SYNTHESIS OF ACYLATED ACTIVE METHYLENE COMPOUNDS WITH *N*-Boc-L-PHENYLALANINE AND THEIR HETEROCYCLIZATION, BOTH ACHIEVED ENANTIOSELECTIVELY

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Abstract : Three active methylene compounds, malononitrile, methyl cyanoacetate and Meldrum's acid, have been found to be acylated effectively with *N*-Boc-L-phenylalanine using carbonyldiimidazole (CDI) activation conditions. Two of the aminoacetyl derivatives isolated in high yield (63-97%), enantioselectively, were readily heterocyclized to the corresponding tetramic acid, 5-Benzyl-4-hydroxy-1-tert-butoxycarbonylpyrrol-2(5H)-one, and 2-amino-3-cyano-2-pyrrolin-4-one, enantioselectively too.

The aminoacetyl derivatives of active methylene compounds such as **4a** and **4b** have been used as synthons for difunctionalized enamines, enol ethers and thioenol ethers which have been reported as modifications for the peptide amide function[1]. On the other hand chiral 2-substituted tetramic acids as **7** have been used in the course of studies directed towards the synthesis of new anti-HIV protease derivatives[2], as well as synthons for statine analogues[3], a class with a wide range of biologically active compounds.

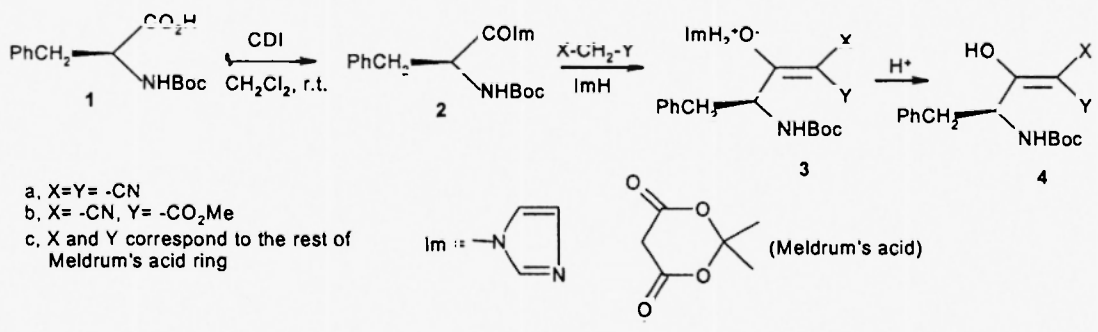
In a previous communication[4] we have reported the *C*-acylation reactions of two active methylene compounds, methyl cyanoacetate and Meldrum's acid, with hippuric acid, using the N,N′-dicyclohexylcarbodiimide (DCC) and the mixed anhydride activation conditions. These reactions were shown to proceed through initial formation of 2-phenyl-5(4H)-oxazolone, the hippuric acid azlactone, under DCC activation conditions only Meldrum's acid could be acylated, while under mixed anhydride conditions both active methylene compounds could be acylated, though in low yields. Later we reported[5] the *C*-acylation reaction of Meldrum's acid with *N*-protected glycines, which was performed by a simple experimental procedure using the imidazolide activation method and the easy cyclization of the acylation compounds to the corresponding *N*-protected tetramic acids.

Meldrum's acid has been used by Yonemitsu et. al.[6] for its acylation with acyl chlorides, in the presence of pyridine, to the corresponding acyl Meldrum's acids, which readily underwent alcoholysis to various β-keto esters. A modification of this acylation reaction was reported by Melilo et. al.[7], who treated a carboxylic acid with 1,1′-carbonyldiimidazole (CDI), followed by treatment with Meldrum's acid in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP). Another process for the acylation of Meldrum's acid was developed by Jouin et. al.[3] using chiral *N*-protected amino acids. These *N*-protected amino acids were activated with isopropenyl chloroformate (IPCF), which was added slowly to a solution of the amino acid, Meldrum's acid and two equivalents of DMAP in dichloromethane at -5 °C. As described by those authors these reaction conditions were very stringent: any change in the procedure (e. g. stoicheiometry of the amine, reversal addition of the reagents) led to a lower yield, and any effort to purify oily products by column chromatography was unsuccessful. The cyclization of these acyl Meldrum's acids to give the optically active tetramic acids was performed by refluxing in acetonitrile, ethyl acetate or methanol for 15-20 minutes.

A variant of this stereoselective synthesis of chiral tetramic acid derivatives was reported by Martinez et. al.[8,9] who used *N*-protected *N*-carboxyanhydrides for the acylation step of Meldrum's acid. In an interesting work Sauvé et. al.[1] reported the condensation of *N*-protected amino acids and active methylene compounds (e.g. methyl cyanoacetate and malononitrile) to difunctionalized enols **4a** and **4b**, which is accomplished by the use of CDI as an activating reagent. In this process, the generated anion of the active methylene compound with sodium hydride at 0^0C, was added to a solution of the amino acid imidazolide (*in situ* prepared) from the corresponding amino acid and CDI at -78^0C. With those specific experimental conditions this application has led to the isolation of the optically active compounds **4a** and **4b**. Recently Kraus et. al.[2] have reported the synthesis of **4c** and its enantiomer by addition of Meldrum's acid to Boc-L-phenylalanine and Boc-D-phenylalanine respectively, in the presence of DCC-DMAP. These results were inconsistent with previous observations reported by Jouin et. al.[3] and by Joullie et. al.[10], who found that the DCC-DMAP activation system was not suitable for this reaction and recommended the use of IPCF as activating reagent. Kraus et. al.[2] also described that **4c** and its chiral underwent a cyclization reaction to the corresponding chiral tetramic acid **7** and its enantiomer, by refluxing for 10 minutes in EtOAc. In the course of our studies recently we have reported[11] the acylation of malononitrile using *N*-protected glycines by simultaneous activation of the amino acid carbonyl group and the active methylene group using CDI.

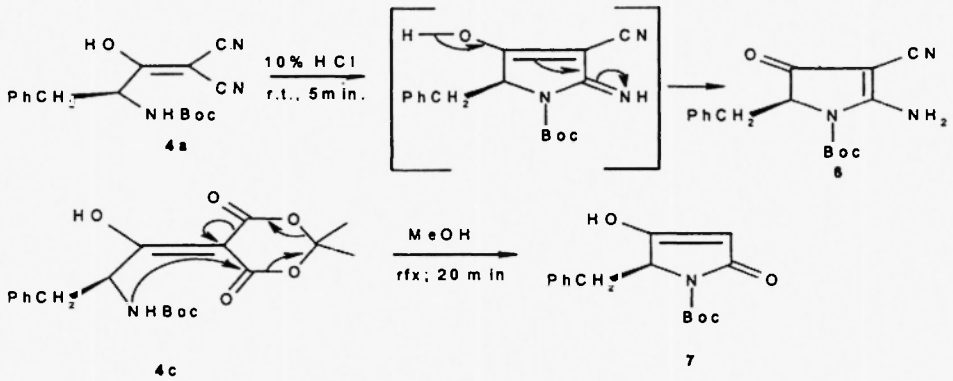
Now we are interested in the *C*-acylation reactions of three active methylene compounds, malononitrile, methyl cyanoacetate and Meldrum's acid with a chiral *N*-protected α-amino acid, the *N*-Boc-L-phenylalanine, using the CDI activation conditions. The acylation proceeds (see Scheme 1) through the imidazolide intermediate **2** of Boc-L-Phenylalanine (**1**) and the subsequent anion formation of the active methylene compound (X-CH_2-Y) from the liberated imidazole. It continues through the nucleophilic substitution on the imidazolide and results to imidazolinium salt **3** which after acidification gives the difunctionalized enols **4**

Scheme 1



Under these smooth, simple and convenient conditions, at room temperature, and without using a different activating reagent for amino acid's carbonyl activation and a base for the active methylene anion formation, we isolated products with nearly the same physical constants with those refered by other investigators[1,2,3] who used specific experimental conditions. The cyclization of **4c** to give the tetramic acid **7** (Scheme 2) was performed simply by refluxing some minutes in methanol as refered and by other authors[2,3], a process which we also applied[5] on glycine analogues. The corresponding adduct **4a** underwent a cyclization reaction to 2-amino-3-cyano-2-pyrrolin-4-one **6** (Scheme 2) under a mild acidic treatment at room temperature for 5 minutes, a process which we have reported recently[11] on *N*-protected-aminoacetyl-malononitriles.

Scheme 2



In conclusion, the *C*-acylation of malononitrile, methyl cyanoacetate and Meldrum's acid with *N*-Boc-L-phenylalanine to the corresponding aminoacetyl derivatives enantioselectively, has been performed by a simple experimental procedure using the imidazolide activation method. Two resulting adducts **4c** and **4a** were used as suitable precursors for the enantioselective synthesis of the corresponding tetramic acid **7** and the 2-amino-3-cyano-2-pyrrolin-4-one **6**. We are currently investigating the application of the imidazolide activation method to other chiral *N*-protected amino acids as well as the demonstration of enantiomeric excesses of their products. The application of this method for the stereoselective synthesis of mimicking dipeptides as potential HIV protease inhibitors is in our immediate plan.

Experimental

Contents:

I. Acylation reactions

II. Cyclization reactions

General. ^{1}H NMR spectra were recorded at ambient temperature at 60MHz using a Varian EM-360 spectrometer. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer (as nujol mulls). Optical rotations measured using a Perkin-Elmer 241 polarimeter with a path length of 1.0 dm at the sodium D-ray. Meldrum's acid was prepared according to the method of Davidson and Bernhard[12]. Unless otherwise noted all reagents were commercially obtained and, when appropriate, purified prior to use. CH_2Cl_2 was dried according to the procedure of Vogel[13].

I. Acylation reactions

4-tert-Butoxycarbonylamino-2-cyano-3-hydroxy-5-phenylpenten-2-nitrile (4a).

To a stirred solution of Boc-L-phenylalanine (1.33 g, 5 mmol) in dichloromethane (20 ml), 1,1'-carbonyldiimidazole (0.90 g, 5.5 mmol) was added, the flask of the reaction was protected with a calcium chloride tube. The resulting solution was stirred for 1hr, until the gas evolution (CO_2) ceased, malononitrile (0.37 g, 5.5 mmol) was then added and the mixture was stirred at room temperature for an additional 20 hours. The suspension, was then concentrated under *vacuum* and the semi-solid residue dissolved in ethyl acetate (20 ml). The solution was successively washed with 5% aqueous citric acid (60 ml), 5% aqueous sodium bicarbonate (10 ml) and brine (20 ml), dried over anhydrous $MgSO_4$

and concentrated under reduced pressure to give (1.08 g) of a semi-solid product which after washing with a small quantity of anhydrous ether gave (0.99 g, 63%) of a solid with a large range of melting point, it was difficult to recrystallize (lit.[1], no given physical state), which was shown (^{1}H NMR) to be pure **4a**; $[a]_D^{22}$ +80^0 (c 1, MeOH) {lit.[1], $[a]_D^{25}$ +92.5^0, c 1, MeOH}. IR (Nujol mull, cm^{-1}) 3380, 2205, 2195 and 1690; ^{1}H NMR (60 MHz, DMSO d_6): δ 1.30 (s, 9H, Boc-), 2.60-2.83 (m, 2H, $PhCH_2$-), 4.40 (m, 1H, >NCH<), 6.47 (d, *J*= 8.5Hz, 1H, >NH), 7.22 (s, 5H, Ph-).

Methyl 4-tert-Butoxycarbonylamino-2-cyano-3-hydroxy-5-phenylpent-2-enoate (4b).

To a stirred solution of Boc-L-phenylalanine (2.65 g, 10 mmol) in dichloromethane (10 ml), 1,1'-carbonyldiimidazole (1.87 g, 11.54 mmol) was added, the reaction flask was protected with a calcium chloride tube. The resulting solution was stirred for 1hr, until the gas evolution (CO_2) ceased, methyl cyanoacetate (0.99 g, 10 mmol) was then added and the mixture was stirred at room temperature for an additional 20 hours. To the solution an additional dichloromethane (10 ml) was added and washed with 10% hydrochloric acid (10 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under *vacuum*, the solid concentrate washed with a small quantity of anhydrous ether to yield **4b** (3.03 g, 87.5%) of a solid (which proved to be almost pure ^{1}H NMR), mp 148-150^0 C; recrystallization from $CHCl_3$/hexane gave analytical product mp 152.5-153^0 C (lit.[1], no given physical state); $[a]_D^{22}$ +85.4^0 (c 1, MeOH) {lit.[1], $[a]_D^{25}$ +77.9^0, c 1.04, MeOH}. IR (Nujol mull, cm^{-1}) 3360, 2220, 1690, 1660 and 1525; ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.39 (s, 9H, Boc-), 3.05 (m, 2H, $PhCH_2$-), 3.83 (s, 3H, -COOMe), 4.80-5.10 (m, 2H, -NH- and >NCH<), 7.20 (s, 5H, Ph-) and 13.7 (v br s, 1H, enolic –OH). Anal. Calcd. For $C_{18}H_{22}N_2O_5$: C, 62.41; H, 6.40; N, 8.09. Found: C, 62.21; H 6.20; N 8.20.

5-[2-(tert-Butoxycarbonylamino)-1-hydroxy-3-phenylpropylidene]–2,2-dimethyl-1,3-dioxane-4,6-dione (4c).

To a stirred solution of Boc-L-phenylalanine (2.65 g, 10 mmol) in dichloromethane (10 ml), CDI (1.85 g, 11.40 mmol) was added, the flask of the reaction was protected with a calcium chloride tube. The resulting solution was stirred for 1hr, until the gas evolution (CO_2) ceased, Meldrum's acid (1.44 g, 10 mmol) was then added and the solution was stirred at room temperature for an additional 20 hours. The solution was cooled with ice-water and acidified dropwise with 10% HCl (12 ml) with vigorous stirring. The resulting precipitate dissolved in CH_2Cl_2 (30 ml), the organic layer was separated and the aqueous layer extracted thrice (3x10 ml) with CH_2Cl_2. The combined organic layers were washed with brine (2x15 ml), dried over anhydrous $MgSO_4$ and concentrated under *vacuum* at r.t. to yield **4c** (3.78 g, 97%) of a solid (which proved to be almost pure ^{1}H NMR), mp 104-110^0 C dec.; recrystallization from $CHCl_3$/hexane gave a white crystalline powder mp 110-112^0 C dec. (lit.[2], 119^0 C), (lit.[3], 120-121^0 C); $[a]_D^{20}$ +89.1^0 (c 1, DMF) {lit.[3], $[a]_D^{20}$ +88^0, (c 1, DMF)}. IR (Nujol mull, cm^{-1}) 3360, 1723, 1695, 1655 and 1525; ^{1}H NMR (60 MHz, DMSO-d_6): δ 1.31 (s, 9H, Boc-), 1.68 (s, 6H, $>CMe_2$), 2.6-3.1 (m, 2H, $PhCH_2$-), 5.60 (br m, 1H, >NCH<), 7.37 (s, 5H, Ph-) and 7.50 (m, 1H, -NH-); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.37 (s, 9H, Boc-), 1.67 and 1.77 (two s equal intensity, 6H, $>CMe_2$), 2.6-3.3 (m, 2H, $PhCH_2$-), 5.00 (m, 1H, -NH-), 5.6-6.2 (m, 1H, >NCH<), 7.37 (s, 5H, Ph-) and 15.60 (br s, 1H, enolic –OH). Anal. Calcd. For $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.51; H 6.61; N 3.43.

II. Cyclization reactions

1-tert –butoxycarbonylpyrrol-2–amino–3–cyano–5–benzyl–2–pyrrolin–4-one (6).

Following the procedure for the preparation of the product 4a till the step of dissolving the reaction concentrate in ethyl acetate, the solution of the reaction concentrate in ethyl acetate (20 ml) was stirred vigorously with 10% HCl (6 ml) for 5 min. The organic layer was separated and concentrated under *vacuum* to a resinous mass which after some hours solidified and was washed with small quantities of dry ether to give (1.35 g, 86%) of a solid, mp>220^{0}C, which proved to be almost pure compound 6 (^{1}H NMR spectrum). Recrystallization from CH_2Cl_2 yielded a analytical sample mp>220^{0}C; $[a]_D^{22}$ –77.8^0 (c 1, MeOH). IR (Nujol mull, cm^{-1}) 3360, 3170, 2220, 1725, 1680 and 1620; ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.64 (s, 9H, Boc-), 3.30 (d, J= 4 Hz, 2H, $PhCH_2$-), 4.37 (t, J =4 Hz, 1H, ring's C5-H), 6.92-7.45 (m, 6H, Ph- and one -NH-), 8.35 (br s, 1H, the second -NH-). Anal. Calcd. For $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.27; H 6.30; N 13.26.

5-Benzyl-4-hydroxy-1-tert –butoxycarbonylpyrrol-2 (5H)-one (7).

Compound 4c (0.9 g, 2.3 mmol) in methanol (20 ml) was warmed at reflux temperature for 20 min. After concentration of the solution, a solid residue (0.66 g, 99%), which proved to be almost pure compound 7 (^{1}H NMR spectrum), mp 135-137^0 C. Recrystallization from $CHCl_3$/hexane yielded a crystalline solid (0.57 g, 85%), mp 136.5-138.5^0 C (lit.[3], mp 141-142^0 C), (lit.[2], mp 141^0 C); $[a]_D^{25}$ +225^0 (c 1, MeOH), {lit.[3], $[a]_D^{20}$ +230^0, (c 1, MeOH)}, {lit.[2], $[a]_D^{25}$ +230.4^0, (c 1.02, MeOH)}; IR (Nujol mull, cm^{-1}) 1765, 1650 and 1575; ^{1}H NMR (60 MHz, DMSO-d_6): δ 1.54 (s, 9H, Boc-), 3.26 (m, 2H, $PhCH_2$-), 4.63 (m, 1H, ring's C5-H), 4.73 (s, 1H, =C-H), 7.23 (m, 5H, Ph-) and 12.5 (br s, 1H, enolic-OH). Anal. Calcd. For $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.51; H 6.50; N 4.61.

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