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Synthesis of new polyfunctional 2-pyrrolidinones from methyl 2-(carboethoxyhydroxymethyl)acrylate

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Abstract—The synthesis of new polyfunctional 2-pyrrolidinone derivatives from methyl 2-(carboethoxyhydroxymethyl)acrylate is described. These alkenes present an extremely high reactivity upon Michael addition with primary amines leading to a simple, mild, and efficient route to the preparation of new polyfunctional pyrrolidinones.

2-Pyrrolidinones have attracted a great amount of interest over the last decade. Many are optically active and have found applications ranging from biology to biochemistry to pharmaceutics.[1–5] The formation of 2-pyrrolidinones from itaconic acid derivatives is a viable approach that has been widely used in the past. For example, racemic 1-benzyl-3-alkyl-4-methoxycarbonyl-2-pyrrolidinones were prepared from β-alkylated itaconates and benzylamine through a conjugate addition–lactamization sequence.[6] (*S*)-(−)-4-Methoxycarbonyl-2-pyrrolidinone was also synthesized by Wyatt et al. starting from itaconic acid and (*S*)-(−)-1-phenylethylamine.[7] Finally, Valentin et al. have reported the formation of aza analogs of paraconic acid methyl ester starting with dimethyl itaconate.[8] Herein, we report new polyfunctional pyrrolidinones derivatives obtained via Michael addition reaction of aliphatic primary amine with methyl 2-(carboethoxyhydroxymethyl)acrylate, which in turn was obtained by the Baylis–Hillman pathway from commercial acrylate.

Methyl 2-(carboethoxyhydroxymethyl)acrylate was first synthesized via the Baylis–Hillman pathway following previously reported literature[9] (Fig. 1).[10] It was noticed that the reaction, slightly exothermic, was essentially complete after 30 min. A change in color was also noticed during the course of the reaction, with color disappearing in the final product isolated by vacuum distillation. The disappearance of the ^{13}C NMR resonance peaks for the acrylate vinyl carbons and the appearance of a new peak corresponding to the new carbon with an alcohol substituent allowed monitoring the course of the reaction.

Prior to the preparation of pyrrolidinone derivatives from the corresponding alkyl 2-(carboethoxyhydroxymethyl)acrylate, we were interested in studying the kinetics of the reaction between the activated alkenes and aliphatic primary amines such as *n*-hexylamine. The reaction between **1** and *n*-hexylamine was carried out at room temperature in chloroform under dilute conditions (5 wt %) and monitored with real time FT-IR. The disappearance of the carbon–carbon stretching bond at 1643 cm^{-1} corresponding to the alkene double bond, and appearance of the amide carbonyl peak at 1695 cm^{-1} of the pyrrolidinone compound was very fast even under such dilute conditions. Cyclization could be monitored by NMR spectroscopy where the appearance of peaks corresponding to ethanol release was recorded, and 90% conversion was reached after only 2 h. ^{1}H and ^{13}C NMR were also used to confirm pyrrolidinone formation and no trace of the Michael adduct intermediate could be detected upon analysis of the product spectra.

The same reaction was carried out with dimethyl itaconate, a commercially available analog, under the same conditions. It was found that alkyl 2-(carboethoxyhydroxymethyl)acrylates reacted orders of magnitude faster

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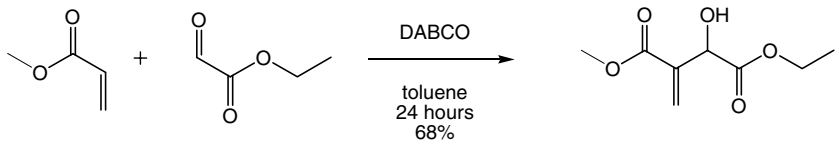

Figure 1. Synthesis of methyl 2-(carboethoxyhydroxymethyl)acrylate **1**.

than the commercially available analog. It is believed that the presence of the secondary hydroxyl group attached to the carbon α to the vinyl may induce hydrogen bonding that leads to preorganization of molecules in the system. This may also activate both the adjacent alkene and the saturated ester carbonyl of the molecule by intramolecular and intermolecular hydrogen bonding.

This unique combination of intra- and intermolecular hydrogen bonding allowed to prepare methyl 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate **2** in a fast and efficient manner by reaction of methyl 2-(carboethoxyhydroxymethyl)acrylate with 1 equiv of *n*-hexylamine.[11]

Carboxylic acid-containing 2-pyrrolidinone derivatives are interesting compounds that may exhibit interesting properties like their naturally occurring oxygen analogs, which are generally known as paraconic acids. Such compounds possess important biological properties.[12]

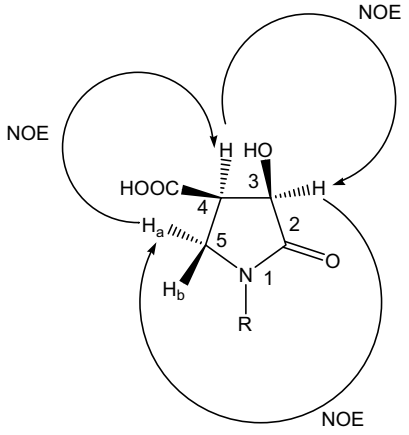

Figure 2. NOE correlations.

Among these numerous compounds, (−)-methylenolactocin,[13] isolated from the culture filtrate of *Penicillium* sp., shows antitumor and antibiotic activity; protolichesterinic acid,[14] isolated from several species of moss *Cetraria*, is an antitumor and antibacterial compound; while (−)-phaseolinic acid[15] is a metabolite of a fungus, *Macrophomina phaseolina*. We decided then to form the carboxylic acid analog of methyl 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate **2** by forming first the sodium carboxylate using 1 equiv of sodium hydroxide in water. Precipitation in cold acetone allowed isolation of the salt in quantitative yield. Treatment of the salt dispersion in acetone with dilute hydrochloric acid led to 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylic acid **3** as a 31:68 mixture of two diastereoisomers (**3a** an **3b**). Separation of the two stereoisomers composing the product mixture was achieved by reprecipitation from acetone at −15 °C over 2 days.[16]

NMR spectroscopy and elemental analysis confirmed compound structure. DEPT and gHMBC experiments allowed accurate assignment of the NMR spectra peaks. The stereochemistry of the newly created diastereoisomers **3a** and **3b** was established by their NOESY spectra in which the strong NOEs between H-3, H-4, H_a-5, and H_b-5 were studied (Fig. 2). The NOE spectra of separated diastereoisomers showed a 3.2% enhancement of H-3 proton for the trans isomer while this enhancement was 9.7% for the cis isomer. Thus, we concluded that the stereochemistry of **3a** and **3b** are of the cis and trans configurations, respectively (Fig. 3). ^{13}C NMR spectra of both isomers are shown in Figure 4.

We were interested finally in a subsequent preparation of a methacrylate-based monomer that incorporates a substituted 2-pyrrolidinone group. Such a monomer could be polymerized via free radical polymerization methods and could potentially confer enhanced mechanical properties, such as adhesion, to various copolymers

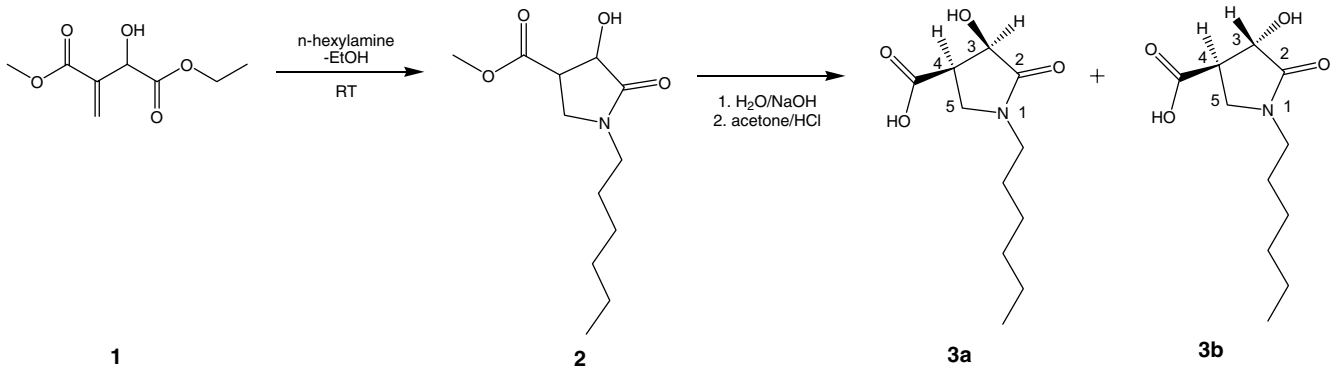

Figure 3. Synthesis of 2-pyrrolidinones **3a** and **3b**.

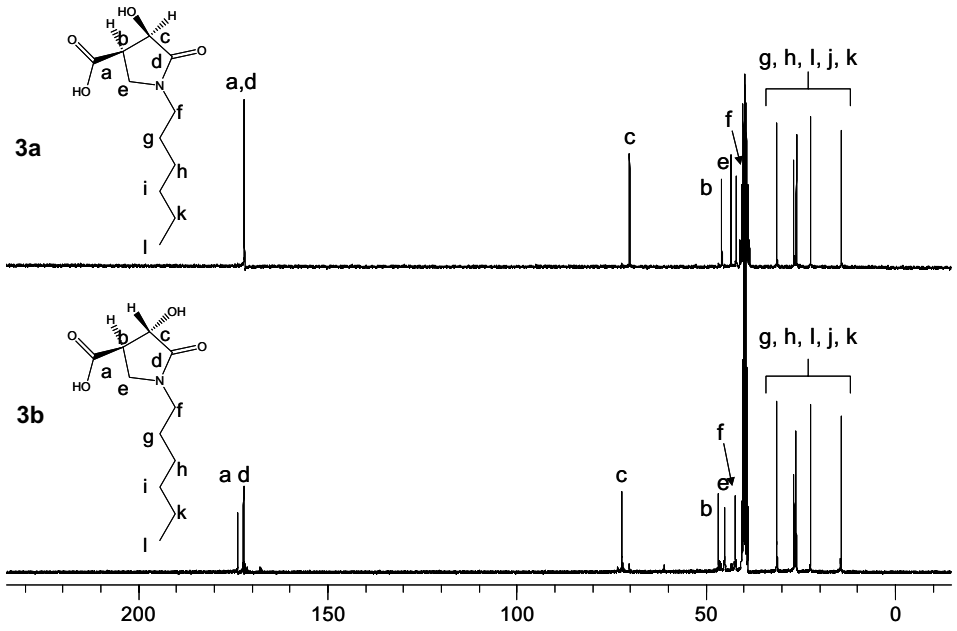

Figure 4. ^{13}C NMR spectra of 2-pyrrolidinones **3a** and **3b** (DMSO-d_6).

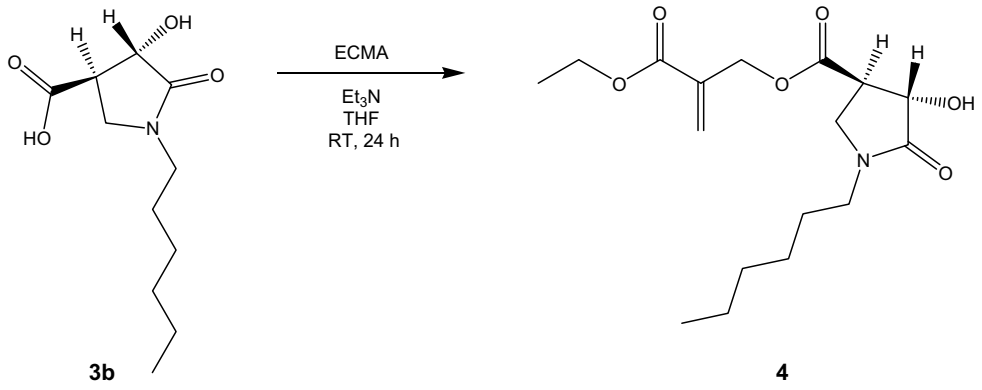

Figure 5. Synthesis of 2-pyrrolidinone-containing monomer **4**.

formed. Ethyl α-(chloromethyl) acrylate (ECMA) was reacted with both isomers individually in the presence of triethylamine in tetrahydrofuran and at room temperature to form the corresponding methacrylate derivative. We found that the reaction would only proceed with **3b** while the same reaction (Fig. 5) carried out with **3a** in DMSO did not lead to any product formation.[17] It is believed that the molecular conformation has a strong effect on its reactivity, as demonstrated by this surprising difference in behavior. The polymerization of this monomer is currently being investigated.

In conclusion, we have demonstrated that multifunctional 2-pyrrolidinone derivatives can easily be synthesized by means of a fast and efficient Michael addition/cyclization reaction involving methyl 2-(carboethoxyhydroxymethyl)acrylate and aliphatic primary amine. Subsequent separation of the two diastereoisomers was achieved by simple recrystallization from acetone, opening up potential exploration of these new heterocycles for application in the synthesis of natural product analogs and new biologically active monomers and polymers.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.122.

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10. Procedure for the synthesis of methyl 2-(carboethoxyhydroxymethyl)acrylate **1**: Ethyl glyoxylate, 50 wt % in toluene (20.39 g, 199.7 mmol), DABCO (3.64 g, 32.4 mmol) and methyl acrylate (199.7 mmol) were added to a 250 mL round-bottomed flask. The mixture was stirred at room temperature for 2 h. The crude solution was then concentrated under reduced pressure. The resulting mixture was washed with three aliquots of saturated sodium chloride solution followed by three aliquots of dionized water. The organic phase was then dried over a bed of sodium sulfate; vacuum distillation of the residue gave the corresponding methyl 2-(carboethoxyhydroxymethyl)acrylate **1** as a clear liquid; bp 135–137 °C (20 mm Hg); in ca. 68% yield (isolated yield).
    Methyl 2-(carboethoxyhydroxymethyl)acrylate **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, $-CH_3$), 3.68 (s, H, –OH), 3.78 (s, 3H, $-OCH_3$), 4.26 (q, 2H, $-CH_2CH_3$), 4.88 (s, H, –CHOH), 5.96 and 6.37 (s, 2H, $-CH_2{=}C$); ^{13}C NMR ($CDCl_3$) δ 14.04 ($-CH_3$), 52.12 ($-OCH_3$), 62.20 ($-CH_2CH_3$), 71.19 (–CHOH), 128.96 ($CH_2{=}C$), 138.08 ($C{=}CH_2$), 165.68 and 172.30 (C=O). FT-IR (NaCl, cm^{-1}) 3515, 2996, 1739, 1643, 1446, 1097, 823. Anal. Calcd for $C_8H_{15}O_5{\cdot}0.25H_2O$: C, 50.59; H, 6.49. Found: C, 50.28; H, 6.28.
11. Procedure for the preparation of methyl 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate **2**: 2-pyrrolidinone **2** was synthesized by adding **1** (10 g, 53.14 mmol) to a 50 mL tube equipped with an argon gas inlet. The reaction tube was then purged with argon for 30 min and sealed with a rubber septum. *n*-Hexylamine (5.47 g, 54.21 mmol) was then added dropwise and the resulting solution was allowed to stir at room temperature under argon blanket. Upon reaction completion, monitored by ^{1}H NMR, the solvent was removed under reduced pressure. The concentrated crude product was purified by column chromatography using an ethyl acetate/hexanes mixture (2:10) as eluent. The resulting product fraction was then concentrated under reduced pressure to afford methyl 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate **2** as a mixture of two diastereoisomers (A and B) in ca. 98% yield.
    Methyl 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate **2**: brown liquid; dr 42:58; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $-CH_3$), 1.28 (m, 2H, $-CH_2$), 1.52 (m, 2H, $-CH_2CH_2N$), $3.74_{(A)}$ and $3.77_{(B)}$ (s, 3H, $-CH_3$), $4.59_{(A)}$ and $4.60_{(B)}$ (d, H, –CHOH); ^{13}C NMR ($CDCl_3$) δ $14.17_{(A+B)}$ ($-CH_3$), $22.52_{(A+B)}$ ($-CH_2CH_3$), 26.38 and 26.85 ($-CH_2CH_2CH_3$), 31.41 and 31.44 ($-CH_2CH_3$), 46.07 and 46.29 ($-CH_2N$), 43.07 and 45.62 ($-CHCH_2N$), 42.96 and 43.04 ($-CH_2N$), 52.16 and 52.53 ($-OCH_3$), 70.46 and 72.43 (–CHOH), 170.74 and 172.25 (C=O), 172.82 and 173.09 (NC=O). FT-IR (NaCl, cm^{-1}) 3363, 2958, 2935, 2866, 1741, 1695, 1278, 740. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.42; H, 8.71; N, 5.84.
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16. Procedure for the synthesis of 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylic acid **3**: Sodium hydroxide (0.5 g, 12.4 mmol) was dissolved in 10 mL of deionized water. Methyl 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate **2** (3 g, 12.33 mmol) was added dropwise to the previous solution. The resulting mixture was allowed to stir for 2 h. Upon reaction completion the salt was precipitated in acetone, filtered off and dried under reduced pressure. The resulting white powder was then dispersed in 20 mL of acetone and further treatment with dilute hydrochloric acid led to 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylic acid **3**. Further recrystallization in acetone led to 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylic acid diastereoisomer **3a** in ca. 22% yield, while removal of the solvent under reduced pressure, from the filtrate, led to 1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylic acid diastereoisomer **3b** in ca. 59% yield.
    1-Hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylic acid diastereoisomer **3a**. White solid (from cold acetone), mp 188 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (t, 3H, $-CH_3$), 1.21 (m, 2H, $-CH_2$), 1.40 (m, 2H, $-CH_2CH_2N$), 4.21 (d, H, –CHOH); ^{13}C NMR ($CDCl_3$) δ 14.32 ($-CH_3$), 22.47 ($-CH_2CH_3$), 26.19 ($-CH_2CH_2CH_3$), 31.35 ($-CH_2CH_3$), 43.46 ($-CH_2N$), 45.90 ($-CHCH_2N$), 40.66 ($-CH_2N$), 70.23 (–CHOH), 172.03 (C=O), 172.05 (NC=O). FT-IR (KBr, cm^{-1}) 3305, 2956, 2933, 2863, 1712, 1656, 1290, 948. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.27; H, 8.50; N, 6.00.
    1-Hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylic acid diastereoisomer **3b**. Brown oil, chromatographed on silica gel hex–EtOAc, ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, 3H, $-CH_3$), 1.23 (m, 2H, $-CH_2$), 1.41 (m, 2H, $-CH_2CH_2N$), 4.20 (d, H, –CHOH); ^{13}C NMR ($CDCl_3$) δ 14.31 ($-CH_3$), 22.44 ($-CH_2CH_3$), 26.23 ($-CH_2CH_2CH_3$), 31.29 ($-CH_2CH_3$), 45.19 ($-CH_2N$), 46.74 ($-CHCH_2N$), 42.25 ($-CH_2N$), 72.37 (–CHOH), 172.25 (C=O), 173.83 (NC=O). FT-IR (NaCl, cm^{-1}) 3353, 2904, 2902, 2869, 1727, 1711, 1654, 1273, 737. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.35; H, 8.33; N, 6.03.
17. Procedure for the synthesis of ethyl α-(1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate methyl) acrylate **4**: Compound **3b** (2 g, 8.73 mmol) and 150 ppm of hydroquinone were added to 20 mL of dry THF in a 50 mL round-bottomed flask. ECMA (1.29 g, 8.73 mmol) was then added dropwise to the previous solution and the resulting mixture was allowed to stir overnight at room temperature. Upon reaction completion, monitored by NMR, the precipitate was filtered off and the solvent removed under reduced pressure. Further purification via column chromatography (1:5—ethyl acetate–hexane) gave ethyl α-(1-hexyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate methyl) acrylate **4** as a brown oil in ca. 78% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $-CH_3$), 1.28 (m, 2H, $-CH_2$), 1.52 (m, 2H, $-CH_2CH_2N$), 4.25 (q, 2H, $-CH_2CH_3$), 4.59 (d, H, –CHOH), 4.91 (s, 2H, $-CH_2O$), 5.91 and 6.39 (s, 2H, CH_2=C); ^{13}C NMR ($CDCl_3$) δ 14.01 ($-CH_3$), 14.17 ($-CH_3$), 22.49 ($-CH_2CH_3$), 31.40 ($-CH_2CH_2CH_3$), 26.38 ($-CH_2CH_2CH_2N$), 26.93 ($-CH_2CH_2N$), 46.17 ($-CH_2N$), 43.07 ($-CHCH_2N$), 45.46 ($-CH_2N$), 61.12 ($-CH_2CH_3$), 63.34 ($-CH_2O$), 72.40 (–CHOH), 127.84 ($-CH_2$=C), 134.86 ($-CCH_2$), 165.04 and 171.11 (–C=O), 172.72 (–NC=O). FT-IR (NaCl, cm^{-1}) 3351, 2960, 2935, 2870, 1741, 1729, 1685, 1654, 1277, 819.