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SYNTHESIS OF METHYL 3-AMINO-3-PYRROLIDINECARBOXYLATES : A CONVENIENT ACCESS TO CUCURBITINE AND ANALOGUES.

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Abstract : Cycloaddition of N-benzylazomethine ylide **7** to methyl 2-(diphenylmethyleneamino) or 2-(benzylideneamino) acrylates affords the tittle compounds after deprotection by catalytic hydrogenation.

3-amino-3-pyrrolidine carboxylic acid **1**, or cucurbitine, is a non-proteic aminoacid found in cucurbitaceaes [1] and well known for its antihelmintic activity [2]. A few reports on the synthesis of this aminoacid are found in litterature, through Strecker reaction [1] or a multistep rearrangement procedure [3]. We report and improved procedure according to the following retrosynthetic analysis (scheme A) :

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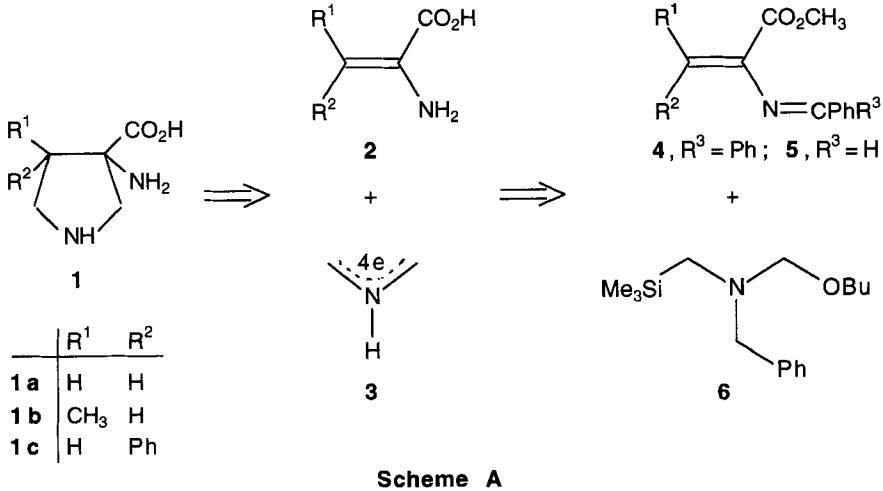
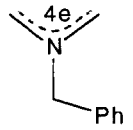


	R^1	R^2
1a	H	H
1b	CH_3	H
1c	H	Ph

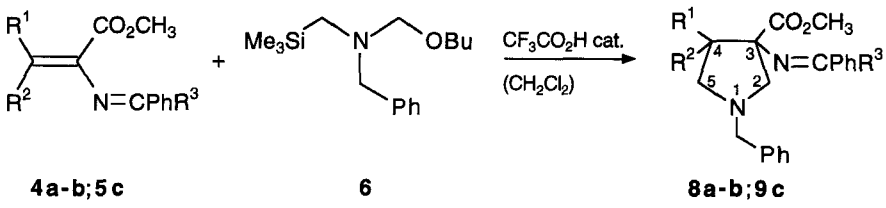
Scheme A

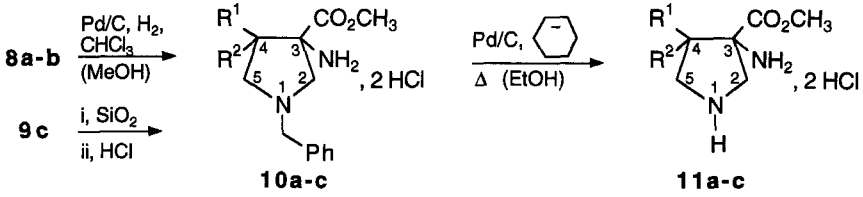
A 1,3-dipolar disconnection affords didehydroaminoacids **2** and the "naked" non substitued azomethine ylide **3** as synthons. Diphenylmethylene or benzylidene Schiff bases **4** [4] or **5** [5] are valuable synthetic equivalents of **2** ; the imino protective group is readily introduced and removed and furthermore is expected to activate the α,β-double bond in cycloaddition with electron rich 1,3-dipoles. Non stabilized azomethine ylides have been widely used for the construction of the pyrrolidine ring [6]. N-benzyl-N-(butoxymethyl)-N-(trimethylsilylmethyl) amine **6** is an efficient precursor of the non-stabilized azomethine ylide **7** [7].



7

Methyl 3-amino-3-pyrrolidinecarboxylates **11** were synthetized in three steps according to scheme B.





	R^1	R^2	R^3
4a;8a	H	H	Ph
4b;8b	CH_3	H	Ph
5c;9c	H	Ph	H

	R^1	R^2
10a;11a	H	H
10b;11b	CH_3	H
10c;11c	H	Ph

Scheme B

Cycloadditions were performed according to the procedure described by Achiwa [7] by addition of a catalytic amount of CF_3CO_2H to a mixture of the Schiff bases **4**, **5** and of the precursor **6**. Yields of pyrrolidines **8**, **9** were notably improved by increasing the amount of catalyst to 0.3 equivalent. Imine **5d** (R^1 = R^2 = CH_3, R^3 = H) was also investigated but proved to be unreactive, probably for steric reasons. Pyrrolidines **8b** and **9c** were obtained as a single stereoisomer, in good agreement with the stereospecificity of the cycloaddition.

Amine deprotections were performed in two steps. Hydrolysis of the benzylidene Schiff base **8c** occured during chromatographic purification and the free aminoester was immediately converted to the stable bis-hydrochloride **9c**. Diphenylmethylene Schiff bases **8a-b** were deprotected by catalytic hydrogenation

in presence of chloroform [8] leading to bis-hydrochloride **10a-b**. Debenzylation was achieved by Pd/C in boiling ethanol in presence of cyclohexene [9].

EXPERIMENTAL

All compounds were characterized by their ^{1}H-NMR and ^{13}C-NMR spectra as well as by microanalysis or HRMS spectra. NMR spectra were recorded on Bruker AC 300 P (300 MHz for ^{1}H and 75,5 MHz for ^{13}C) spectrometer (δ-ppm/TMS, J-Hz); for ^{13}C NMR, the multiplicities were determined through DEPT or non decoupled spectra. Microanalysis were performed by the "Laboratoire Central de Microanalyse du CNRS" (Lyon). Mass spectra were recorded on a Varian MAT 311 spectrometer. Melting points were measured using a Köfler apparatus and were uncorrected. Column chromatography was carried out by use of silica gel 60 Merck (230-400 Mesh).

Diphenylmethylene or benzylidene Schiff bases **4** and **5** were obtained according to the litterature procedure [4,5].

Methyl 3-imino-3-pyrrolidinecarboxylates 8a-b

General procedure : A 0.1 M solution of trifluoroacetic acid (12 mL, 0.3 equiv.) in CH_2Cl_2 was added at 0°C to a stirred solution of **6** [7] (4 mmol) and Schiff base **4** (3 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 4 h at room temperature and the mixture washed with a 0.5 M solution of sodium bicarbonate (2.4 mL) and with brine, then dried over $MgSO_4$. Solvent was evaporated *in vacuo*. Chromatography on silica gel (hexane/ether - 4/1 - as eluent) of the crude product gave pure **8** as a yellow oil.

8a : 80% yield. ^{1}H NMR ($CDCl_3$) : 2.20 (ddd, 1H, J = 12.6, 7.7 and 6.2, H^4 or $H^{4'}$), 2.54 (ddd, 1H, J = 12.6, 7.0 and 5.5, $H^{4'}$ or H^4), 2.66 (ddd, 1H, J = 8.9, 7.0, and 6.2, H^5 or $H^{5'}$), 2.78 (ddd, 1H, J = 8.9, 7.7 and 5.5, $H^{5'}$ or H^5), AB system : 3.06 and 3.09, J = 9.7 ($H^{2'}$ or H^2), 3.29 (s, 3H, OCH_3), AB system : 3.62 and 3.68, J = 13.1 (CH_2Ph), 7.03-7.59 (m, 15H, Ar*H*). ^{13}C NMR

($CDCl_3$) : 39.4 (C^4), 51.6 (OCH_3), 53.5, 59.7 (C^2, C^5), 67.0 (N-CH_2Ph), 72.5 (C^3), 126.8, 127.7, 127.8, 128.1, 128.3, 128.6, 128.7, 130.1, 137.2, 138.8, 140.2 (Ar*C*), 167,9 (C=N), 174.0 (C=O). Elemental analysis : $C_{26}H_{26}N_2O_2$ (398.5) calcd : C 78.39, H 6.53, N 7.03 ; found : C 78.48, H 6.42, N 6.95.

8b : 78% yield. ^1H NMR ($CDCl_3$) : 1.04 (d, 3H, J = 6.7, CH_3), 2.33 - 2.43 (m, 1H, H^4), 2.78 (d, 1H, J = 10.3, H^2 or $H^{2'}$), 2.90 - 3.06 (m, 2H, H^5 and $H^{5'}$), 3.17 (d, 1H, J = 10.3, $H^{2'}$ or H^2), 3.40 (s, 3H, OCH_3), AB system : 3.61 and 3.66, J = 13.1 (CH_2Ph), 6.99-7.64 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$) : 14.2 (CH_3), 48.4 (C^4), 51.1 (OCH_3), 59.1, 60.3 (C^2, C^5), 64.1 (N-CH_2Ph), 75.7 (C^3), 126.8, 127.9, 128.0, 128.2, 128.3, 128.6, 128.7, 128.8, 130.2, 137.9, 139.6, 140.6 (Ar*C*), 168.3 (C=N), 173.2 (C=O). Elemental analysis : $C_{27}H_{28}N_2O_2$ (412.5) calcd : C 78.64, H 6.79, N 6.79; found : C 78.37, H 6.76, N 6.70.

Methyl N-benzyl-3-aminopyrrolidinecarboxylates hydrochlorides 10a-b

General procedure : A solution of **8** (3 mmol) in methanol (20 mL) and $CHCl_3$ (2 mL) with 10 % Pd/C (150 mg) under vigorous stirring was connected to an atmospheric pressure hydrogenation apparatus. After completion of reaction, the catalyst was removed by filtration then washed with methanol. After distillation of the solvent of the combined organic phases, the resulting oil was extracted with water (20 mL) and the extract washed with ether (2 x 20 mL). The extremely hygroscopic bis-hydrochloride **10** was obtained by elimination of water *in vacuo* and recristallization from ethanol.

10a : 85% yield. mp 170-3°C. ^1H NMR (D_2O) : 2.54 (dt, 1H, J = 14.8 and 7.3, H^4 or $H^{4'}$), 2.83 (dt, 1H, J = 14.8 and 7.3, $H^{4'}$ or H^4), 3.72 (t, J = 7.3, 2H, H^5 and $H^{5'}$), 3.76 (d, 1H, J = 13.8, H^2 or $H^{2'}$), 3.87 (s, 3H, OCH_3), 4.14 (d, 1H, J = 13.8, $H^{2'}$ or H^2), AB system : 4.50 and 4.53, J = 13.0 (CH_2Ph), 7.49 (br s, 5H, Ar*H*). ^{13}C NMR (D_2O) : 36.5 (C^4), 57.6 (OCH_3), 55.5, 61.2, 61.5 (C^2, C^5, CH_2Ph), 64.4 (C^3), 131.7, 132.2, 133.2, 133.3 (Ar*C*), 172.0 (C=O). HRMS, m/z : 234 (M^+), calcd for $C_{13}H_{18}N_2O_2$: 234.136, found : 234.135.

10b : 84% yield. mp 232-4°C. ^{1}H NMR (D_2O) : 1.03 (d, 3H, J = 6.8, CH_3), 2.80 - 2.95 (m, 1H, H^4), 3.33 (t, 1H, J = 12.0, H^5 or $H^{5'}$), 3.74 (dd, 1H, J = 12.0 and 7.3, $H^{5'}$ or H^5), 3.87 (s, 3H, OCH_3), AB system : 3.86 and 4.13, J = 14.0 ($H^{2'}$ or H^2), AB system : 4.44 and 4.50, J = 12.9 (CH_2Ph), 7.46 (br s, 5H, Ar*H*). ^{13}C NMR (D_2O) : 12.7 (CH_3), 43.5 (C^4), 57.3 (OCH_3), 60.0, 60.8, 62.0 (C^2, C^5, CH_2Ph), 67.8 (C^3), 131.4, 132.1, 133.1, 133.4 (Ar*C*), 170.8 (C=O). HRMS, m/z : 248 (M^+), calcd for $C_{14}H_{20}N_2O_2$: 248.152, found : 248.151.

Methyl N-benzyl-3-aminopyrrolidinecarboxylate hydrochloride 10c

Treatment of **5** according to the procedure for **4** afforded **9c** which was hydrolyzed during chromatography on silica gel (dichloromethane/ether - 4/1 - as eluent), leading to the corresponding unstable free 3-aminopyrrolidine as a yellow oil. Anhydrous ether was then added and the solution was saturated with dry HCl. The precipitated pyrrolidine hydrochloride **10c** was filtered, washed with ether (2 x 5 mL) and dried.

free 3-aminopyrrolidine : TLC, R_f = 0.30 (CH_2Cl_2/ether - 4/1). 66% yield. ^{1}H NMR ($CDCl_3$) : 2.37 (br s, 2H, NH_2), 2.62 (d, 1H, J = 9.8, H^2 or $H^{2'}$), AB part of ABX system : 3.01 (A) and 3.09 (B), J_{AB} = 8.8, $J_{AX} \approx J_{BX} \approx$ 8.2 (H^5 and $H^{5'}$), 3.29 (d, 1H, J = 9.8, $H^{2'}$ or H^2), 3.68 (s, 3H, OCH_3), AB system : 3.66 and 3.75, J = 13,0 (CH_2Ph), 3.82 (X part of ABX system, $J_{AX} \approx J_{BX} \approx$ 8.2, H^4), 7.11-7.42 (m, 10H, Ar*H*). ^{13}C NMR ($CDCl_3$) : 52.5 (OCH_3), 52.6 (C^4), 57.5 and 60.3 (C^2 and C^5), 65.8 (CH_2Ph), 66.1 (C^3), 127.2, 127.3, 128.4, 128.6, 128.8, 129.0, 137.1, 138.6 (Ar*C*), 176.0 (C=O).

10c : 96% yield. mp 210-3°C. ^{1}H NMR (D_2O) : 3.84 (d, 1H, J = 14.2, H^2 or $H^{2'}$), 3.95 (s, 3H, OCH_3), 4.10-4.40 (m, 3H, H^4, H^5 and $H^{5'}$) ; 4.52 (d, 1H, J = 14.2, $H^{2'}$ or H^2), AB system : 4.62 and 4.67, J = 13.1 (CH_2Ph), 7.22-7.57 (m, 10H, Ar*H*). ^{13}C RMN (D_2O) : 52.5 (C^4), 57.7 (OCH_3), 56.6, 61.6, 62.5 (C^2, C^5, CH_2Ph), 67.8 (C^3), 130.5, 131.2, 131.7, 132.2, 132.5, 132.7, 133.1, 133.3 (Ar*C*), 171.4 (C=O). HRMS, m/z : 310 (M^+), calcd for $C_{19}H_{22}N_2O_2$: 310.168, found : 310.170.

Methyl 3-amino-3-pyrrolidinecarboxylates hydrochlorides 11a-c

General procedure : A stirred solution of the hydrochloride **10** (2 mmol) and cyclohexene (2 mL) in ethanol (40 mL) was refluxed with 10 % Pd/C (100 mg) for 24 h. The catalyst was filtered off and the filtrate evaporated. The resulting oil was extracted with water and the extract washed with ether (2 x 20 mL). The extremely hygroscopic bis-hydrochloride **11** was obtained by elimination of water *in vacuo* and recristallisation from ethanol.

11a : 87% yield. ^{1}H NMR (D_2O) : 2.52 (dt, 1H, J = 14.8 and 7.9, H^4 or $H^{4'}$), 2.79 (dt, 1H, J = 14.8 and 7.3, $H^{4'}$ or H^4), 3.58 - 3.72 (m, 2H, H^5, $H^{5'}$), 3.87 (s, 3H, OCH_3), 3.69 (d, 1H, J = 13.6, H^2 or $H^{2'}$), 4.10 (d, 1H, J = 13.6, $H^{2'}$ or H^2). ^{13}C NMR (D_2O) : 36.7 (C^4), 54.1, 54.5 (C^2, C^5), 57.2 (OCH_3), 64.9 (C^3), 172.2 (C=O). HRMS, m/z : 144 (M^+), calcd for $C_6H_{12}N_2O_2$: 144.101, found : 144.102.

11b : 88% yield. ^{1}H NMR (D_2O) : 1.12 (d, 3H, J = 6.8, CH_3), 2.91 (ddq, 1H, J = 6.8, 8.1 and 12.1, H^4), 3.30 (t, 1H, J = 12.1, H^5 or $H^{5'}$), 3.70 (d, 1H, J = 13.5, H^2 or $H^{2'}$), 3.82 (dd, 1H, J = 12.1 and 8.1, $H^{5'}$ or H^5), 3.95 (s, 3H, OCH_3), 4.14 (d, 1H, J = 13.5, $H^{2'}$ or H^2). ^{13}C NMR (D_2O) : 12.8 (CH_3), 43.6 (C^4), 52.6, 53.3 (C^2, C^5), 57.1 (OCH_3), 67.9 (C^3), 171.1 (C=O). HRMS, m/z : 158 (M^+), calcd for $C_7H_{14}N_2O_2$: 158.105, found : 158.106.

11c : 82% yield. ^{1}H NMR (D_2O) : 3.77 (d, 1H, J = 14.0, H^2 or $H^{2'}$), 3.94 (s, 3H, OCH_3), 3.90 - 4.20 (m, 3H, H^4, H^5, $H^{5'}$), 4.29 (d, 1H, J = 14.0, $H^{2'}$ or H^2), 7.25 - 7.45 (m, 5H, Ar*H*). ^{13}C NMR (D_2O) : 51.5 (C^4), 54.3, 55.6 (C^2, C^5), 57.3 (OCH_3), 67.7 (C^3), 131.2, 131.8, 132.3, 132.4 (Ar*C*), 172.7 (C=O). HRMS, m/z : 220 (M^+), calcd for $C_{12}H_{16}N_2O_2$: 220.145, found : 220.145.

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