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Synthesis of Cyclic Hydroxamic Acids from Aliphatic Nitro Compounds#

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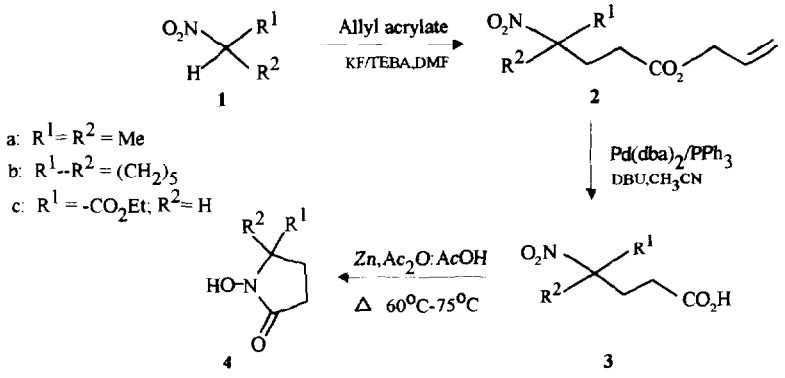
Abstract: *A novel method for the synthesis of five membered α-substituted cyclic hydroxamic acids from aliphatic nitro compounds including nitro acetic acid derivatives is described. Michael addition of allyl acrylate to these compounds followed by Pd(0) catalyzed intra molecular allyl transfer and subsequent reduction of the tertiary nitro group results in a new class of compounds related to N-hydroxy pyroglutamic acid.*

In a recent communication from this laboratory[1] we had reported the synthesis of several 1-hydroxy-2-substituted-5-oxoproline derivatives from nitroacetic acid esters and amides. The molecular structure of these products presents a rare combination of three desirable features : i) presence of a pyroglutamic acid skeleton, ii) possibility of creating a quaternary α-carbon atom on the proline nucleus, and iii) incorporation of a cyclic hydroxamic acid moiety. Derivatives of glutamic acid and pyroglutamic acid are of interest in connection with their effect on glutamate receptors in the CNS[2], and as starting materials for the synthesis of various enantiomerically pure products[3]. The importance of hydroxamic acid siderophores in iron-solubilization and transport has already been highlighted[4].

The present article deals more fully with the development of the concept which led to the above synthesis.

We have been involved in the use of the nitroacetyl group as a synthon for the preparation of dipeptides in which the N-terminal aminoacid incorporates several 'non-natural' substituents.[5,6,7] Essentially this involves the use of the nitro group both to activate the adjacent methylene group, as well as to function as a latent primary amino group. The methodology involves the following steps : i) synthesis of N-nitroacetyl α-aminoacid esters from 1,1-bismethylmercapto-2-nitroethene[8]; ii) mono or bis alkylation at the activated α-methylene by either a Pd(0) catalyzed allylation or a Michael addition [6,7] and iii) final reduction of the NO_2 to an amino or an acylamino group. The strategy for extrapolation of this to the synthesis of cyclic hydroxamic acids would require i) introduction of a propionic acid unit at the α-position of nitroalkanes having at least one hydrogen atom at that position; ii) reduction of the NO_2 to NHOH, and iii) cyclization by attack of the newly created hydroxylamine on the carboxylic acid group situated three atoms away, thereby creating an N-hydroxypyrrolidinone unit (Scheme 1). If the starting aliphatic nitro compound is a nitroacetic acid derivative (1, R^1 = COOR or $CONR_2$) this sequence would result in the formation of the desired N-hydroxypyroglutamic acid. The introduction of the propionic acid side-chain in the first step of this sequence could be done most conveniently by a Michael addition to an acrylic acid derivative. A further dimension could be added by starting

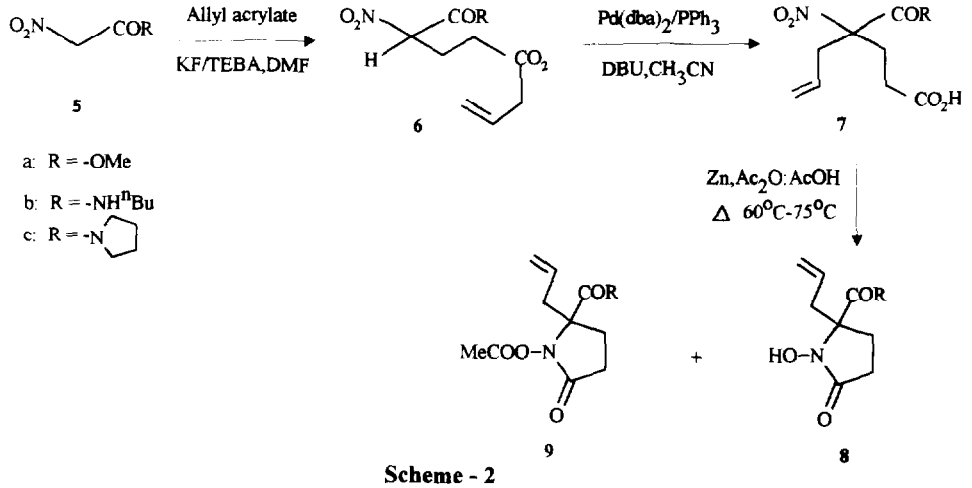


Scheme - 1

with a nitromethylene compound (**1**; R^2=H) and sequentially introducing two new substituents at the α-CH_2, one of which is a propionic acid.

Results and discussion

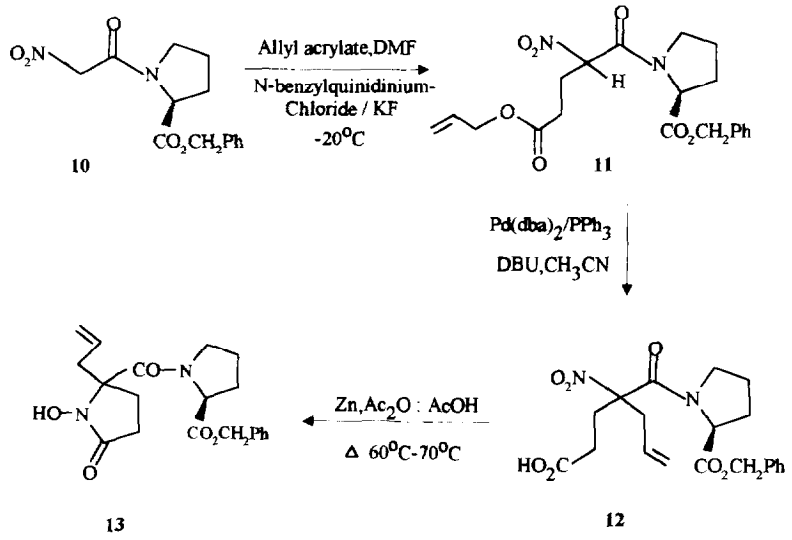
In order to introduce a propionic acid side-chain at the α-carbon of secondary nitroalkanes, we have developed a two-step procedure. In the first step, allyl acrylate[9] is used as the Michael acceptor in presence of fluoride ion as the base; subsequently, deallylation is achieved by Pd(0) catalysis. Thus, 2-nitropropane (**1a**) gave the adduct (**2a**) as a colorless liquid in 87% yield. Pd(0) catalyzed deallylation gave the carboxylic acid (**3a**) in 78% yield. Similarly, nitrocyclohexane (**1b**) gave (**3b**) in two steps. Reduction of the nitro group in (**3a**) by zinc dust in a mixture of acetic acid and acetic anhydride resulted in the formation of the N-hydroxypyrrolidinone (**4a**) (46%) and its O-acetyl derivative (35%). Obviously the initially generated hydroxylamine had been trapped intramolecularly by the mixed anhydride formed from the carboxylic acid and acetic anhydride. Similarly the nitrocyclohexane derivative (**3b**) gave the spiro compound (**4b**) in 54% yield.



Scheme - 2

As reported earlier[1], direct addition of acrylic acid to ethyl nitroacetate (**1c**)[10] was successful, providing access to the 2-nitroglutaric acid derivative (**3c**). Zinc-acetic acid - acetic anhydride reduction[11] of this gave (±)1-hydroxypyroglutamic acid ethyl ester (**4c**) in 44% yield. This approach, however, could not be extended to other nitro aliphatics. Thus, 1-nitro-2-phenylethane, on treatment with acrylic acid in presence of KF, gave an inseparable mixture of the mono and bis adducts. Nitroethane too behaved similarly.

The allyl acrylate approach could be used to generate a quaternary carbon on the methylene adjacent to a nitro group. Initial Michael addition followed by an intramolecular Pd(0)-catalyzed allyl group transfer from the oxygen atom to the nucleophilic carbon gave rise to a 4-nitrohept-6-enoic acid system (Scheme 2). Since the resultant compounds (e.g. **7**) possess the necessary δ-nitrobutyric acid unit, these could be cyclized to 1-hydroxy-2-pyrrolidinones (e.g. **8**) by reduction with Zn-AcOH-Ac_2O. These products are structurally related to pyroglutamic acid, being 1-hydroxy derivatives thereof. Thus methyl nitroacetate yielded the adduct (**6a**) in 85% yield. Treatment of this with a catalytic amount of $Pd(dba)_2$ in presence of PPh_3 and base (DBU) in acetonitrile, led to a smooth intramolecular C-allylation, yielding the acid (**7a**) in 63% yield. This was converted to the cyclic hydroxamic acid (**8a**) (55%) and its O-acetyl derivative (**9a**) (40%). The reductive cyclization was thus seen to proceed in excellent yield. The nitroacetamides (**5b**) and (**5c**) were similarly converted to the 1-hydroxypyroglutamic acid derivatives (**8b, 8c**) and (**9b**) in very good yields.



Scheme - 3

In all the cases discussed so far, the products were racemic. Our next objective was to attempt diastereoselective generation of the quaternary α-carbon atom. The starting material for this was N-nitroacetyl (L)-proline benzyl ester (**10**), which we had synthesized earlier.[12] Michael addition to allyl acrylate using KF as base in presence of the chiral phase transfer agent N-benzylquinidinium chloride gave the adduct (**11**) in 80% yield, with a diastereomeric excess (*de*) of 39%. Conversion of this to the C-allylglutaric acid derivative (**12**) was achieved as usual by means of Pd(0) catalysis; the product (**12**) had a *de* of 40%. Reduction of the tertiary nitro group to the hydroxylamine, followed by cyclization gave the 2-allyl-1-hydroxypyroglutamylproline ester (**13**) in 54% yield as a mixture of two diastereomers.

^{13}C NMR spectra were especially helpful in characterizing the above products. Thus, on monoalkylation of the methylene group in (**5**) the carbon atom showed a downfield shift from 77 ppm to about 83-85 ppm in (**6**). The second alkylation to (**7**) caused a further downfield shift of this carbon to 94-96 ppm. This peak also served well to estimate the *de* in (**11**) and (**12**). On reduction and cyclization to form the 1-hydroxypyrrolidinones, this carbon peak moved upfield by 20-30 ppm. All the cyclic hydroxamic acids showed the characteristic deep violet color with $FeCl_3$.

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Experimental Section:

Michael addition of allyl acrylate to nitroaliphatic compounds: General procedure.

To 1 mmol of the compound, dissolved in DMF (3ml), 1 eq of solid potassium fluoride was added along with a catalytic amount of TEBA. This mixture was stirred for about 5 min. at room temperature. Allyl acrylate (1eq), dissolved in DMF (2ml) was then added dropwise. After addition was complete the reaction mixture was allowed to stir at room temperature for 7-8 h. The reaction was monitored by TLC. After completion of reaction, 5% aq HCL (5ml) was added slowly into the reaction mixture. The aqueous layer was washed with ethyl acetate (3x10ml) to extract the compound. The organic layer thus collected was washed (3x10ml) with water, then with brine and dried over Na_2SO_4. The solvent was removed under vacuum to yield the crude adduct. The crude sample was purified by column chromatography over silica gel using pet.ether : ethyl acetate.

Allyl 4-nitro-4-methyl pentanoate (2a)

Yield = 87%; Colorless liquid; IR (neat), 3100, 2980, 1760, 1550, 1370, 1200 cm^{-1}; ^1H NMR ($CDCl_3$), 1.40 (s, 6H, 2-CH_3), 2.60 - 2.70 (m, 4H, 2-CH_2), 4.50 (d, 2H, -OCH_2), 5.13 - 5.44 (m, 2H, =CH_2), 5.64 - 5.20 (m, 1H, -CH=); ^{13}C NMR ($CDCl_3$), 25.19 (2-CH_3), 29.24 (-CH_2), 35.31 (-CH_2), 65.41 (-OCH_2), 87.33 (-CNO_2), 118.44 (=CH_2), 132.03 (-CH=), 171.75 (CO); Anal. calc. for $C_9H_{15}NO_4$: C, 53.73; H, 7.46; N, 6.96. Found : C, 53.39; H, 7.84; N, 7.08.

Allyl 3-(1-nitrocyclohexyl) propionate (2b)

Yield = 86%; Colorless liquid; IR (neat), 2980, 2900, 1750, 1550, 1470, 1400, 1320, 1200, 1010 cm^{-1}; ^1H NMR ($CDCl_3$), 1.30 - 1.70 (m, 10H, 5-CH_2), 2.10 - 2.45 (m, 4H, 2-CH_2), 4.55 (d, 2H, -OCH_2), 5.25 - 5.40 (m, 2H, =CH_2), 5.85 - 5.98 (m, 1H, -CH=); ^{13}C NMR ($CDCl_3$), 22.24, 24.66, 28.21, 33.8, 34.8, (7-CH_2), 65.18 (-OCH_2), 90.49 (-CNO_2), 118.06 (=CH_2), 132.05 (-CH=), 171.56 (CO); Anal. calc. for $C_{12}H_{19}NO_4$: C, 59.75; H, 7.88; N, 5.8. Found: C, 60.16; H, 8.18; N, 6.30.

General procedure for Pd(0) catalyzed deallylation or intramolecular allyl transfer in the Michael adducts.

To a solution of the compound (1 mmol) in 5 ml dry degassed acetonitrile, DBU (1 eq) was added and stirred for about 10 min. To this reaction mixture under argon at room temperature $Pd(dba)_2$ (5 mol%) was added followed by the addition of PPh_3 (10 mol%). In about 15-20 min. the reaction mixture became a clear solution. The reaction was left to stir at room temperature for 12 h. The progress was monitored by TLC. After completion of reaction the reaction was quenched by the addition of 5% aq. HCL (5-6 ml). The aqueous layer was washed with ethyl acetate several times (15 ml x 5). All the extracts were collected, washed with water, brine solution and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the product obtained was purified through a column (silica gel, pet.ether:ethyl acetate)

4-Methyl-4-nitro pentanoic acid (3a)

Yield = 78%; Colorless solid mp = 43°C; IR ($CHCl_3$), 3500, 2600, 1720, 1550, 1450, 1410, 1230 cm^{-1}; ^1H NMR ($CDCl_3$), 1.65 (s, 6H, 2-CH_3), 2.25 - 2.50 (m, 4H, 2-CH_2), 8.85 - 9.25 (b, 1H, -OH); ^{13}C NMR ($CDCl_3$), 25.15 (-CH_3), 28.76, 34.70 (2-CH_2), 87.22 (-CNO_2), 177.78 (CO); Anal. calc. for $C_6H_{11}NO_4$: C, 44.72; H, 6.83; N, 8.69. Found : C, 44.97; H, 7.49; N, 9.03.

3-(1-Nitrocyclohexyl) propionic acid (3b)

Yield = 75%. White solid mp = 93°C; IR (nujol), 2980, 2880, 1730, 1550, 1480, 1400, 1320 cm^{-1}; ^1H NMR ($CDCl_3$), 1.20 - 1.80 (m, 8H, 4-CH_2), 8.64 - 8.72 (b, 1H, -OH); ^{13}C NMR ($CDCl_3$), 22.45 (-CH_2), 24.90 (-CH_2), 28.42 (-CH_2), 34.13, 34.72 (2-CH_2), 90.64 (-CNO_2), 178.84 (CO); Anal. calc. for $C_9H_{15}NO_4$: C, 53.73; H, 7.46; N, 6.96. Found: C, 53.89; H, 7.36; N, 6.75.

Ethyl 2-nitroglutarate (3c)

Yield = 78%; Thick liquid; IR (neat) 3500-3200, 1730, 1540, 1370, 1200, 1010 cm^{-1}; ^1H-NMR ($CDCl_3$): 1.20 (t, 3H, -CH_3), 2.40 -2.70 (m, 4H, 2-CH_2), 4.28 (q, 2H, -OCH_2), 5.17 - 5.37 (m, 1H, -$CHNO_2$), 6.00 - 6.20 (b, 1H, -OH); ^{13}C-NMR ($CDCl_3$): 13.77 (-CH_3), 25.06, 29.39 (2-CH_2), 63.38 (-OCH_2), 86.67 (-$CHNO_2$), 164.41 (CO), 176.45 (CO); Anal. calc. for $C_7H_{11}NO_6$: C, 40.97; H,5.36; N, 6.82. Found: C, 41.53; H, 5.54.

General procedure for the reduction of the tertiary nitro group using Zn, Ac_2O : AcOH.

2mmols of the compound were dissolved in a mixture of Ac_2O : AcOH (1:1, 5 ml) and warmed to 50°C. To this stirried mixture zinc dust (500 mg) was added in small portions. After the addition was complete the reaction mixture was warmed to 60-75°C. After 8-10h. the reaction did not show the presence of the starting material on the TLC plate (Benzene : EtOAc 70:30). The TLC showed two polar compounds in the mixture. The reaction mixture was filtered and the zinc salt precipitated was washed with small quantities of AcOH (2 x 3 ml). It was then washed with excess ethyl acetate. The washings and the filtrate together were evaporated under vacuum. The resulting thick gum was redissolved in ethyl acetate and washed with minimum water twice (2 x 3 ml). The organic layer was then washed with saturated sodium chloride solution. It was then dried over sodium sulfate (anhydrous) and concentrated under vacuum. The resulting mixture was

purified by column chromatography (silica gel, benzene:ethyl acetate) to yield the corresponding hydroxamic acid and the O-acetyl derivatives.

5,5-Dimethyl-1-hydroxy-2-pyrrolidinone (4a)

Yield = 46%; IR (nujol), 3500- 3400, 1688, 1470, 1388, 1108 cm^{-1}; ^1H NMR ($CDCl_3$), 1.25 (s, 6H, 2-CH_3), 1.85 (t, 2H, -CH_2), 2.40 (t, 2H, -CH_2), 7.20 - 7.30 (b, 1H, -OH); ^{13}C NMR ($CDCl_3$), 29.14 (2-CH_3), 30.88, 35.32 (2-CH_2), 56.98 (-CNO_2), 177.68 (CO); Anal. calc. for $C_6H_{11}NO_2$: C, 55.81; H, 8.52; N, 10.85. Found : C, 55.57; N, 10.80.

1-Hydroxy-1-azaspiro [4.5] 2-decanone (4b)

Yield = 54%; Colorless solid, mp = 83°C; IR ($CHCl_3$), 3221-3100, 1713, 1535, 1453, 1371, 1164 cm^{-1}; ^1H NMR ($CDCl_3$), 1.30 - 1.60 (m, 10H, 5-CH_2), 1.80 (t, 2H, -CH_2), 2.35 (t, 2H, -CH_2), 7.70 - 7.90 (b, 1H, -OH); ^{13}C NMR ($CDCl_3$), 23.05, 25.27, 30.18, 32.78, 38.43, (5-CH_2), 59.62 (quaternary carbon), 177.76 (CO); Anal. calc. for $C_9H_{15}NO_2$: C, 63.90; H, 8.87; N, 8.28. Found: C, 64.53; H, 9.10; N, 9.11.

1-Hydroxy-5-carboethoxy-2-pyrrolidone (4c)

Yield = 44%; IR ($CHCl_3$): 3500-3440, 1730, 1720, 1380, 1200 cm^{-1}; ^1H-NMR ($CDCl_3$): 1.25 (t, 3H, -CH_3), 1.95 - 2.15 (m, 4H, 2-CH_2), 4.15 - 4.40 (m, 3H, -OCH_2, -$CHCO_2Et$), 7.50 - 7.75 (b, 1H, -OH); ^{13}C-NMR ($CDCl_3$): 14.05 (-CH_3), 19.45, 25.93 (-CH_2), 59.80 (-$CHCO_2Et$), 62.79 (-OCH_2), 170.9 (CO), 174.01 (CO); Anal. calc. for $C_7H_{11}NO_4$: C, 48.55; H, 6.35. Found: C, 47.82; H, 5.92.

General procedure for the synthesis of nitroacetamides (5b & 5c).

The corresponding amine (10mmol) was dissolved in acetonitrile and added dropwise into a stirring solution of 1,1-bismethylthio-2-nitroethene (10.2mmol) with a catalytic amount of PTSA. The reaction mixture was stirred at room temperature overnight. Excess solvent was removed and the adduct was purified by column chromatography. The adduct was dissolved in a mixture of acetonitrile and water (3:1, 5ml) and added dropwise to a stirring mixture of $HgCl_2$ in acetonitrile, water (3:1, 5ml). After 6h. the reaction mixture was filtered over a celite pad. The filterate was the evaporated to obtain the crude product which was purified by column chromatography,(silica gel; petether: ethyl acetate).

N-Nitroacetyl n-butylamine (5b)

Yield = 90%; Red liquid. IR ($CHCl_3$), 3300, 2980, 1670, 1570, 1400, 1340, 1230 cm^{-1}.; ^1H NMR ($CDCl_3$), 0.85 (t, 3H, -CH_3), 1 - 1.68 (m, 4H, 2-CH_2), 2.76 - 3.30 (m, 2H, -NCH_2), 5.00 (s, 2H, -CH_2NO_2), 7.40 - 7.65 (b, 1H,-NH); ^{13}C NMR ($CDCl_3$), 14.20 (-CH_3), 21.60, 31.10 (2-CH_2), 40.00 (-NCH_2), 76.90 (-$CHNO_2$), 165 (CO); Anal. cal. for $C_6H_{12}N_2O_3$: C, 45.00; H, 7.50. Found: C, 44.78; H, 7.63.

N-Nitroacetyl pyrrolidine (5c)

Yield = 85%, Pale yellow solid mp = 105°C; IR (nujol), 1665, 1565, 1385 cm^{-1}; ^1H NMR ($CDCl_3$), 1.87 (m, 4H, 2-CH_2), 3.42 (m, 4H, 2-NCH_2), 5.12 (s, 2H, -CH_2NO_2); Anal. calc. for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.72. Found: C, 45.68; H, 6.75; N, 17.40.

Methyl O^5-allyl-2-nitroglutarate (6a)

Yield = 85%, Colorless liquid. IR (neat), 2980, 1760, 1750, 1570, 1450, 1180, 1000 cm^{-1}; ^1H NMR ($CDCl_3$), 2.36 - 2.60 (s, 4H, 2-CH_2), 3.80 (s, 3H, -OCH_3), 4.60 (d, 2H, -OCH_2), 5.15 - 5.40 (m, 3H, =CH_2, -$CHNO_2$), 5.75 - 6.00 (m, 1H, -CH=); ^{13}C NMR ($CDCl_3$), 25.37, 29.57 (2-CH_2), 53.69 (-OCH_3), 65.63 (-OCH_2), 86.61 (-$CHNO_2$), 118.6 (=CH_2), 131.91 (-CH=), 164.76 (-CO), 171.21 (CO); Mass (Mol. wt 231): 200, 174, 145, 127, 113, 100, 95, 85 (base peak), 59, 55; Anal. calc. for $C_9H_{13}NO_6$: C, 46.75; H, 5.62; N, 6.06. Found: C, 46.50; H, 5.78; N, 6.11.

N-^{n}Butyl O^5-allyl-2-nitroglutaramide (6b)

Yield = 88%; Pale yellow liquid; IR (neat), 3380-3300 (b), 2980, 2960, 1750, 1740, 1680, 1690, 1580, 1190 cm^{-1}; ^1H NMR ($CDCl_3$), 0.85 (t, 3H, -CH_3); 1.25 1.40 (m, 2H, -CH_2), 1.40 - 1.55 (m, 2H, -CH_2), 2.35 - 2.55 (m, 4H, 2-CH_2), 3.25 (q, 2H, -NCH_2), 4.50 (d, 2H, -OCH_2), 5.18 - 5.35 (m, 3H, =CH_2, -$CHNO_2$), 5.85 6.00 (m, 1H, -CH=), 7.05 - 7.20 (b, 1H, -NH); ^{13}C NMR ($CDCl_3$), 13.68 (-CH_3), 20.00, 25.68, 29.74, 31.18, (4-CH_2), 40.06 (-NCH_2), 65.65 (-OCH_2), 87.82 (-$CHNO_2$), 118.65 (=CH_2), 131.85 (-CH=), 163.50 (CO), 171.84 (CO); Mass, 258, 229, 212, 200, 171, 155, 112; Anal. calc. for $C_{12}H_{20}N_2O_5$: C, 52.94; H, 7.35; N, 10.29. Found: C, 52.42; H, 7.52; N, 10.09.

N-[O^5-Allyl-2-nitroglutaryl] pyrrolidine (6c)

Yield 90%; Pale yellow liquid, IR ($CHCl_3$), 3100, 1730, 1660, 1570, 1450, 1220 cm^{-1}, ^1H NMR ($CDCl_3$), 1.80 - 2.00 (m, 4H, 2-CH_2), 2.25 - 2.55 (m, 4H, 2-CH_2), 3.35 - 3.60 (m, 4H, 2-NCH_2), 4.55 (d, 2H, -OCH_2), 5.10 - 5.25 (m, 2H, =CH_2), 5.45 (t, 1H, -$CHNO_2$), 5.75 - 5.95 (m, 1H, -CH=); ^{13}C NMR ($CDCl_3$), 23.44, 24.37, 25.24, 28.79 (4-CH_2), 45.84, 46.30 (2-NCH_2), 64.52 (-OCH_2), 84.79 (-$CHNO_2$), 117.37 (=CH_2), 131.58 (-CH=), 161.08 (CO), 171.0 (CO); Mass, 224, 167, 155, 126, 98, 85, 70 (100%) 55; Anal. calc. for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.66; N, 10.37. Found: C, 53.51; H, 6.01; N, 10.25.

O^1-Methyl 2-allyl-2-nitroglutarate (7a)

Yield = 63%; Red brown liquid; IR (neat), 3500-3100, 2600, 1760, 1730, 1560, 1450, 1230 cm^{-1}; ^1H NMR ($CDCl_3$), 2.45 - 2.60 (bs, 4H, 2-CH_2), 2.80 - 3.10 (m, 2H, -CH_2), 3.85 (s, 3H, -OCH_3), 5.15 - 5.31 (m, 2H, =CH_2), 5.55 - 5.75 (m, 1H, -CH=), 6.50 - 7.00 (b, 1H, -OH); ^{13}C NMR ($CDCl_3$), 28.29 (2-CH_2), 38.90 (-CH_2), 53.24 (-OCH_2), 94.12 (-CNO_2), 121.51 (=CH_2), 128.74 (-CH=), 166.22 (CO), 177.40 (CO); Mass, 214, 200, 184, 153, 135, 107, 79, 55; Anal. calc. for $C_9H_{13}NO_6$: C, 46.75; H, 5.62; N, 6.06. Found: C, 47.03; H, 6.03; N, 6.11.

N-^{n}Butyl 2-allyl-2-nitroglutaramide (7b)

Yield = 56%; Pale yellow solid, mp = 73°C; IR (nujol), 3854, 3751, 3330, 2960, 1714, 1666, 1555, 1440, 1356, 1278 cm^{-1}; ^1H NMR ($CDCl_3$), 0.90 (t, 3H, -CH_3), 1.20 - 1.55 (m, 4H, 2-CH_2), 2.30 - 2.60 (m, 4H, 2-CH_2), 2.85 - 3.05 (m, 2H, -NCH_2), 3.3 (q, 2H, -CH_2CH=), 5.15 - 5.3 (m, 2H, =CH_2), 5.50 - 5.75 (m, 1H, -CH=), 6.65 - 6.75 (b, 1H, NH), 9.15 - 9.65 (b, 1H, -OH); ^{13}C NMR ($CDCl_3$), 13.79 (-CH_3), 20.15, 28.98, 29.88, 31.27 (4-CH_2), 40.34 (-NCH_2), 40.77 (-CH_2CH=), 96.56 (-CNO_2), 121.87 (=CH_2), 129.57 (-CH=),

165.48 (CO), 176.77 (CO); Mass , 256, 242, 226, 213, 185, 149, 129, 97; Anal. calc. for $C_{12}H_{20}N_2O_5$: C, 52.94; H, 7.35; N, 10.29. Found: C, 53.75; H, 7.71; N, 9.98.

N-[2-Allyl-2-nitroglutaryl] pyrrolidine (7c)

Yield 45%; White solid, mp = 113°C; IR ($CHCl_3$), 3100, 2900, 1720, 1640, 1550, 1430, 1210 cm^{-1}. ^1H NMR ($CDCl_3$), 1.75 - 2.05 (m, 4H, 2-CH_2), 2.35 - 2.60 (m, 4H, 2-CH_2), 3 (d, 2H, -CH_2), 3.10 - 3.35 (m, 2H, -CH_2), 3.50 - 3.65 (m, 2H, -CH_2), 5.10 - 5.30 (m, 2H, =CH_2), 5.50 - 5.70 (m, 1H, -CH=), 6.10 - 6.40 (b, 1H, -OH); ^{13}C NMR ($CDCl_3$), 23.23 (-CH_2), 26.89 (-CH_2), 28.24, 28.75 (2-CH_2), 39.91 (-CH_2CH=), 46.46, 48.53 (2-CH_2), 95.18 (-CNO_2), 121.69 (=CH_2), 129.75 (-CH=), 163.38 (CO), 176.94 (CO); Mass, 224 (M - 46), 182, 166, 135, 125, 98, 70.

1-Hydroxy-5-allyl-5-carbomethoxy-2-pyrrolidinone (8a)

Yield = 55%; Solid. m.p = 91°C; IR (neat), 3852, 1698, 1435, 1225, 1160 cm^{-1}; ^1H NMR ($CDCl_3$), 2.00 - 2.25 (m, 2H, -CH_2), 2.30 - 2.50 (m, 2H, -CH_2), 2.60 - 2.95 (m, 2H, -CH_2), 3.75 (s, 3H, -OCH_3), 4.20 - 4.55 (b,1H, -OH), 5.15 - 5.30 (m, 2H, =CH_2), 5.60 - 5.85 (m, 1H, -CH=); ^{13}C NMR ($CDCl_3$), 24.45 (-CH_2), 26.31 (-CH_2), 37.28 (-CH_2), 52.79 (-OCH_3), 67.50 (-quaternary carbon), 126.60 (=CH_2), 131.06 (-CH=), 170.80 (CO), 172.59 (CO); MS, 199 (M+), 185, 182, 158, 140, 130, 124. Anal. cal. for $C_9H_{13}NO_4$: C, 54.27; H, 6.53; N, 7.03. Found: C, 54.33; H, 6.60; N, 6.64.

5-Allyl-1-hydroxypyrrolidin-2-one-5-carboxylic acid N-^{n}butylamide (8b)

Yield = 53%; IR ($CHCl_3$), 3648-3363, 1645, 1542, 1457 cm^{-1}; ^1H NMR ($CDCl_3$), 0.95 (t, 3H, -CH_3), 1.25 - 1.55 (m, 4H, 2-CH_2), 2.25 - 2.55 (m, 4H, 2-CH_2), 2.80 2.95 (dd, 2H, -CH_2), 3.20 - 3.30 (m, 2H, -NCH_2), 5.10 - 5.30 (m, 2H, =CH_2), 5.60 - 5.80 (m, 1H, -CH=), 6.60 - 6.75 (b, 1H, -OH), 6.95 - 7.15 (b, 1H, -NH); ^{13}C NMR ($CDCl_3$), 13.53 (-CH_3), 19.89, 29.8, 31.38, 31.66, 39.43, 42.97 (6-CH_2), 65.92 (-CNOH), 120.14 (=CH_2), 131.76 (-CH=), 173.08 (CO), 178.49 (CO); Mass, 182, 154, 140, 124, 96; Anal. calc. for $C_{12}H_{20}N_2O_3$: C, 60.00; H, 8.33; N, 11.66. Found: C, 60.15; H, 8.15; N, 11.89.

5-Allyl-1-hydroxypyrrolidin-2-one-5-carboxylic acid pyrrolidide (8c)

Yield = 50%; Colorless solid mp = 96°C; IR ($CHCl_3$), 3500-3300, 1640, 1510, 1475, 1200 cm^{-1}; ^1H NMR ($CDCl_3$), 1.90 - 2.75 (m, 8H, 4-CH_2), 2.85 - 3.00 (m, 2H, -CH_2), 3.40 - 3.65 (m, 4H, 2-CH_2), 5.20 - 5.30 (m, 2H, =CH_2), 5.60 - 5.80 (m, 1H, -CH=), 6.85 - 6.95 (b, 1H, -OH); ^{13}C NMR ($CDCl_3$), 22.45, 23.5, 25.23, 25.62 (4-CH_2), 30.31 (-CH_2), 45.51, 45.97 (2-CH_2), 66.10 (quaternary carbon), 118.24 (=CH_2), 131.7 (-CH=), 171.30 (CO),172.20 (CO); Anal. calc. for $C_{12}H_{18}N_2O_3$: C, 60.50; H, 7.56; N, 11.76. Found: C, 59.84; H, 7.11; N, 12.14.

1-(Acetoxy)-5-allyl-5-carbomethoxy-2-pyrrolidinone (9a)

Yield = 40%; Colorless liquid; IR (neat), 3838, 3447, 2955, 1804, 1741, 1559,1437 cm^{-1}; ^1H NMR ($CDCl_3$), 2.08 - 2.60 (m, 9H, 3-CH_2, -$COCH_3$), 3.71 (s, 3H, -OCH_3), 4.95 - 5.21 (m, 2H, =CH_2), 5.46 - 6.0 (m, 1H, -CH=); ^{13}C NMR ($CDCl_3$), 18.27 (CH_3), 25.71 (-CH_2), 25.96 (-CH_2), 38.77 (-CH_2), 53.04 (-OCH_3), 67.88

(quaternary carbon), 120.39 (=CH_2), 131.34 (-CH=), 167.26 (CO), 170.85 (CO), 171.42 (CO); MS, 241 (M^+), 200, 182, 158, 140, 130; Anal. calc. for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.22; N, 5.80. Found: C, 54.18; H, 5.95; N, 5.56.

1-(Acetoxy)-5-allylpyrrolidin-2-one-5-carboxylic acid N ^{n}butyl amide (9b)

Yield = 21%; IR ($CHCl_3$), 3853-3750, 1792, 1734, 1670, 1540 cm^{-1}; ^1H NMR ($CDCl_3$), 1.90 (t, 3H, -CH_3), 1.25 - 1.55 (m, 4H, 2-CH_2), 2.15 - 2.50 (m, 4H, 2-CH_2), 2.60 - 2.90 (m, 2H, -CH_2), 3.15 - 3.30 (m, 2H, -CH_2), 5.15 - 5.30 (m, 2H, =CH_2), 5.50 - 5.80 (m, 1H, -CH=), 7.20 - 7.25 (b, 1H, -NH); ^{13}C NMR ($CDCl_3$), 13.89 (-CH_3), 18.47 (-$COCH_3$), 20.23, 25.84, 27.66, 31.82, 39.61 (6-CH_2), 69.20 (quaternary carbon), 121.44 (=CH_2), 131.37 (-CH=), 169.02 (CO), 171.82 (CO), 172.28 (CO); Mass: 282, 182, 140, 124, 98, 83; Anal. calc. for $C_{14}H_{22}N_2O_4$: C, 59.57; H, 7.80. Found: C, 59.83; H, 7.95.

Benzyl N-[O^5-allyl-2-nitroglutaryl]-L-prolinate (11)

Yield = 80%; Pale yellow liquid; IR (neat), 2980, 1740, 1730, 1670, 1470, 1450, 1190 cm^{-1}; ^1H NMR ($CDCl_3$), 2.00 - 2.25 (m, 8H, β, γ-CH_2, 2-CH_2), 3.65 - 3.85 (m, 2H, δ-CH_2), 4.55 - 4.65 (m, 3H, α-CH, -OCH_2), 5.15 - 5.40 (m, 4H, -OCH_2, =CH_2), 5.55 - 5.70 (m, 1H, -$CHNO_2$), 5.80 - 6.05 (m, H, -CH=), 7.30 (s, 5H, -Ph); ^{13}C NMR ($CDCl_3$); 24.80, 25.20, 29.03, 29.16 (2-CH_2, β-C, γ-C), 47.71 (47.59) (δ-C), 59.59 (59.83) (α-C), 65.57, 67.20 (2-OCH_2), 84.70 (85.26) (-$CHNO_2$), 118.65 (=CH_2), 128.27, 128.51, 128.72, 128.87, 132.0, 135.58, (-Ph, -CH=), (162.05), 162.56 (CO) 171.09 (170.84) (CO), 172.26 (172.08) (CO).

Benzyl N-[2-allyl-2-nitroglutaryl]-L-prolinate (12)

Yield = 72%; Pale Yellow solid. IR (nujol), 3500, 3300, 1730, 1640, 1540, 1450, 1210 cm^{-1}; ^1H NMR ($CDCl_3$), 1.85 - 2.20 (m, 4H, 2-CH_2), 2.35 - 2.65 (m, 4H, 2-CH_2), 2.85 -3.10 (m, 2H, -CH_2CH=), 3.10 - 3.35 (m, 1H, δ-CH_2), 3.40 - 3.60 (m, 1H, δ-CH_2), 4.55 - 4.70 (m, 1H, α-CH), 5.10 - 5.30 (m, 4H, -OCH_2, CH_2), 5.55 - 5.70 (m, 1H, -CH=), 7.40 (s, 5H, -Ph); ^{13}C NMR ($CDCl_3$), 24.93, 25.66 (2-CH_2), 28.22, 28.65 (2-CH_2), 39.19 (-CH_2CH=), 47.11 (47.25) (δ-C), 61.19 (61.30) (α-C), 67.33 (67.23) (-OCH_2), 95.17 (94.57) (-CNO_2), 128.85 (=CH_2), 128.43, 128.63, 128.82, 129.48, 129.64, 132.27, 132.48, 135.65 (-Ph,-CH=), 163.98 (CO), 171.73 (171.60) (CO), 176.71 (176.60) (CO).

Benzyl N-[5-allyl-1-hydroxypyrrolidine-2-one-5-carbonyl]-L-prolinate (13)

Yield = 54%; Pale yellow solid mp 65°C; IR ($CHCl_3$), 3400-3600, 1740, 1670, 1500, 1440, 1240 cm^{-1}; ^1H NMR ($CDCl_3$), 1.90 - 2.65 (m, 8H, 4-CH_2), 3.01 - 3.35 (m, 2H, -CH_2), 3.50 - 3.75 (m, 2H, δ-CH_2), 4.60 - 4.75 (m, 1H, α-CH), 5.20 - 5.35 (m, 4H, -OCH_2, =CH_2), 5.80 - 6.00 (m, 1H, -CH=), 7.40 (s, -5H, -Ph); ^{13}C NMR ($CDCl_3$), 25.43, 27.34, 27.88, 28.11, 28.4, 29.07 (4-CH_2); (39.0), 40.12 (-CH_2); 46.90 (δ-C); 60.90 (61.10) (α-C); 66.90 (-OCH_2); (69.09) 69.10 (quaternary carbon); 121.40 (=CH_2); 128.20, 128.50, 128.77, 129.60, 132.00, 132.20 (Ph, CH=); 167.84 (CO); 171.44 (CO); 174.50 (CO); Anal. calc. for $C_{20}H_{24}N_2O_5$: C, 64.51, H, 6.45; N, 7.52. Found: C, 65.10; H, 6.83; N, 8.03.

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