USE OF CHIRAL AMIDALS IN THE SYNTHESIS OF 6-METHYLPERIHYDROPYRIMIDIN-4-ONES, PROTECTED FORM OF β-AMINO ACIDS

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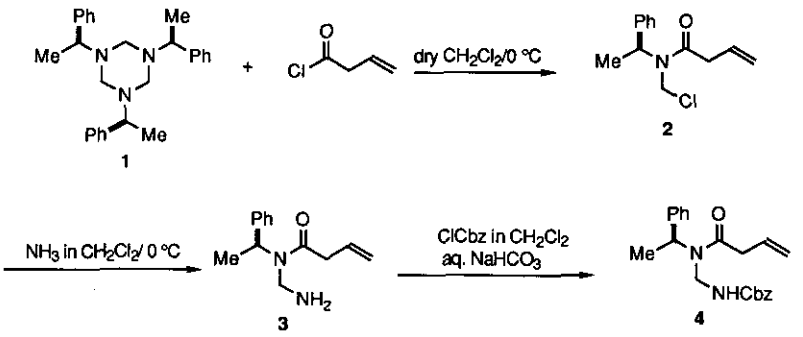
Abstract - The synthesis of 6-methylperihydropyrimidin-4-ones (**7a** and **7b**) is described by mercury cyclization of the β,γ-unsaturated amidal (**3**). After reduction of the intermediate organomercury compound (**6**) and separation of the diastereomeric mixture, the perihydropyrimidin-4-ones (**7a** and **7b**) have been obtained. Their structure has been fully characterized by means of ^{1}H nmr spectroscopy and, after acid hydrolysis, the 3-aminobutyric acids (**8a** and **8b**) have been obtained.

Perihydropyrimidin-4-ones are interesting heterocyclic compounds that represent protected forms of β-amino acids and are chiral precursors for the asymmetric synthesis of α-substituted-β-amino acids.[1] The synthesis of β-amino acids is receiving growing interest, due to the importance of these compounds either as components of natural products or as starting material for biological active molecules.[2]

Earlier work in our laboratory [3] showed the utility of mercury promoted cyclofunctionalization of α,β-unsaturated amidals containing as a chiral source the (*S*)-phenylethylamine in the synthesis of 5-substituted imidazolidin-4-ones, precursors of enantiomerically pure α-amino acids.

Utilising the same strategy, we envisaged a new synthesis of the 6-methylperihydropyrimidin-4-ones (**7a** and **7b**), precursors of the (*S*)- and (*R*)-3-aminobutyric acids (**8a** and **8b**), starting from the amidal obtained from the reaction of hexahydrotriazine (**1**) and 3-butenoyl chloride.[4] It is known in fact that reaction of hexahydrotriazines with acyl chlorides affords the corresponding *N*-chloromethyl adducts in quantitative yield.[5] Thus by treatment of **1** with 3-butenoyl chloride, the adduct (**2**) is obtained in quantitative yield and transformed in situ into the corresponding amidal (**3**) by reaction with ammonia. Compound (**3**) is then protected with benzyloxycarbonyl chloride to give **4** in 85% overall yield from **1**. The adduct (**4**) is practically pure and can be utilized for further

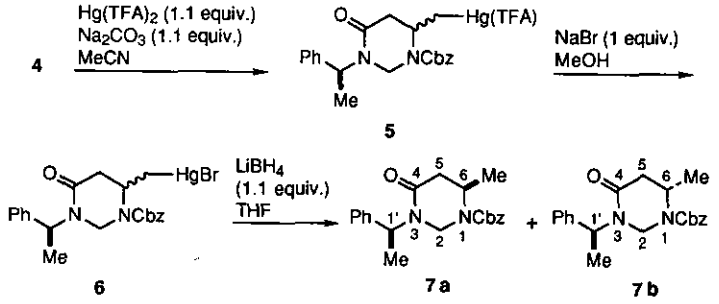
transformations. On the other hand the purification on silica gel chromatography occurs with partial decomposition (Scheme 1).



Scheme 1

The addition of $Hg(TFA)_2$ (1.1 equiv.) to a solution of **4** in dry CH_2Cl_2 at 0 °C promotes the cyclization.[6] Under these conditions the reaction monitored with tlc chromatography shows the presence of starting **4** even after prolonged reaction times. On the contrary the cyclization in MeCN with 1.1 equivalents of dry Na_2CO_3 is complete in 2 hours.[7]

As the reductive removal of mercury performed on compound (**5**) affords **7** in low yield, **5** has been reacted with NaBr (1 equiv.) in MeOH to afford **6** in quantitative yield.[7] By treatment of **6** with $LiBH_4$ (1.1 equiv.) in THF at -78 °C and after the usual work-up, a mixture of 6-methylperihydropyrimidin-4-ones (**7a** and **7b**) is obtained in 70% yield and 63:37 diastereomeric ratio, as shown by the nmr spectra and by GCms (gas chromatography - mass spectrometer) analysis.[8] The separation of 6-methylperihydropyrimidin-4-ones (**7**) by flash chromatography on silica gel, affords pure **7a** ($[\alpha]_D$ -71.6°, c = 0.7, $CHCl_3$) and **7b** ($[\alpha]_D$ -34.2°, c = 1.4, $CHCl_3$) in the above reported diastereomeric ratio (Scheme 2). The ir absorption at 1650 cm^{-1} is diagnostic for the expected six-membered ring formation.



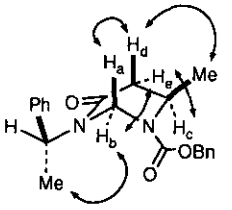
Scheme 2

The structure of **7a** and **7b** has been established by detailed ^{1}H nmr studies. Two factors are peculiar for the determination of the configuration and of the conformation that these mobile molecules assume. As already observed [9] for heterocycles containing a (*S*)-phenylethylamide moiety, the chiral group on C_1' shows a strong tendency to assume a rigid conformation with the hydrogen eclipsing the carbonyl group. In this conformation the hydrogen in front of the phenyl group is strongly shielded. Moreover the carbonyl of the protecting carbobenzoxy group deshields preferentially the hydrogen lying in the same plane, thus H_a or H_b, depending on the conformation of the perihydropyrimidin-4-one (see Figure 1 and Figure 2).

The presence of the carbobenzoxy group is also responsible for the formation of rotamers, which can be observed recording the ^{1}H nmr spectra at -30 °C.[10] While the ^{1}H nmr spectra of **7a** and **7b** show a bad resolution at room temperature, due to the coalescence point of the molecule, they show a perfect resolution, if recorded at 50 °C.

The ^{1}H nmr spectrum of the less polar isomer (**7a**) shows that the hydrogens H_d and H_e, resonating at δ 2.32 and 2.71 respectively, have a large geminal coupling constant ($J_{Hd,He}$ = 15.7 Hz) and two coupling constants ($J_{Hd,Hc}$ = 8.2 Hz; $J_{He,Hc}$ = 6.4 Hz) that are in line with the methyl group in the equatorial position. Moreover the doublet at δ 4.14 (J = 13.2 Hz) is very shielded: this result suggests that it experiences the presence of the phenyl group, and therefore is attributed to H_a. Furthermore H_b (δ 4.91, J = 13.2 Hz) results deshielded by the carbonyl group lying in the same plain. These results agree with a **(1'*S*,6*R*)-7a** configuration in the preferential conformation reported in Figure 1.

The results of NOE experiments performed on **7a** confirm the stereochemical assignment. Thus the irradiation of the methyl at C_1' (δ 1.47) produces an enhancement of the doublet at 4.91, that is therefore assigned to H_b. On the other hand the irradiation of the dd at δ 2.32 attributed to H_d produced an enhancement of the H_a signal (δ 4.14) and an enhancement of the methyl at C_6 (δ 1.20). Irradiation of H_e (δ 2.71) produces an enhancement of the H_c signal at δ 4.20 and a very weak enhancement of H_b (δ 4.91). The irradiation of H_b and of the methyl at C_6 confirm these results.



(1'*S*,6*R*)-7a

Figure 1

In a similar way the structure of **7b** has been established by means of ^{1}H nmr analysis. In fact the coupling constants of H_d-H_c and H_e-H_c ($J_{Hd,He}$ = 15.7 Hz, $J_{Hd,Hc}$ = 6.3 Hz, $J_{He,Hc}$ = 6.6 Hz) account for a rather flat conformation with the methyl in the equatorial position. The structure of **(1'*S*,6*S*)-7b** is therefore forced in the conformation shown in Figure 2. The chemical shifts of H_a (δ 4.74) and H_b (δ 4.54) agree with this assignment: in this conformation H_a is strongly deshielded

by the carbonyl of the carbobenzoxy protecting group and it does not suffer the shielding effect of the vicinal phenyl group. These effects account for the H_a chemical shift at low field.

The NOE experiments performed on **7b** confirm the attribution and show that the irradiation on H_e causes an enhancement of the methyl on C_6 (δ 1.47) and of the doublet resonating at δ 4.54, that can be attributed to H_b. The irradiation of the methyl on C_6 causes the enhancement of H_e, and the irradiation of H_d causes an enhancement of H_c and a weak enhancement (~1%) of the doublet resonating at δ 4.74 that can be attributed to H_a. The NOE experiment performed on H_a and H_b confirm the above reported results. Finally the irradiation of the methyl on C_1' causes a very weak enhancement of H_a and H_b. These results allow to attribute the conformation of **(1'*S*,6*S*)-7b** as reported in Figure 2.

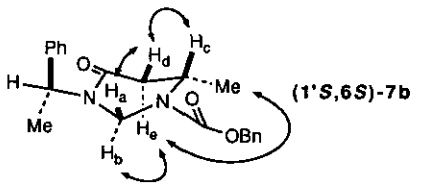
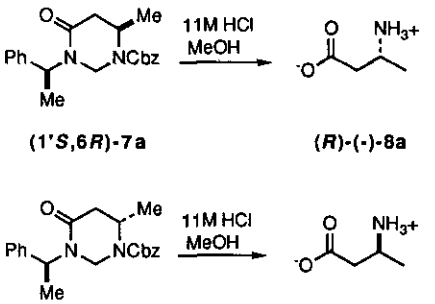


Figure 2

The absolute configuration of these perihydropyrimidin-4-ones is confirmed by conversion of **(1'*S*,6*R*)-7a** and **(1'*S*,6*S*)-(7b)** into the corresponding 3-aminobutyric acids (**(*R*)-(-)-8a** and **(*S*)-(+)-8b**). In fact **8a** and **8b** are obtained by acid hydrolysis of **7a** and **7b** respectively in 6M HCl at reflux. The β-amino acids are purified by treatment with aqueous sodium carbonate followed by extraction with ethyl acetate to separate the (*S*)-phenylethylamine. Acidification of the aqueous layer and elution of the mixture from a cation exchange resin (BIORAD AG 50W-X2) with 1.5M NH_4OH affords pure **(8a** and **8b)** that show $[\alpha]_D$ and mp values in agreement with those reported in the literature (Scheme 3).[11]



Scheme 3

In conclusion the presence of the (*S*)-phenylethylamide moiety is useful in the determination of the structure of such complex heterocycles and this work represents a simple route to the synthesis of (*S*)- and (*R*)-6-methylperihydropyrimidin-4-ones.

EXPERIMENTAL

General Methods. ^{1}H Nmr and ^{13}C nmr spectra were recorded at 300 MHz and 75 MHz, respectively, on a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm relative to the solvent. The nmr tubes containing samples of **7a** and **7b** have been degased with the freeze-pump-thaw technique before running NOE experiments. Ir spectra were recorded with a Perkin-Elmer 682 infrared spectrophotometer. Melting points were determined in open capillaries and are uncorrected. GCms analyses were performed with a cross linked methyl silicone column. Flash chromatography was performed with silica gel 60 (230-400 mesh). Methylene chloride was distilled over CaH_2 and stored over molecular sieves. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Other solvents were used as purchased. (*S*)-1-Phenylethylamine was purchased by Janssen and distilled.

(*S*)-*N*-(1-Phenyleth-1-yl)-*N*-benzyloxycarbonylaminomethyl-acrylamide 4

A solution of 3-butenoyl chloride (2.5 g, 24 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise to a solution of hexahydrotriazine **1** (3.2 g, 8 mmol) in dry CH_2Cl_2 (30 ml) at 0 °C and under argon. After 20 min at 0 °C the tlc analysis of the reaction mixture showed a single spot corresponding to the *N*-chloromethyl-*N*-(*S*)-phenylethylamide (**2**).

Meanwhile in a 500 ml four-necks flask dry CH_2Cl_2 (200 ml) was saturated with gaseous NH_3. The solution of *N*-chloromethyl-*N*-(*S*)-phenylethylamide (**2**) (24 mmol) in CH_2Cl_2 was added dropwise at 0 °C, bubbling NH_3. After 20 min a white precipitate (ammonium chloride) was formed and the bubbling was stopped. The mixture was filtered and the white solid was washed with CH_2Cl_2. The liquid was concentrated under vacuum and the corresponding *N*-aminomethyl-*N*-(*S*)-phenylethylamide (**3**) was obtained in quantitative yield.

To a solution of *N*-aminomethyl-*N*-(*S*)-phenylethylamide **3** in CH_2Cl_2 (50 ml) and aqueous $NaHCO_3$ (50 ml), benzyl chloroformate (2.55 ml, 18 mmol) in CH_2Cl_2 (10 ml) was added dropwise at 0 °C. The mixture was stirred 10 min at room temperature then separated in a funnel. The organic layer was dried over Na_2SO_4 and concentrated. The amidal (**4**) was obtained practically pure in 85% yield and could be used without any further purification. Silica gel chromatography (cyclohexane:ethyl acetate 8:2) afforded pure **4** (5.07 g, 60%), owing to partial decomposition of the amidal to the corresponding *N*-(*S*)-phenylethylamide.

ν_{max} (film): 3420, 3300, 1720, 1640, 1600 cm^{-1}; δ_H ($CDCl_3$) 1.70 (3H, d, J = 7.1 Hz, N-CH-C<u>H</u>$_3$), 3.28 (2H, d, J = 6.5 Hz, OC-C<u>H</u>$_2$-CH), 4.52 (2H, m, N-C<u>H</u>$_2$-N), 5.12 (5H, m, OC<u>H</u>$_2$Ph + CH=C<u>H</u>$_2$ + N-C<u>H</u>-CH$_3$), 6.05 (2H, m, C<u>H</u>=CH$_2$ + NH), 7.32 (10H, m, Ph); δ_C ($CDCl_3$) 18.12, 38.54, 49.88, 54.97, 66.27, 117.99, 126.45, 127.41, 127.56, 127.72, 128.14, 128.46, 136.17, 139.68, 155.13, 172.32; $[\alpha]_D$ -76.5 ° (c = 2, $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.48, H, 6.82, N, 7.90.

1-Benzyloxycarbonyl-3-(1'-phenyleth-1'-yl)-6-methylperihydropyrimidin-4-ones 7a and 7b

To a stirred solution of amidal **4** (1.06 g, 3.0 mmol) in dry CH_2Cl_2 (60 ml) $Hg(TFA)_2$ (1.36 g, 3.2 *mmol*) was added at room temperature and under argon. After 2 h the reaction was complete and NaBr (0.33 g, 3.2 mmol) in MeOH (10 ml) was added dropwise. After 20 min the mixture was concentrated and replaced with dry THF (100 ml). The solution was cooled at -78 °C and $LiBH_4$ (2M solution in THF, 1.5 ml, 3 mmol) was added. The mixture was stirred overnight and the reaction mixture was allowed to warm up. Elemental mercury precipitated and was filtered, the solution was concentrated under vacuum, water and ethyl acetate were added and the organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was chromatographed on silica gel (cyclohexane:ethyl acetate 9:1) and the perihydropyrimidin-4-ones **7a** (0.46 g, 44%) and **7b** (0.27 g, 26%) were obtained.

(1'*S*,6*R*)-7a: mp 110-112 °C; ν_{max} (nujol): 1710, 1650 cm^{-1}; δ_H ($CDCl_3$, 50 °C) 1.20 (3H, d, J = 6.3 Hz, OC-CH_2-CH-C$\underline{H}_3$), 1.47 (3H, d, J = 7.1 Hz, N-CH-C$\underline{H}_3$), 2.32 (1H, dd, $J_{Hd,Hc}$ = 8.2 Hz, $J_{Hd,He}$ = 15.6 Hz, H_d), 2.71 (1H, dd, $J_{He,Hc}$ = 6.4 Hz, $J_{He,Hd}$ = 15.6 Hz, H_e), 4.14 (1H, d, $J_{Ha,Hb}$ = 13.2 Hz, H_a), 4.20 (1H, m, H_c), 4.91 (1H, d, $J_{Hb,Ha}$ = 13.2 Hz, H_b), 5.12 (2H, AB, O-C$\underline{H}_2$-Ph), 5.83 (1H, q, J = 7.1 Hz, N-C$\underline{H}$-CH_3), 7.27 (10H, m, Ph); δ_C ($CDCl_3$, 50 °C) 16.33, 20.55, 39.66, 47.07, 50.01, 51.91, 67.64, 127.23, 127.65, 128.06, 128.28, 128.58, 128.66, 136.21, 139.98, 168.86; $[\alpha]_D$ -71.6 ° (c = 0.7, $CHCl_3$); ms(m/z) 353 (1.1%), 352 (M^+) (4.7%), 261 (2.7%), 247 (3.9%), 203 (2.7%), 174 (1.4%), 157 (13.1%), 120 (18.9%), 105 (26.5%), 91 (100%), 79 (7.4%), 77 (11.1%), 65 (11.1%), 56 (20.9%). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.51, H, 6.79, N, 7.88.

(1'*S*,6*S*)-7b: oil; ν_{max} (film): 1710, 1650 cm^{-1}; δ_H ($CDCl_3$, 50 °C) 1.26 (3H, d, J = 6.3 Hz, OC-CH_2-CH-C$\underline{H}_3$), 1.51 (3H, d, J = 7.1 Hz, N-CH-C$\underline{H}_3$), 2.38 (1H, dd, $J_{He,Hc}$ = 6.6 Hz, $J_{He,Hd}$ = 15.7 Hz, H_e), 2.71 (1H, dd, $J_{Hd,Hc}$ = 6.3 Hz, $J_{Hd,He}$ = 15.7 Hz, H_d), 4.21 (1H, m, H_c), 4.54 (1H, d, $J_{Ha,Hb}$ = 12.7 Hz, H_b), 4.74 (1H, d, $J_{Hb,Ha}$ = 12.7 Hz, H_a), 5.05 (2H, AB, O-C$\underline{H}_2$-Ph), 5.90 (1H, q, J = 7.1 Hz, N-C$\underline{H}$-CH_3), 7.27 (10H, m, Ph); δ_C ($CDCl_3$, 50 °C) 16.39, 20.41, 39.37, 46.87, 50.06, 52.17, 67.39, 127.13, 127.63, 127.88, 128.13, 128.49, 128.60, 136.24, 139.91, 168.79; $[\alpha]_D$ -34.2 ° (c = 1.4, $CHCl_3$); ms(m/z) 353 (1.5%), 352 (M^+) (7.1%), 261 (4.1%), 247 (2.4%), 203 (2.4%), 174 (1.6%), 157 (15%), 120 (22.7%), 105 (9.8%), 91 (100%), 79 (7.4%), 77 (9.32%), 65 (9.8%), 56 (22.2%). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.59, H, 6.88, N, 7.93.

(*R*)-(-)-3-Aminobutyric acid 8a

A solution of perihydropyrimidin-4-one (**7a**) (0.35 g, 1 mmol) in 6M HCl (5 ml) was refluxed for 12 h. The mixture was then concentrated and extracted with ethyl acetate/aqueous Na_2CO_3 to separate the (*S*)-1-phenylethylamine. To the aqueous layer 6M HCl was added until acid pH, concentrated and replaced with water. The mixture was adsorbed on cation exchange resin BIORAD AG 50W-X2 and the resin was washed with distilled H_2O till the washing came out neutral, then with NH_4OH 1.5M to recover the β-amino acid. Evaporation of the aqueous solution

afforded the 3-aminobutyric acid (**8a**) in the zwitterionic form (70 mg, 68%). mp 210-211 °C (lit., [11] 212 °C); δ_H (D_2O) 1.11 (3H, d, J = 6.6 Hz, N-CH-C<u>H</u>$_3$), 2.28 (2H, d, J = 7.1 Hz, OC-C<u>H</u>$_2$-CH), 3.40 (1H, m, CH_2-C<u>H</u>-CH_3); δ_C (D_2O) 17.26, 40.24, 44.97, 177.61; $[\alpha]_D$ -38.1° (c = 0.7, H_2O).

(*S*)-(+)-3-Aminobutyric acid 8b

The β-amino acid (**8b**) was obtained from **7b** with the same procedure (65% yield). mp 209-211 °C (lit., [11] 212 °C); $[\alpha]_D$ +37.8° (c = 0.1, H_2O), lit., [11] $[\alpha]_D$ +38.8° (c = 0.48, H_2O).

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