A Convenient Synthesis of 2-(3-Methyl-2,5-dioxopyrrolidin-1-yl)benzoic Acid

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Abstract: A new procedure for the synthesis of 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoic acid (3) is reported via hydrogenation of 2-(3-methyl-2,5-dihydropyrrol-1-yl)benzoic acid (9) that in turn is available from fusion of anthranilic acid with citraconic anhydride. This method provides cleaner material in higher overall yield than that obtained using previously reported methods.

Key words: amines, acids, anhydrides, hydrogenation, alkaloids

Diterpenoid alkaloids derived from Delphinium and Acnonitum species constitute a structurally diverse class of biologically active natural products with a long history of use as medicines, poisons, and insecticides.1 Methylycalconitine (MLA, 1) is the principal toxic component isolated from Delphinium browni and is found in at least 30 Delphinium species.2 Both its insecticidal action and its toxicity are attributed to nicotinic acetylcholine receptor (nAChR) antagonism. At one subset of nAChR, namely α-bungarotoxin-sensitive nAChR, MLA (1) is the most potent small molecule competitive antagonist yet reported. Structure activity studies on MLA (1) have shown the N-substituted anthranilate ester moiety to be an essential structural feature for pharmacological activity.3 A dramatic example of the importance of this structural unit for biological activity is given by comparison of methyllycalconitine (1), and its parent alkaloid lycoctonine (2) (Figure 1). In competitive ligand binding studies at neuronal nicotinic acetylcholine receptors, MLA (1) containing the 2-(3-methyl-2,5-dioxopyrrolidinyl)benzoate sidechain, displays ca. 10³ times more potent inhibition of α-bungarotoxin binding than its unsubstituted counterpart 2.4

The N-substituted anthranilate ester moiety is an essential structural feature for the observed insecticidal activity of MLA (1), therefore evaluation of simpler compounds related to MLA (1) that incorporate this moiety is an area of on-going research by several research groups5–9 including ours.10 The most attractive method for attachment of the biologically important N-substituted anthranilate ester pharmacophore involves direct addition of the entire 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate group to the alkaloid framework by esterification of an alcohol with 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoic acid (3). Kraus and Dnevprovaia9 successfully esterified primary alcohols with acid 3 by intial formation of the acid chloride. For more hindered alcohols the sodium salt of the acid 3 was treated with the mesylate derivative of the alcohol.5a Bergmeier et al.5a have also reported the successful esterification of acid 3 using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate. A convenient synthesis of acid 3 is therefore of prime importance for the conversion of alkaloids like lycoctonine (2) to more potent N-substituted anthranilate derivatives such as MLA (1).

Scheme 1 Reagents and conditions: a) 5 (1.0 equiv), 4 (1.0 equiv), 125 °C, 3 h, 3 (10% isolated yield); b) 5 (1.0 equiv), 4 (1.0 equiv), Et3N, reflux, complex mixture of 3, 6 and 7
During the course of our studies towards the synthesis of simple analogues of MLA (1)\(^\text{10}\) we required substantial quantities of acid 3. Kraus and Dneprovskai\^a\(^\text{9}\) synthesized acid 3 using the method described by Kumar and co-workers (Scheme 1).\(^\text{11}\) Following this procedure equimolar amounts of anthranilic acid (4) and methylsuccinimide anhydride (5) were fused together for 24 h at 125 °C without solvent. After workup, the desired acid 3 was obtained in 10% yield as a sticky, pale foam.

The high resolution mass spectrum of the product obtained in this manner was correct for the desired molecular formula C\(_{12}\)H\(_{11}\)NO\(_4\). The IR spectrum of the acid 3 showed a broad absorbance at 3078 cm\(^{-1}\) due to the hydroxyl group of the carboxylic acid together with a carboxyl stretch at 1713 cm\(^{-1}\) due to the amide and acid groups. Importantly, a weak absorbance at 1774 cm\(^{-1}\) indicated that a cyclic imide had formed. The \(^1\)H NMR spectrum of the acid 3 exhibited a broad three proton doublet at \(\delta = 1.43\) (\(J = 6.9\) Hz) which was assigned to the 3′-methyl group. A one proton multiplet at \(\delta = 2.50–2.57\) was assigned to 3′-H, whilst a two proton multiplet at \(\delta = 3.07–3.15\) was assigned to the 4′-methylene protons. The broadening of the resonances on the cyclic imide ring has been proposed to arise due to hindered rotation of the imide ring around the aromatic–nitrogen bond (C2–N) due to steric hindrance of the two imide carbonyls.\(^\text{6,8}\) It was noticeable in the \(^1\)H NMR spectrum that trace amounts of the ring-opened diacids 6 and 7 were also present along with the desired product 3. It was also noted that a slightly impure sample of acid 3 underwent hydrolysis (ca. 50% conversion) to diacids 6 and 7 when left to stand in air for 48 hours.

Using the method of Jacyno and co-workers\(^\text{12}\) equimolar amounts of anthranilic acid (4), methylsuccinimide anhydride (5) and triethylamine were heated under reflux using a Dean–Stark apparatus. After workup the \(^1\)H NMR spectrum showed that a complex mixture of diacids 6 and 7 together with acid 3 had formed. Due to the low yield of the desired acid 3 obtained using these reported methods, an alternative synthesis of acid 3 was investigated. It was envisaged that fusion of citraconic anhydride (8) with anthranilic acid (4) might form the desired cyclic imide 9 in greater yield due to the presence of the cis double bond in the five-membered cyclic imide. Hydrogenation of 9 would then afford the desired acid 3 (Scheme 2).

To this end anthranilic acid (4) and citraconic anhydride (8) were fused together for 20 hours at 120–140 °C. The crude reaction mixture was then dissolved in hot ethyl acetate, cooled and washed with 1 M hydrochloric acid and water. Evaporation of the solvent afforded unsaturated acid 9 in 95% yield. The high resolution mass spectrum of the product thus obtained, exhibited a molecular ion at \(m/z = 231.05328\), which was correct for the desired molecular formula C\(_{12}\)H\(_9\)NO\(_4\). The IR spectrum exhibited a strong absorbance at 1713 cm\(^{-1}\) assigned to the acid and amide carbonyl groups whilst the weak absorbance at 1784 cm\(^{-1}\) showed that the cyclic imide had formed. The \(^1\)H NMR spectrum of the product 9 exhibited a three proton doublet at \(\delta = 2.17\) (\(J = 1.8\) Hz) assigned to the 3′-methyl group whilst a one proton quartet at \(\delta = 6.51\) (\(J = 1.8\) Hz) was assigned to 4′-H. The four aromatic resonances at \(\delta = 7.32, 7.52, 7.69\) and 7.79 were assigned to the 3-H, 5-H, 4-H and 6-H, respectively. Importantly the \(^1\)H NMR spectrum indicated that no ring-opened product was present.

Hydrogenation of unsaturated acid 9 was achieved by stirring a solution of acid 9 in methanol with 10% palladium on charcoal, under a balloon of hydrogen gas for 3 days. Filtration of the reaction mixture through Celite followed by evaporation of the solvent afforded the desired acid 3 in quantitative yield. The \(^1\)H and \(^{13}\)C NMR spectra of the product obtained in this manner was identical to an authentic sample. In this case no trace of the undesired diacids 6 and 7 was observed. It was noted that acid 3, although obtained pure after the hydrogenation step, underwent slow decomposition to diacids 6 and 7, therefore acid 3 was used immediately after its preparation.

The synthesis of acid 3 reported herein offers significant advantages in terms of the yield obtained in the imide-forming step and the lack of undesired ring-opened byproducts that complicate subsequent purification.

Melting points were determined using a Reichert heating stage with microscope or a Kofler hot stage apparatus, and are uncorrected. IR absorption spectra were obtained using a Perkin-Elmer 1600 series FTIR spectrometer as a thin film on NaCl plates. \(^1\)H NMR spectra were recorded on a Bruker AC 200B (200.13 MHz) or Bruker AMX 400 (400.13 MHz) spectrometer at ambient temperature. \(^{13}\)C NMR spectra were recorded on a Bruker AC 200B (50.3 MHz) or Bruker AMX 400 (100.4 MHz) spectrometer. Spectra were recorded in CDCl\(_3\) unless otherwise stated. The chemical shifts are reported relative to CHCl\(_3\) (\(\delta = 7.26\) and 77.0). Determination of \(^{13}\)C multiplicty was aided by DEPT 135 and DEPT 90 experiments. Low resolution mass spectra were recorded on an AEI model Kratos MS50 double focusing mass spectrometer with an accelerating voltage of 8000V using electron ion impact ionization at 70 eV. High resolution mass spectra were recorded at a nominal resolution of 8000 to 9000.

\(\text{Scheme 2} \quad \text{Reagents and conditions: a) } 8 \text{ (1.0 equiv)}, 4 \text{ (1.0 equiv), } 120–140 °C, 20 h; \text{ b) } H_2, 10\% \text{ Pd/C, MeOH, } 3 \text{ d} \)
2-(3-Methyl-2,5-dioxopyrrol-1-yl)benzoic Acid (9)  
Anthrаниlic acid (4; 2.4 g, 17.8 mmol) and citraconic anhydride (8; 2 g, 17.8 mmol) were heated together without solvent at 140 °C for 20 h. After this time, the hot crude mixture was dissolved in EtOAc (30 mL) with stirring and allowed to cool to r.t. The solution was then washed withaq 1 M HCl (20 mL), H₂O (20 mL), and brine (20 mL). The organic layer was dried (Na₂SO₄) and the solvent was removed in vacuo to yield the title compound 9 (3.87 g, 95%) as a pale oil.

IR (film): 3078 (OH), 1774 (N–C=O), 1713 (C=O) cm⁻¹.

EI-MS: m/z (%) = 231 (M⁺, 100), 214 (M–OH, 4), 187 (M–CO₂H, 63), 42 (100).

References

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