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A CONVENIENT SYNTHESIS OF SUBSTITUTED PYRROLES FROM ESTERS OF AMINO ACIDS

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Abstract : A new simple synthesis of substituted pyrroles from alkyl, aryl or heteroaryl substituted α-amino acids is described. Esters of α-amino acids are first reacted with dimethyl acetylenedicarboxylate and in the *in situ* formed enamines are thereafter cyclized in presence of sodium methoxide to pyrroles.

Among various synthetic methods for pyrroles, cyclization reactions involving amines, enamines or amino carbonyl compounds as precursors are well documented.[1] However, there are only a few reports on amino acids or their esters as starting compounds.

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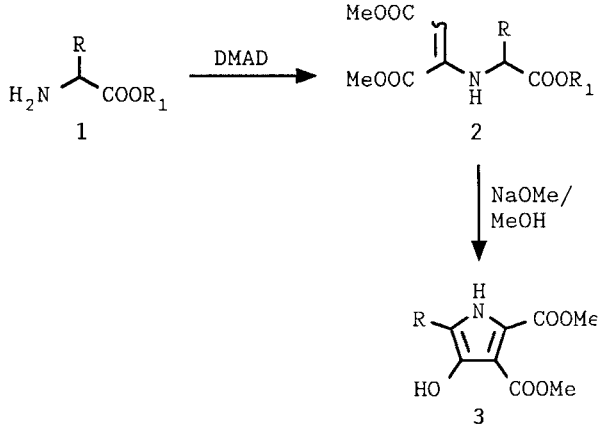
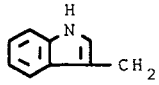
Cyclization of enamines, derived from α-amino acids and 1,3-diketones or β-keto esters[2-5] and the reaction of 3-alkoxyacroleins with subsequent cyclization[6] are reported. Also a direct transformation of methyl N,N-diethylglycinate with dimethyl acetylenedicarboxylate (DMAD) to give a N-substituted 4-hydroxypyrrole is described.[7] In another synthesis, α-amino acids were first transformed into iminophosphoranes which gave with DMAD two pyrroles as by-products in low yield.[8]

We report herewith a new and simple approach for the synthesis of 5-alkyl, -aryl or -heteroaryl substituted 2,3-di(methoxycarbonyl)-4-hydroxypyrroles. The reaction involves the addition of esters of α-amino acids **1** to DMAD at room temperature and further cyclization of the corresponding enamines **2** which were not isolated, in the presence of sodium methoxide into pyrroles **3** in moderate to good yield.



Scheme

Table

Entry 1	R	R_1	Reaction Time with NaOMe (h)	Isolated Yield (%)
a	Me	Et	24	28
b	Me_2CH	Me	18	42
c	Me_2CHCH_2	Me	18	68
d	$MeSCH_2CH_2$	Me	19	54
e	$PhCH_2$	Et	0.5	65
f	3-pyridyl	Et	24	38
g	Ph	Et	20	70
h		Et	5	95
i	$MeOOCCH_2$	Me	18	41

Experimental

Melting points were determined on a Kofler micro hot stage and are uncorrected. ^1H NMR spectra were recorded on a Varian 360L spectrometer, using TMS as internal standard. Mass spectra were obtained on a VG Analytical Autospec Q spectrometer, using electron ionization at 70 eV. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 2400 Analyzer. The progress of reactions was monitored by TLC, using Fluka TLC-Silicagel 60778 and a mixture of chloroform and methanol (7:3) as a mobile phase. Esters of amino acids 1 were obtained from commercially available hydrochlorides after treatment with

aqueous sodium hydroxide solution and following extraction with diethyl ether. Ethyl α-(3-pyridyl)glycinate **1f** was obtained by the procedure which we have published recently.[9]

General procedure for pyrroles 3a-h

To a stirred solution of the corresponding ester of the amino acid **1** (5-15 mmol) in 6-10 ml of methanol DMAD was added dropwise in 10-15 % molar excess at room temperature during 5-10 min. Stirring was continued as necessary (30 min. to 3h) by monitoring the reaction progress by TLC. The reaction mixture was then evaporated in vacuo and the residue, an orange-yellow oil, was dissolved in 8-10 ml of methanol and under stirring at room temperature the equivalent amount of a methanolic solution of sodium methoxide was added. Stirring was continued for the time indicated in the table and thereafter the mixture was acidified with 10 % acetic acid. The separated product was filtered and crystallized from the appropriate solvent. In this manner the following compounds were prepared :

3a: m.p. 148-151 °C (from n-heptane); MS: 213 (M^+,45 %); ^{1}H NMR ($CDCl_3$): δ= 2.15 (3H,s,Me), 3.78 (3H,s,COOMe), 3.85 (3H,s,COOMe), 7.95 (1H,s,OH), 9.14 (1H,broad s,NH). Anal. $C_9H_{11}NO_5$ (213.19), calcd.: C 50.70, H 5.20, N 6.57, found: C 50.48, H 4.91, N 6.53 %.

3b: m.p. 102-104 °C (from n-heptane); MS: 241 (M^+,32 %); ^{1}H NMR ($CDCl_3$): δ= 1.25 (6H,d,Me_2), 3.03

(1H,m,CH), 3.76 (3H,s,COOMe), 3.83 (3H,s,COOMe), 8.09 (1H,s,OH), 8.94 (1H,broad s,NH); J_{i-Pr}= 6.7 Hz. Anal. $C_{11}H_{15}NO_5$ (241.24), calcd.: C 54.76, H 6.27, N 5.81, found: C 54.44, H 5.91, N 5.63 %.

3c: m.p. 99-101 °C (from n-hexane); MS: 255 (M^+,28 %); ^{1}H NMR ($CDCl_3$): δ= 0.89 (6H,d,Me_2), 1.85 (1H,m,CH), 2.42 (2H,d,CH_2), 3.79 (6H,s,two COOMe), 7.83 (1H,s,OH), 8.95 (1H,broad s,NH); J_{CH-CH_2}= 6.7 Hz, J_{Me-CH}= 6.6 Hz. Anal. $C_{12}H_{17}NO_5$ (255.26), calcd.: C 56.46, H 6.71, N 5.49, found: C 56.93, H 6.53, N 5.89 %.

3d: m.p. 90-91 °C (from n-hexane); MS: 273 (M^+,36 %); ^{1}H NMR ($CDCl_3$): δ= 2.05 (3H,s,MeS), 2.69 (4H,m,CH_2CH_2), 3.68 (3H,s,COOMe), 3.78 (3H,s,COOMe), 7.88 (1H,s,OH), 9.33 (1H,broad s,NH). Anal. $C_{11}H_{15}NO_5S$ (273.30) calcd.: C 48.34, H 5.53, N 5.12, found: C 48.83, H 5.20, N 5.42 %.

3e: m.p. 140-141 °C (from methanol); MS: 289 (M^+,34 %); ^{1}H NMR (DMSO-d_6): δ= 3.57 (6H,s,two COOMe), 3.73 (2H,s,CH_2), 6.96 (5H,s,Ph), 7.91 (1H,s,OH), 11.45 (1H,broad s,NH). Anal. $C_{15}H_{15}NO_5$ (289.28), calcd.: C 62.28, H 5.23, N 4.84, found: C 62.79, H 4.89, N 4.48 %.

3f: m.p. 208-213 °C (dec.) (from methanol); MS: 276 (M^+,25 %); ^{1}H NMR (DMSO-d_6): δ= 3.62 (6H,s,two COOMe), 7.08 (1H,dd,H_5), 7.90 (1H,m,H_4), 8.06 (1H,m,H_6), 8.57 (1H,broad s,OH), 8.73 (1H,m,H_2), 11.74 (1H,broad s,NH), $J_{H4,H5}$ = 7.6 Hz, $J_{H5,H6}$ = 4.7 Hz. Anal. $C_{13}H_{12}N_2O_5$ (276.24), calcd.: C 56.52, H 4.38, N 10.14, found: C 57.03, H 4.02, N 9.79 %.

3g: m.p. 142-142 °C (from n-heptane), lit.[8] m.p. 145-146 °C; MS: 275 (M^+,35 %); ^{1}H NMR ($CDCl_3$): δ= 3.78 (3H,s,COOMe), 3.84 (3H,s,COOMe), 7.20-7.43 (3H,m,Ph), 7.49-7.75 (2H,m,Ph), 8.73 (1H,s,OH), 9.19 (1H,broad s,NH). Anal. $C_{14}H_{13}NO_5$ (275.25), calcd.: C 61.09, H 4.76, N 8.53, found: C 61.03, H 4.55, N 5.13 %.

3h: m.p. 197-199 °C (from aqueous methanol); MS 328 (M^+,34 %); ^{1}H NMR (DMSO-d_6): δ= 3.57 (6H,s,two COOMe), 3.83 (2H,s,CH_2), 6.66-7.93 (5H,m,indolyl), 7.94 (1H,s,OH), 10.45 (1H,broad s,NH), 11.45 (1H,broad s,NH). Anal. $C_{17}H_{16}N_2O_5$ (328.31), calcd.: C 62.19, H 4.91, N 8.53, found: C 61.98, H 4.67, N 8.74 %.

Methyl [2,3-di(methoxycarbonyl)-4-hydroxy-pyrrol-5-yl]acetate (3i) :

A solution of dimethyl L-aspartate 1i (5.63 g, 34.93 mmole) in methanol (30 ml) was cooled to 0 °C and during 5 min. DMAD (4.97 g, 34.97 mmole) was added dropwise. Stirring of the ice-cooled reaction mixture was continued for 3h and thereafter evaporated in vacuo. The residual yellow oil was dissolved in methanol (25 ml) and under stirring at room temperature a solution of sodium methoxide (prepared from 0.8 g of sodium and 15 ml of methanol) was added portionwise. After 5 min the solid separated and stirring was continued for 18h. The separated solid was filtered, washed with methanol and dissolved in water (60 ml). The stirred solution was neutralized with 10 % acetic acid, the separated product was filtered and crystallized from aqueous methanol

(yield 41 %); m.p. 105-106 °C; MS: 271 (M^+,34 %); ^1H NMR ($CDCl_3$): δ= 3.52 (2H,s,CH_2), 3.59 (3H,s,COOMe), 3.78 (3H,s,COOMe), 7.98 (1H,s,OH), 9.46 (1H,broad s,NH). Anal. $C_{11}H_{13}NO_7$ (271.22), calcd.: C 48.71, H 4.83, N 5.16, found: C 48.83, H 4.50, N 5.14 %.

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