ONE-POT SYNTHESIS OF PENTASUBSTITUTED PYRROLES FROM TERTIARY AMIDES AND MALONONITRILE VIA AN INDIRECT CONDENSATION REACTION ON AMIDIC CARBONYL GROUP

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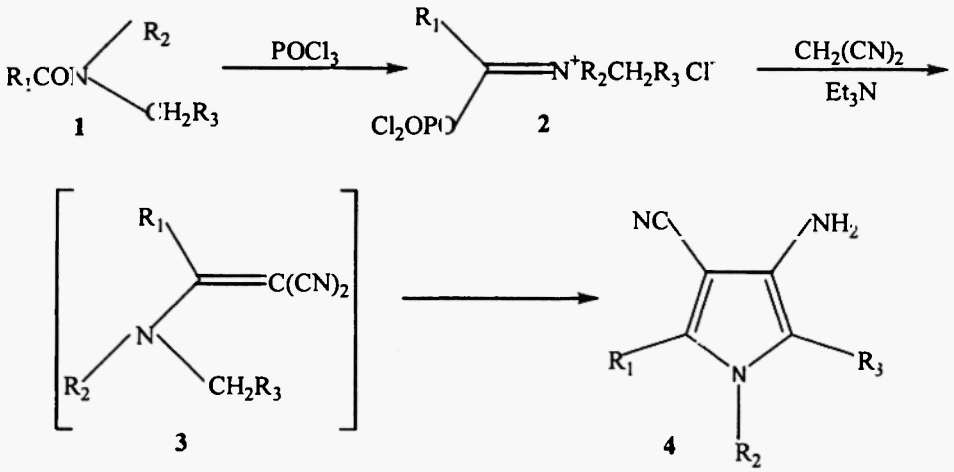
Abstract: An one-pot procedure for the preparation of pentasubstituted pyrrole derivatives, using tertiary acid amides-phosphorus oxychloride adducts on reaction with malononitrile, in the presence of triethylamine, is described.

Given the ubiquitous nature of pyrrole core in natural and synthetic products, we were interested in investigation of possible routes for the synthesis of known and new functionalized pyrrole derivatives. Recently polyfunctional pyrroles have been referred as mineralocorticoid receptor antagonists for use against cancer and other disorders.[1] 3-Aminopyrrole derivatives, have been shown to exhibit antibacterial, antiviral and anticonvulsant activities,[2] have been used as intermediates for the synthesis of azo dyes for synthetic fibers,[3] and as starting materials for the synthesis of pyrrolo[3,2-d] and pyrrolo[3,4-d]pyrimidines.[4] Polyfunctional pyrroles bearing substituents such as, cyano-, aryl-, halo-, carboxylate-, have been reported[5] as agrochemical fungicides.
We specifically required a new simple and efficient route for the synthesis of pentasubstituted pyrroles. Based on a literature report[6] on condensation reactions of some acid amides-phosphorus oxychloride adducts with active methylene derivatives, we were interested in application of the method for the preparation of the properly designed intermediates 1,1-dicyano-2-aminoethylene derivatives bearing an active methylene on one of the amidic nitrogen substituents.
Analogous ethylene derivatives have been prepared, as intermediates, by Gewald et.al.[3,7a,b] using α-cyano-β-chloro- or β-alkoxy-acrylonitriles on reaction with active aminomethylenes or by alkylation of β-aminoacrylonitriles with active bromomethylene derivatives.

In this communication, we wish to present our results on the preparation of some 3-amino pentasubstituted pyrroles **4** starting from the tertiary amides **1,** their reaction with phosphorus oxychloride to the acid amides-phosphorus oxychloride complexes **2** formation, which on the consequent treatment with malononitrile followed by triethylamine were converted to the desired pyrroles **4**, evidently through the intermediacy of the dicyanoethylenes **3**, (Scheme-1). This reaction sequence was based, as mentioned above, on a literature report[6] employed for the conversion of acid amides to the corresponding amidines or the dicyanomethylene derivatives. Otherwise, this reaction constitutes an indirect condensation reaction on amidic carbonyl group. The novelty of this report consists in the use of tertiary amides **1** on which a nitrogen substituent bears an active methylene moiety such as methylene carboxylate or methylene carbonitrile, so the resulting dicyanoethylenes **3** can be transformed to the corresponding pyrroles **4** *via* a Thorpe-Ziegler cyclization reaction.



R_1, R_2, R_3: (a) Me, Me, CN; (b) Me, Me, CO_2Me; (c) Me, Me, $PhCH_2$, CN; (d) Me, $PhCH_2$, CO_2Me; (e) Me, Ph, CN; (f) Me, Ph, CO_2Me; (g) Ph, Me, CN; (h) Ph, Ph, CN; (i) Ph, $PhCH_2$, CN

Scheme -1

In conclusion, the condensation of malononitrile with the prepared tertiary acid amides-phosphorus oxychloride adducts, results in one-pot procedure to the synthesis of polyfunctional pyrroles, through a Thorpe-Ziegler cyclization of the corresponding intermediates 1,1-dicyano-2-aminoethylene derivatives. The application of the method to other tertiary amides as well as to other active methylene compounds is in our immediate plan.

Experimental

General. NMR spectra were recorded at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer and solvent DMSO-d_6. ^1H NMR data are reported as follows: chemical shifts are quoted in ppm on δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in Hz. ^{13}C NMR spectra were carried out with complete ^1H decoupling and the assignments were made by additional DEPT experiments. 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 potassium bromide pellets).

N-Acetyl-N-methylaminoacetonitrile[8] **(1a), glycine N-acetyl-N-methyl-methyl ester**[9] **(1b), N-acetyl-N-benzylaminoacetonitrile**[10] **(1c), glycine N-acetyl-N-benzyl-methyl ester**[11] **(1d), N-acetyl-N-phenylaminoacetonitrile**[12] **(1e), glycine N-acetyl-N-phenyl-methyl ester**[13] **(1f), N-benzoyl-N-methylaminoacetonitrile**[14] **(1g), N-benzoyl-N-phenylaminoacetonitrile**[15] **(1h),** and **N-benzoyl-N-benzylaminoaceto-nitrile**[16] **(1i)** were prepared by published procedures.

General procedure for the preparation of pyrroles 4. In a solution of the amide **1** 0.4 mol in absolute benzene 50 ml, a solution of phosphorus oxychloride 0.2 mol in absolute benzene 20 ml was added, the reaction was allowed under stirring at room temperature for about two hours. Malononitrile 0.2 mol was added, the mixture was cooled on an ice-water bath, and triethylamine 0.7 mol was added dropwise. The reaction was allowed at this temperature under stirring for one hour, then was heated

on a water bath 60-70 ^{0}C for two hours, and finally was concentrated under vacuum. The solid residue was triturated and washed well with water, after drying it was recrystallized from the proper solvent to give the desired pyrrole in yields 57-76%.

3-Amino-2,4-dicyano-1,5-dimethylpyrrole 4a. Yield 65%, mp 267-268 ^{0}C (EtOH), lit.[4] mp 266-268 ^{0}C. IR: 3410, 3330, 2205, 2195, 1632. ^{1}H NMR: 2.23 (s,3H, Me, C5), 3.42 (s, 3H, >NMe), 5.73 (s br, 2H, -NH_2). ^{13}C NMR: 13.03 (CH_3), 31.87 (CH_3), 107.45 (C), 108.17 (C), 113.11 (C), 117.22 (C), 120.44 (C), 134.31 (C).

3-Amino-4-cyano-1,5-dimethylpyrrole-2-methoxycarbonyl 4b. Yield 57%, mp 188-189 ^{0}C (EtOH), lit.[4] 187-187.5 ^{0}C. IR: 3415, 3325, 2208, 1657, 1608. ^{1}H NMR: 2.19 (s, 3H, Me, C5), 3.37 (s, 3H, >NMe), 3.77 (s, 3H, -OMe), 5.30 (s br, 2H, -NH_2). ^{13}C NMR: 12.20 (CH_3), 32.06 (CH_3), 50.49 (CH_3), 109.11 (C), 117.03 (C), 121.33 (C), 136.90 (C), 142.80 (C), 163.20 (C).

3-Amino-1-benzyl-2,4-dicyano-5-methylpyrrole 4c. Yield 61%, mp 243-245 ^{0}C (i-PrOH). Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.15; H, 5.12; N, 23.72. Found: C, 70.94; H, 5.22; N, 23.54. IR: 3430, 3327, 2212, 2205, 1610. ^{1}H NMR: 2.16 (s, 3H, Me, C5), 5.18 (s, 2H, -CH_2Ph), 5.62 (s br, 2H, -NH_2), 7.07-7.33 (m, 5H, arom.). ^{13}C NMR: 12.17 (CH_3), 42.23 (CH_2), 107.83 (C), 109.06 (C), 112.31 (C), 117.09 (C), 121.01 (C), 125.81 (CH), 128.70 (CH), 129.21 (CH), 134.06 (C), 136.27 (C).

3-Amino-1-benzyl-4-cyano-2-methoxycarbonyl-5-methylpyrrole 4d. Yield 54 %, mp 119-120 ^{0}C (EtOH), lit.[4] 116-118 ^{0}C. IR: 3348, 3347, 2210, 1685, 1618. ^{1}H NMR: 2.21 (s, 3H, Me, C5), 3.65 (s, 3H, -OMe), 5.21 (s, 2H, -CH_2Ph), 5.57 (s br, 2H, -NH_2), 7.09-7.28 (m, 5H, arom.). ^{13}C NMR: 12.33 (CH_3), 42.13 (CH_2), 50.47 (CH_3), 110.90 (C), 117.08 (C), 120.31 (C), 125.81 (CH), 128.67 (CH), 129.22 (CH), 135.48 (C), 138.17 (C), 165.31 (C).

3-Amino-2,4-dicyano-5-methyl-1-phenylpyrrole 4e. Yield 58%, mp 271-273 ^{0}C (aq. DMF). Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.24; H, 4.54; N, 25.22. Found: C, 70.31; H, 4.40; N, 25.47. ^{1}H NMR: 2.12 (s, 3H, Me, C5), 5.65 (s br, 2H, -NH_2), 7.36 (s, 5H, arom.). ^{13}C NMR: 12.42 (CH_3), 109.13 (C), 110.81 (C), 117.09 (C), 119.08 (C), 113.20 (C), 121.57 (CH), 122.63 (CH), 129.41 (CH), 133.07 (C), 142.20 (C).

3-Amino-4-cyano-5-methyl-2-methoxycarbonyl-1-phenylpyrrole 4f. Yield 64%, mp 128-129 ^{0}C (EtOH), lit.[4] 126-127 ^{0}C. IR: 3423, 3327, 2207, 1674, 1618. ^{1}H NMR: 2.20 (s, 3H, Me, C5), 3.60 (s, 3H, -OMe), 5.43 (s br, 2H, -NH_2), 7.33 (s, 5H, arom.). ^{13}C NMR: 12.13 (CH_3), 50.22 (CH_3), 110.03 (C), 117.41 (C), 121.61 (CH), 122.23 (C), 125.63 (CH), 128.87 (CH), 135.47 (C), 139.43 (C), 145.30 (C), 165.31 (C).

3-Amino-2,4-dicyano-1-methyl-5-phenylpyrrole 4g. Yield 60%, mp 174-176 ^{0}C (EtOH), lit.[7a] 173-175 ^{0}C. IR: 3420, 3310, 2210, 2200, 1600. ^{1}H NMR: 3.48 (s, 3H, Me), 5.55 (s br, 2H, -NH_2), 7.20-7.54 (m, 5H, arom.). ^{13}C NMR: 31.60 (CH_3), 107.89 (C), 107.91 (C), 113.67 (C), 117.07 (C), 121.81 (C), 122.37 (C), 127.47 (CH), 128.80 (CH), 129.30 (CH), 133.51 (C).

3-Amino-2,4-dicyano-1,5-diphenylpyrrole 4h. Yield 64%, mp 193-195 ^{0}C (i-PrOH). Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.03; H, 4.26; N, 19.72. Found: C, 75.86; H, 4.30; N, 19.51. ^{1}H NMR: 5.64 (s br, 2H, -NH_2), 7.21-7.52 (m, 10H, arom.). ^{13}C NMR: 109.31 (C), 109.62 (C), 113.40 (C), 117.02 (C), 118.45 (C), 118.69 (C), 121.57 (CH), 125.55 (CH), 127.47 (CH), 128.78 (CH), 129.33 (CH), 129.47 (CH), 134.10 (C), 141.20 (C).

3-Amino-1-benzyl-2,4-dicyano-5-phenylpyrrole 4i. Yield 58%, mp 167-169 ^{0}C (i-PrOH). Anal. Calcd for $C_{19}H_{14}N_4$: C, 76.48; H, 4.73; N, 18.79. Found: C, 76.51; H, 4.67; N, 18.53. IR: 3388, 3347, 2212, 2195, 1600. ^{1}H NMR: 3.68 and 5.25 (dd, 16.5 Hz, 2H, -CH_aH_bPh), 5.53 (s br, 2H, -NH_2), 7.07-7.52 (m, 10H, arom.). ^{13}C NMR: 42.56 (CH_2), 108.70 (C), 108.91 (C), 113.37 (C), 117.07 (C), 121.20 (C), 122.06 (C),

125.61 (CH), 127.38 (CH), 128.78 (CH), 129.20 (CH), 129.31 (CH), 133.12 (C), 136.41 (C).

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