ASYMMETRIC SYNTHESIS OF 2-SUBSTITUTED 3-AMINO-4-CYANOPYRROLES VIA A TWO-STEP PROCEDURE CONSISTING OF A S_NV REACTION ON ETHOXYMETHYLENEMALONONITRILE FOLLOWED BY A THORPE-ZIEGLER CYCLIZATION

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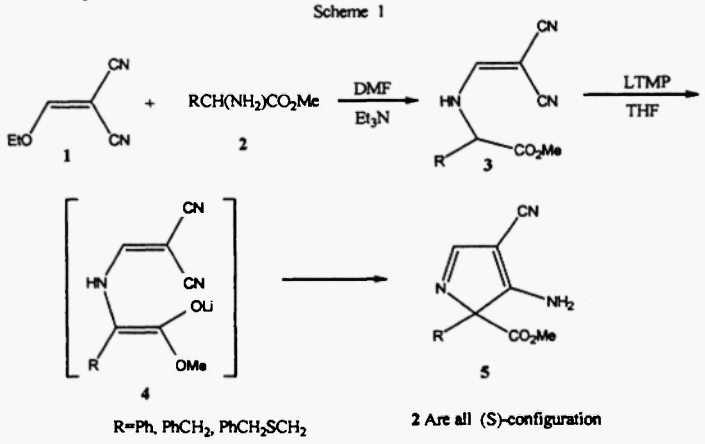
Abstract : An asymmetric synthesis of 2-Substituted 3-amino-4-cyanopyrroles via a two-step procedure consisting of a nucleophilic vinylic substitution (S_NV), of ethoxymethylenemalononitrile (EMM), with optically pure α-amino acid esters, resulting to the corresponding aminomethylemalononitriles, followed by a Thorpe-Ziegler cyclization, is described.

The pyrrole moiety is among the more widespread heterocyclic structures in natural products,[1,2] drugs,[3,4] conducting materials,[5,6] insecticides[7] and others. 3-Aminopyrrole derivatives, have been shown to exhibit antibacterial, antiviral and anticonvulsant activities,[8] specifically 3-aminopyrrole-2-carboxylates have exhibited anticonvulsant activity by blocking sodium channels.[9] Moreover 3-amino-4-cyanopyrroles have been used for synthesizing pyrolopyrimidines as new anticancer drugs.[10]

In the course of our studies concerning the preparation of pyrrole derivatives we were interested in the synthesis of pyrrole derivatives based on a procedure reported by Gewald,[11] a method including a Thorpe-Ziegler cyclization. We envisioned a two-step sequence which involves: (a) a nuclephilic vinylic substitution (S_NV), of the electrophilic alkene, ethoxymethylenemalononitrile 1 (EMM), by enantiomerically pure α-amino acid esters 2, to the formation of the corresponding aminosubstituted methylenemalononitriles 3, and (b) the enantiomeric Thorpe-Ziegler cyclization of 3 to 3-amino-4-cyanopyrrole derivatives 5, through the intermediate 4, (Scheme 1).

Scheme 1



The asymmetric synthesis of obtained pyrroles 5, through the generated enolates 4 of the optically active aminomethylenemalononitriles 3, could proceed without using any external chiral source (utilizing chiral auxiliaries). Usually this has not been possible due to the loss of chirality at the α-carbon of α-amino acids moiety in the

corresponding enolates due to their achiral nature. But it has been proposed[12] that central chirality of a carbon α- to a carbonyl group is preserved as transient axial chirality of the intermediate enolate and is then regenerated as central chirality in the reaction product. This concept has been applied[12,13] in asymmetric alkylations of chiral carbon adjacent to a carbonyl group. In an analogous manner in this communication the asymmetric induction can be rationalized in terms of a two-step transfer of chirality. In the first step, the central chirality of 3 is transferred through the enolate anion 4, (E) or (Z) configuration to the C2 asymmetric carbon of the pyrrole ring via a nucleophilic attack of the enolate anion 4 on the electrophilic nitrile group, through a Thorpe-Ziegler cyclization. EEM is a typical push-pull system containing two electron withdrawing groups. In such enol ethers or trifunctional electrocyclophiles[14] the nucleophilic replacement of the ethoxy group is the predominant reaction,[15] versus addition. EMM has very often been exploited in preparation of different heterocycles.[16a,b,c,d,e f]

Here we used as nucleophiles the following chiral α-amino acid methyl esters with (S)-configuration: (a) phenylglycine, (b) phenylalanine and (c) S-benzyl cysteine, all obtained from the corresponding hydrochlorides after neutralization with triethylamine. The resulting enantiomerically pure, (as proved to be by NMR spectroscopy), aminomethylenemalononitriles 3, were converted in high enantiopurity >76 %, as was determined by HPLC analysis chiral column, to the corresponding pyrrole derivatives 5 using as base lithium 2,2,6,6-tetramethylpiperidine (LTMP), their absolute configuration has not yet been assessed.

Conclusively, we have developed a new method for asymmetric synthesis of some 2-substituted 3-amino-4-cyanopyrroles in which no external chiral sources are employed. The anionic species 4 generated from 3 and LTMP can be expected to contain some chiral information, by the nucleophilic attack of which on the cyano group results in the asymmetric induction.

EXPERIMENTAL

Infrared spectra were recorded on a Nicolet Magna 560 spectrometer, as potassium bromide pellets, or as neat samples. NMR spectra were measured on a Varian Gemini 2000 300 MHz spectrometer. High-performance liquid chromatography, (HPLC), was performed on Shimadzu 10A Instruments using a chiral column (DAICEL chiralpack AS) with hexane-ethanol as solvent. For TLC analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. THF was distilled from sodium benzophenone under an argon atmosphere. DMF was dried by distillation under reduced pressure and storage over 4-Å molecular sieves. All other solvents were distilled prior to use.

General procedure for the preparation of aminomethylenemalononitriles 3. To a solution of 20 mmol of α-amino acid ester 2 and 20 mmol of ethoxymethylemalononitrile, 1, in 20 ml of absolute DMF, 2.0 g (20 mmol) of triethylamine was added dropwise under stirring. The mixture was allowed under stirring at room temperature for 3 h, and then was added to ice-water under stirring, and the formed precipitate was filtered and washed well with cold water and dried. After recrystallization from ethanol an analytically pure sample of 3 was obtained in yields 78-91 %. In the NMR spectra signals due to only one enantiomer were detected.

Benzeneacetic acid –α[(2,2-dicyanoethene)amino] methyl ester, 3a: 91 %, mp 157-159 ^{0}C. Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.71; H, 4.60; N, 17.42. Found: C, 64.48; H, 4.51; N, 17.19. IR (KBr): 3340, 2220, 1743, 1706, 1595. ^{1}H NMR (DMSO-d_6): 3.77 (s, 3H, OMe), 5.11 (br s, 1H, NH), 5.80 (d, J=7Hz, 1H, αCH), 7.11-7.33 (m, 5H, arom.), 8.85 (d, J=13.5 Hz, 1H, =CH). ^{13}C NMR (DMSO-d_6): 53.72, 57.10, 66.40, 110.11, 113.21, 127.57, 129.23, 129.71, 136.72, 171.70, 175.24.

Phenylpropionic acid–α[(2,2-dicyanoethene)amino] methyl ester, 3b: yield 84 %, mp 167-169 ^{0}C. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.86; H, 5.14; N, 16.47. Found: C, 65.66; H, 5.23; N, 16.58. IR (KBr): 3352, 2218, 1745 1710, 1587. ^{1}H NMR (DMSO-d_6): 3.20-3.35 (m, 2H, CH_2Ph), 3.43 (br s, 1H, NH), 3.76 (s, 3H, OMe), 5.05-5.16 (m, 1H, αCH), 7.14-7.31 (m, 5H, arom.), 8.91 (d, J=14.00, 1H, =CH). ^{13}C NMR (DMSO-d_6): 38.12, 53.70, 53.90, 66.51, 111.40, 114.20, 126.10, 127.71, 128.81, 139.40, 171.48, 175.45.

(S)-Cysteine-S-(phenylmethyl)–α[(2,2-dicyanoethene)amino] methyl ester, 3c: yield 78 %, mp 181-183 ^{0}C. Anal. Calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.95; S, 10.62. Found: C, 59.95; H, 5.21; N, 14.11; S, 10.40. IR (KBr): 3347, 2220, 1738, 1708, 1585. ^{1}H NMR (DMSO-d_6): 2.37 (br s, 1H, NH), 2.67 (dd, J=13.5 Hz and 4.70 Hz, 1H of two CH_AH_B), 2.83 (dd, J=13.50, and J=7.50 Hz, 1H of two CH_AH_B), 3.60 (dd, J=7.50 and J=4.70, 1H, CH), 3.71 (s, 2H, CH_2Ph), 3.75 (s, 3H, OMe), 7.07-7.30 (m, 5H, arom.), 8.78 (d, J=13.60, 1H, =CH). ^{13}C NMR (DMSO-d_6): 31.94, 36.78, 53.15, 53.80, 66.20, 112.14, 113.36, 127.23, 128.31, 129.54, 138.43, 169.37, 175.30.

General procedure for the preparation of 3-amino-4-cyanopyrroles 5: At 0 ^{0}C, 1.6 M n-BuLi (25 ml, 40 mmol) was added dropwise to freshly distilled 2,2,6,6-tetramethylpiperidine (6.80 ml, 40.0 mmol) in 20 ml of THF. After 15 minutes the resulting LTMP solution was cannulated to a stirred solution of 3 (20 mmol) in 50-80 ml of THF at -78 ^{0}C for 4 h, the hydrolysis was performed at -10 ^{0}C with a saturated NH_4Cl solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and chromatographed on silica gel with hexane/ether (1:1) furnishing an optically active mixture in yields 45-57 %. The enantiomeric excessesses were determined by HPLC analysis using Daicel chiralpack As, with 3 % EtOH/hexane as solvent and were found 76-81 %. The absolute configuration of the resolvent enantiomers is not determined.

2H-Pyrrole-2-carboxylic acid-2-phenyl-3-amino-4-cyano methyl ester 5a: yield 57 %, colorless oil, ee 81 %. Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.71; H, 4.60; N, 17.42. Found: C, 64.59; H, 4.77; N, 17.51. IR (neat): 3510, 3440, 2217, 1735. ^{1}H NMR ($CDCl_3$): 3.75 (s, 3H, OMe), 6.07 (br s, 2H, NH_2), 7.18-7.37 (m, 5H, arom.), 7.82 (s, 1H, C5). ^{13}C NMR ($CDCl_3$): 53.60, 73.27, 83.76, 114.63, 127.55, 129.23, 129.71, 137.40, 141.70, 152.35, 163.60, 166.81, 172.30.

2H-Pyrrole-2-carboxylic acid-2-benzyl-3-amino-4-cyano methyl ester 5b: yield 51 %, colorless oil, ee 76 %. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.86; H, 5.14; N, 16.47. Found: C, 66.11; H, 5.21; N, 16.34. IR (neat): 3480, 3420, 2219, 1738, 1595. ^{1}H NMR ($CDCl_3$): 2.90 and 3.63 (two d, J=13.50 Hz, 2H, CH_2Ph), 3.68 (s, 3H, OMe), 5.86 (br s, 2H, NH_2), 7.07-7.30 (m, 5H, arom.), 7.85 (s, 1H, C5). ^{13}C NMR ($CDCl_3$): 40.33, 52.58, 73.30, 92.11, 114.53, 127.05, 127.60, 135.71, 163.65, 166.75, 172.33.

2H-Pyrrole-2-carboxylic acid-2-[(benzylthio)methyl]-3-amino-4-cyano methyl ester 4c: yield 45 %, colorless oil, ee 78%. Anal. Calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.95; S, 10.62. Found: C, 59.61; H, 4.88; N, 13.80; S, 10.45. IR (neat): 3480, 3395, 2221, 1738, 1590. ^{1}H NMR ($CDCl_3$): 2.88 and 2.95 (dd, J=12 Hz, AB, 2H, CH_2S), 3.71 (s, 2H, CH_2Ph), 3.74 (s, 3H, OMe), 4.90 (br s, 2H, NH_2), 7.09-7.25 (m, 5H, arom.), 7.91 (s, 1H, C5). ^{13}C NMR ($CDCl_3$): 32.11, 36.78, 53.15, 73.20, 78.75, 114.47, 127.20, 128.65, 128.73, 136.95, 163.70, 166.47, 172.43.

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