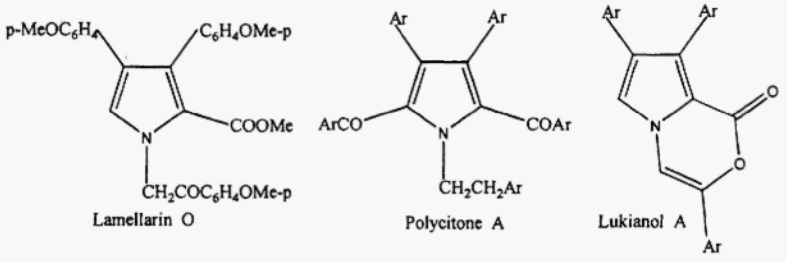
A NEW ROUTE TO THE SYNTHESIS OF 3-AMINOMETHYLENE DERIVATIVES OF 2-CYANO-3-PHENYLACRYLONITRILES AND THE POLYFUNCTIONALIZED PYRROLES SYNTHESIS THEREOF

Georgia Tsolomiti, Kyriaki Tsolomiti and Athanase Tsolomitis*
The Laboratory of Organic Chemistry, The School of Chemical Engineering, The National Technical University of Athens, Athens157 80, Greece

Abstract: A new route to the synthesis of 3-aminomethylene derivatives of 2-cyano-3-phenylacrylonitrile, useful intermediates for the synthesis of tetrasubstituted 1H-pyrroles, starting from N-benzoylaminomethylene compounds, their conversion to the corresponding N-chlorophenylmethylenes and reaction with malononitrile, is described here.
Key words: 3-Aminopyrroles; Pyrrole-2-carboxylates; Dicyanoethylenes.

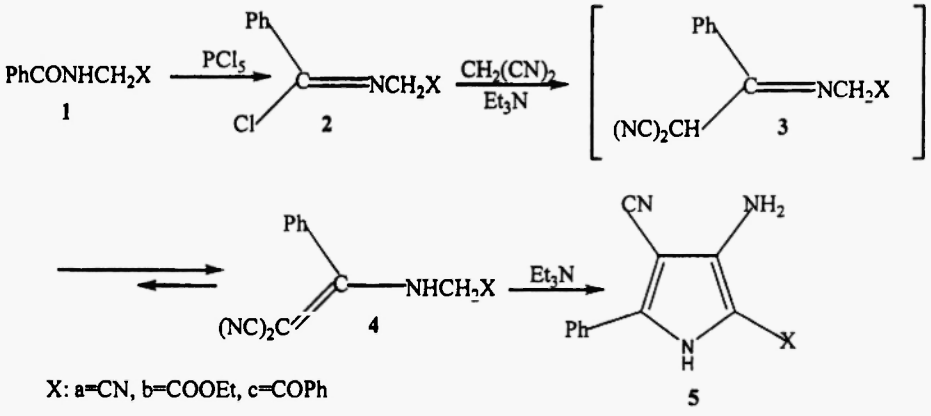
In recent years the focus has turned to pyrrole natural products derived from marine organisms. Examples of such compounds include lukianol A, lamellarin O, ningalin B and polycitone A and B. These compounds have been shown to exhibit interesting antitumor activity as well as multidrug resistant reversal activity.[1]



The pyrrole ring, either in its unadorned form or as the pyrrole-2-carboxylate moiety commonly encountered in natural products, possesses many useful chemical and electronic features that are readily exploited in biological contexts. The 2-carboxylate moiety provides a nucleophilic center for derivatization, hydrogen bonding and reaction with biological targets.[2] Derivatives of 3-aminopyrroles have been shown to exhibit antibacterial, antiviral, anticonvulsant, antiinfammatory, analgesic, and antipyretic activities. It has also been found that ethyl 3-amino-5-phenyl-1H-pyrrole-2-carboxylate is a useful intermediate in the synthesis of other nitrogen heterocycles.[3] 3-Aminopyrroles are important synthetic targets for preparation of azo dyes.[4] Some pyrrole derivatives have also been referred as agrochemical fungicides.[5] Among the methods used for synthesis of polyfunctional 3-aminopyrroles are those described by Gewald et. al.[4,6,7] using: (a) α-cyano-β-chloroacrylonitriles or β-alcoxyacrylonitriles on reaction with amino derivatives bearing active methylenes, followed by a Thorpe-Ziegler cyclization or (b) by alkylation of the β-aminoacrylonitriles with active bromomethylene derivatives and then cyclization.

Here we wish to report our preliminary results on a different preparation route of these polyfunctional 3-aminopyrroles, starting from N-benzoylamino derivatives of active aminomethylene compounds **1** which after conversion to the corresponding imidoyl chlorides **2** reacted with malononitrile to give the corresponding dicyanoethylenes **4** and the consequent conversion of these to 3-aminopyrroles **5**. Evidently the formation of dicyanoethylenes **4** can

be explained by the intermediate formation of the imines **3** (Scheme-1). Although the preparation and use of imidoyl chlorides have been reported



Scheme 1

frequently,[8] an examination of the literature indicated that few of these species had actually been isolated and characterized. Common precursors to imidoyl chlorides are secondary amides, and among the most typical reagents which have been employed for their conversion to imidoyl chlorides are phosphorus pentachloride, thionyl chloride, phosgene, and triphenyl phosphine-carbon tetrachloride.[9] However for a given substitution patern in the imidoyl chloride, the use of any one of these traditional preparative methods may give rise to various coproducts which may seriously impact the ability to isolate imidoyl chlorides in a pure state. Taken together with their instability, these factors have led in many instances to their preparation and use without intervening isolation.

We were thus drawn a reported methodology[10]for their preparation according to which a solution of the amide derivative in a mixture of absolute diethyl ether-1,4-dioxane was treated with phosphorus pentachloride. These products were used immediately without further purification because of their instability. Using this protocol we prepared the imidoyl chlorides **2a,b,c** which were isolated as spectroscopically pure materials. The reactions of imidoyl chlorides with malononitrile were carried out in absolute benzene in the presence of triethylamine as base, to furnish, after the imine-enamine tautomerism, (**3⇄ 4**), the enamines **4**. Analogous to this tautomeric equili-brium have been observed.[11,12] The reverse enamine-imine tautomerism has also been reported[13].These dicyanoethylenes **4** upon treating with triethylamine were converted, through a Thorpe-Ziegler cyclization to the corresponding 3-aminopyrroles **5**, which were also prepared directly from the preparation reaction of dicyanoethylenes **4** by treating the reaction mixture with an additional amount of triethylamine (see experimental).

Conclusively, we have developed a simple method for the synthesis of 3-aminomethylene derivatives of 2-cyano-3-phenylacrylonitrile, from N-benzoyl-aminomethylene compounds, bearing active methylenes, their conversion to the corresponding imidoyl chlorides and reaction of these with malononitrile. These dicyanoethylenes have been used for the synthesis 2,4,5-trisubstituted 3-amino-1H-pyrroles, useful synthons for pharmaceuticals, azo dyes and other nitrogen heterocycles. The expansion of the method to other imidoyl chlorides 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. The data are reported as follows: chemical shift are quoted in ppm on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz). 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, and were calibrated against the polystyrene 1600 cm^{-1} band, and given in reciprocal centimetres..

General procedure for the preparation of imidoyl chlorides 2. In accordance to the method reported by Sheeham and Corey,[10] to a solution, under an Argon atmosphere, of the amide derivative **1** (16 mmol) in dry diethyl ether-1,4-dioxan (4:1), (20 ml), phosphorus pentachloride (3.4 g, 16 mmol) was added. The mixture was allowed under stirring at room temperature for 20 min and then the resulting yellow solution was concentrated under reduced pressure (0.05 mmHg), at room temperature, to give spectroscopically pure imidoyl chlorides **2**, in yields 67-81%. These products were not purified further but used immediately, because of their transformation to other products.

N-(Chlorophenylmethylene)-aminoacetonitrile 2a. Yield 77%. IR (KBr): 2210, 1610. ^1H NMR ($CDCl_3$): 4.63 (s, 2H, -CH_2-), 7.25-7.48 (m, 3H, arom. C3, C4, C5), 7.63-7.81 (m, 2H, arom. C2, C6). ^{13}C NMR ($CDCl_3$): 31.90, 114.69, 128.87, 129.20, 13126, 135.30, 147.15.

N-(Chlorophenylmethylene)-glycine ethyl ester 2b[14]. Yield 81%. IR (KBr): 1738, 1610. ^1H NMR ($CDCl_3$): 1.28 (t, J=7.1 Hz, 3H, -CH_3), 4.23 (q, J=7.1 Hz, 2H, CH_2O-), 4.47 (s, 2H, -CH_2CO-), 7.31-7.48 (m, 3H, arom. C3, C4, C5), 7.57-7.87 (m, 2H, arom. C2, C6). ^{13}C NMR ($CDCl_3$): 14.21, 55.40, 61.56, 128.80, 129.33, 131.45, 135.35, 147.40, 168.70.

N-(Chlorophenylmethylene)-2-aminoacetophenone 2c. Yield 67%. IR (KBr): 1685, 1610. ^1H NMR ($CDCl_3$): 4.89 (s, 2H, -CH_2-), 7.23-7.88 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 52.60, 128.33, 129.30, 129.61, 131.20, 133.40, 136.21, 147.63, 195.80.

General procedure for the preparation of dicyanoethylenes 4. To a solution, under an Argon atmosphere, of the imidoyl chloride (8.0 mmol) in absolute benzene (20 ml), malononitrile (8.0 mmol) was added. The solution was cooled in an ice-bath and triethylamine (8.0 mmol) was added dropwise, the mixture was stirred for 30 minutes at this temperature and then additional 30 minutes at room temperature, solids were removed by filtration. The filtrate was concentrated under vacuum and the solid residue was recrystallized from ethanol to give the pure dicyanoethylenes **4** in yields 75-87%.

Acrylonitrile-2-cyano-3-phenyl-3-aminoacetonitrile 4a. Yield 81%, mp 68-70 ^0C. Anal. Calcd for $C_{12}H_8N_4$: C, 69.21; H, 3.88; N, 26.92. Found: C, 69.37; H, 3.91; N, 26.70. IR (KBr): 3350, 2205, 2185, 1600. ^1H NMR ($CDCl_3$): 2.47 (br s, 1H, >NH, exchangeable), 3.81 (s, 2H, $>CH_2$), 7.20-7.67 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 34.06, 51.41, 113.84, 114.70, 126.33, 128.01, 128.71, 135.20, 186.41.

Acrylonitrile-2-cyano-3-phenyl-3-aminoacetic acid ethyl ester 4b. Yield 87%, mp 83-85 ^0C. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.86; H, 5.14; N, 16.47. Found: C, 65.59; H, 5.21; N, 16.36. IR (KBr): 3275, 2210, 2190, 1738, 1600. ^1H NMR ($CDCl_3$): 1.30 (t, J=7.1 Hz, 3H, -CH_3), 2.86 (br s,1H, >NH, exchangeable), 3.57 (s, 2H, -CH_2CO-), 4.16 (q, J=7.1 Hz, 2H, -CH_2O-), 7.18-7.61 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 14.20, 42.87, 51.10, 60.91, 68.87, 113.71, 114.05, 126.37, 128.03, 128.70, 133.89, 186.51.

Acrylonitrile-2-cyano-3-phenyl-3-(2-aminoacetophenone) 4c. Yield 75%, mp 101-103 ^0C. Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.23; H, 4.56; N, 14.63. Found: C, 75.47; H, 4.42; N, 14.71. IR (KBr): 3327, 2205, 2190, 1687, 1600, 1595. ^1H NMR ($CDCl_3$): 3.06 (br s, 1H, >NH, exchangeable), 4.07 (s, 2H, $>CH_2$), 7.11-7.83 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 47.84, 50.71, 113.67, 114.11, 126.40, 128.03, 128.70, 128.80, 134.43, 136.20, 185.32, 195.67.

General procedure for the preparation of pyrroles 5. (a) To a refluxing solution of dicyanoethylene **4** (10mmol) in 60 ml of absolute ethanol, triethylamine (10 mmol) was added and the solution was refluxed for 1 hour. After cooling, the solution was added to water, the formed solid was collected and washed with water. Recrystallization from acetonitrile gave an analytical sample of the pyrrole **5**, in yields 65-77%.

3-Amino-2,4-dicyano-5-phenylpyrrole 5a. Yield 65%, mp 293-295 ^{0}C, lit.[6] 290-294 (KBr): 3420, 3310, 3215, 2210, 2195, 1610. ^{1}H NMR (DMSO-d_6): 4.17 br s, 2H, -NH_2), 5.33 (s, 1H, >NH), 7.25-8.08 (m, 5H, arom.). ^{13}C NMR (DMSO-d_6): 107.31, 107.58, 113.27, 114.43, 117.62, 118.06, 127.46, 128.43, 129.32, 133.25.

3-Amino-4-cyano-5-phenylpyrrole-2-carboxylic acid ethyl ester 5b. Yield 73%, mp 202-204 ^{0}C, lit.[6] 204-205 ^{0}C. IR (KBr): 3430, 3330, 3210, 2210, 1670, 1620. ^{1}H NMR (DMSO-d_6): 1.33 (t, J=7.2 Hz, 3H, -CH_3), 4.26 (q, J=7.2 Hz, 2H, >CH_2), 5.21 (br s, 2H, -NH_2), 5.48 (s, 1H, >NH), 7.27-7.98 (m, 5H, arom.). ^{13}C NMR (DMSO-d_6): 14.25, 60.23, 108.37, 11.23, 114.88, 119.31, 122.40, 127.31, 128.73, 129.33, 133.21, 160.13.

3-Amino-2-benzoyl-4-cyano-5-phenylpyrrole 5c. Yield 77%, mp 271-273 ^{0}C, lit.[6] 270-274 ^{0}C. IR (KBr): 3433, 3325, 3223, 2207, 1610, 1590. ^{1}H NMR (DMSO-d_6): 5.15 (br s, 2H, -NH_2), 5.41 (s, 1H, >NH, 7.23-8.67 (m, 10H, arom.). ^{13}C NMR (DMSO-d_6): 109.11, 114.41, 120.17, 126.80, 127.31, 128.80, 128.90, 129.31, 129.70, 132.10, 133.21, 182.27.

(b) In the procedure referred above for the preparation of dicyanoethylenes a modification at the point prior the filtration can give the desired pyrroles without the isolation of the intermediates dicyanoethylenes **4**. So in this point if an additional equal amount of triethylamine, to the used, was added and the mixture was refluxed for 1h the desired pyrroles were analogously obtained but at slightly lower yields.

References and Notes

1. J. T. Gupton Abstracts of papers, 231st ACS National Meeting, Atlanta, U.S. March, 26-30, 2006.
2. C. T. Walsh, S. Gameau-Tsodikova, A. R. Howard-Jones, *Nat. Prod. Rep.* **2006**, *23*, 517-531.
3. N. Chen, Y. Lu, K. Gadamasetti, C. R. Hurt, M. H. Norman, C. Fotsch, *J. Org. Chem.* **2000**, *65*, 2603-2605 and references therein.
4. K. Gewald, H. Schäefer, P. Bellmann, Pat. App. DD 80-225548 19801128.
5. ,l. Teruyuki, H. Kenji, M. Shinji, S. Shinsuke, S. Susumu, H. Yuji, Pat. Appl. JP 98-30259. CAN 130:81399.
6. K. Gewald, H. Schäefer, E. Schindler, Pat. Appl. DD 78-208049 19780925.
7. K. Gewald, H. Schäefer, P. Bellmann, U. Hain, *J. Prakt. Chem.* **1992**, *334*, 491-496.
8. (a) A. R. Katritzky, A. E. Hayden, K. Kirichenko, P. Pelphrey, Y. Ji, *J. Org. Chem.* **2004**, *69*, 5108-5111 and references therein. (b) W. Kantlehner, W.W. Mergen, In *Comprehensive Organic Functional Group Transformations*; A. R. Katrizky, O. Meth-Cohn, C. W. Rees, Eds.; Pergamon: Oxford, UK, 1995; Vol. 5, pp 654-660. (c) W. Kantlehner, In *Comprehensive Organic Synthesis*; B. M. Trost, I.. Fleming, Eds.; Pergamon: Oxford, UK, 1991; Vol. 6, pp 523-529. (d) R. Sustmann, H. G. Korth, In *Methoden der Organische Chemie*; Thieme: Stuttgart, Germany, 1985; Vol. E5, pp 628-631. (e) H. Ulrich, *The Chemistry of imidoyl Halides*; Plenum: New York, 1968.
9. (a) R. Appel, K. Warning, K. D. Ziehn, *Chem. Ber.* **1973**, *106*, 3450-3454. (b) This method has also been used to form imidoyl chlorides directly from mixtures of carboxylic acids and primary amines: K. Tamura, H. Mizukami, K. Maeda, H. Watanabe, K. Uneyama, *J. Org. Chem.* **1993**, *58*, 32-35.
10. J. C. Sheeham, E. J. Corey, *J. Amer. Chem. Soc.* **1952**, *74*, 4555-4559.
11. R. L. Riggs, C. J. H. Morton, A. M. Z. Slawin, D. M. Smith, N. J. Westwood, W. S. D. Austen, K. E. Stuart, *Tetrahedron*, **2005**, *61*, 11230-11243.
12. P. Langer, J. Wuckelt, M. Döring, *J. Org. Chem.* **2000**, *65*, 729-734.
13. J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Commun.* **2004**, 1400-1401.
14. D. J. Collins, T. C. Hughes, W. M. Johnson, *Aust. J. Chem.* **1996**, *49*, 463-468.

Received on November 1, 2006.