γ-LACTAM 4E

4-Methyl-5-methylene-2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonitrile (4e). To a solution of 5-hydroxylactam **3e** (0.256 g, 1.0 mmol) in dry acetonitrile (5 mL) was added thionyl chloride (0.1 mL, 1.37 mmol) and the mixture was refluxed for 40 min. The darkened solution was then concentrated *in vacuo* to a brown oil, which was dissolved in EtOAc and washed with sodium bicarbonate solution. The solution was then dried (Na_2SO_4) and evaporated onto silica gel (high vacuum). Column chromatography (SiO_2) eluting with hexanes:EtOAc (2:1) gave, after concentration of pure fractions, the product as a yellow/brown solid (0.185 g, 78%), mp 128–129°C. Recrystallization from EtOH/water gave an olive green solid, mp 130–131°C (Lit mp: 130–131°C) [14]. A second recrystallization from a larger volume of hexanes gave fine yellow crystals, mp 131–133°C; IR (cm^{-1}): 3058, 3009, 2968, 2939, 2225, 1715, 1633, 1612, 1354, 1190, 1129, 865, 760, 706, 640; ^1H NMR: 2.32 (s, 3H), 2.78 (t, 2H), 3.79 (t, 2H), 5.48 (d, J = 2.9 Hz, 1H), 5.51 (d, J = 2.9 Hz, 1H), 7.18–7.26 (m, 5H); ^{13}C NMR: 12.0, 33.5, 40.6, 101.8, 105.8, 112.4, 126.3, 128.2, 128.7, 138.1, 143.4, 158.9, 163.2. This reaction could also be accomplished in comparable yield using $POCl_3$.

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