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Synthesis and characterization of new N-substituted 2-aminopyrrole derivatives

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Abstract: In this work, new N-substituted 2-aminopyrrole derivatives were synthesized. Initially, some crotonitriles were prepared by condensation of malononitrile with arylmethylketones, which was followed by conversion of them to the bromocrotonitriles. Finally, the synthesis of new N-substituted 2-aminopyrrole derivates were successfully achieved by cyclization of the bromocrotonitriles of (R)-1-phenylethylamine applying Gewald method.

Keywords: Pyrrole; aminopyrrole; Knoevenagel condensation; Gewald reaction.

1. Introduction

Pyrrole is an important class of heterocyclic compounds, which is found in some well known biologically active natural products such as chlorophyll A, chlorophyll B and hemin in blood cells.[2] Synthesis of pyrrol derivatives, as part of various natural products having important biological activities, has been in the interest of various research groups.

In this study, we report an improved synthesis of the new N-substituted 2-aminopyrrole derivatives **(4a-d)** by using stepwise Gewald reaction (Figure 1).

2. Background

Aminopyrroles cannot be synthesized following the general synthetic methods of pyrrole ring, for which although there are many methods available in the literature, there are limited number of studies for the synthesis of aminopyrrole. This is due to the fact that aminopyrrols and their derivatives are unstable compounds.[3-7] 3-Aminopyrroles are more stable compounds compare with 2-aminopyrroles.[8] There are two general methods known in the literature for the synthesis of 2-aminopyrrole and its derivatives. While in one of the methods, 2-aminopyrrole is obtained by reduction of 2-nitropyrrols,[9] in the second method, 2-aminopyrrole derivatives are synthesized as a

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result of the formation of the pyrrole ring by using appropriate straight chain structures.[10] 3-Cyano-2-aminopyrroles are stable compounds due to the cyano group. However, in the methods used for the synthesis of these compounds, the use of commercial starting molecules and multistage processes are required.[11,12]

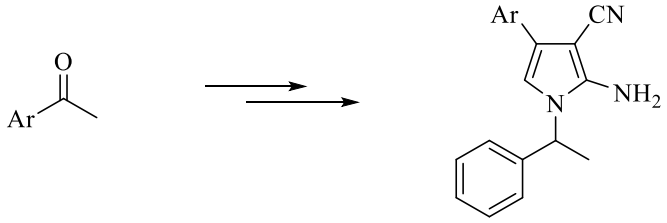


Figure 1. N-substituted 2-aminopyrrole from aryl ketones

3. Experimental

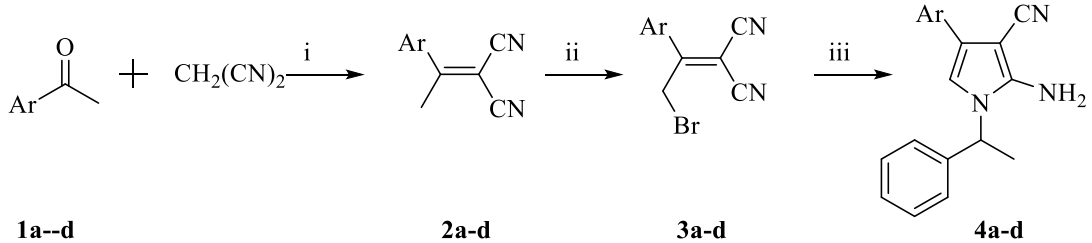
General: All solvents and reagents were purchased from Sigma & Aldrich and Merck without further purification. The ^{1}H and ^{13}C-NMR spectra were recorded on a Varian 400 MHz and a Bruker 400 MHz spectrometer. Chemical shifts are given in parts per million (ppm). Shortened forms are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet). The FT-IR spectra were recorded on a Perkin Elmer spectrophotometer using KBr in the range of 4000- 600 cm^{-1}. M.p. was measured with a Thermo Scientific melting point device. The mass spectra were recorded on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS. The UV-Vis spectra were recorded using a UV-1800 Shimadzu model spectrophotometer at room temperature.

*General procedure for the preparation of crotonitriles **2a-d** and bromocrotonitriles **3a-d** :* The synthesis of crotonitriles (**2a-d**) and bromocrotonitriles (**3a-d**) were carried out using a method available in the literature.[13]

General method for the synthesis of N-substituted 2-aminopyrroles: 2-(2-Bromo-1-naphthalene-1-yl-ethylidene)malononitrile (450 mg, 1.51 mmol) (**3a**) was dissolved in 15 mL of freshly distilled THF. To the magnetically stirred solution was added 1-phenylethylamine (310 mg, 2.55 mmol). Then, the reaction mixture was stirred at room temperature for 16 h. After the solvent was evaporated under reduced pressure, the crude product was filtered through 50 g of neutral alumina, using ethyl acetate/hexane (1:4) mixture. A dark green amorphous solid, aminopyrrole **4°**, was obtained. Yield: 75% (320 mg). 2-Amino pyrroles **4b**, **4c** and **4d** were also synthesized following the same procedure, which gave 71%, 78% and 82% of the products, respectively.

4. Present Study

For the simple synthesis of N-substituted 2-aminopyrroles, we applied the reaction of bromocrotonitrile **(3a-d)** with (*R*)-1-phenylethylamine. For this purpose, crotonitriles **(2a-d)** were synthesized by condensation of aryl methyl ketones with malononitrile using a known literature procedure.[13] Bromination was performed in the allylic position to form an active methylene group. Although there are many different methods available in the literature for this type of bromination, the method developed by our group was used.[13] Finally, bromocrotonitriles were cyclized using (*R)*-1-phenylethylamine and the desired N-substituted 2-amino-3-cyano-4-arylpyrroles were synthesized in high yields (71-88%) (Scheme 1).



1a--d **2a-d** **3a-d** **4a-d**

Ar = **a;** α-napthyl, **b;** β-napthyl, **c;** phenanthren-9-yl, **d;** phenanthren-3-yl

i) Ammonium acetate, benzene, reflux,12 h. ii) Br_2, *hv*, CCl_4, 6 h. iii) 1-phenylethylamine, THF, rt. 16 h.

Scheme 1. The synthesis of 2-aminopyrroles **4a-d**

In conclusion, the present work provides a facile synthesis of polysubstituted-2-aminopyrroles *via* a stepwise Gewald reaction. Allylic bromination is important for the cyclization, which directly affects the yield. This method,[13] developed by our group, was used in the synthesis of aminopyrrol. As a result of all the synthetic studies, N-substituted 2-amino-3-cyano-4-arylpyrroles have been successfully synthesized for the first time and the structural characterizations have been made. This methodology represents an improvement over the other methods in terms of total reaction yields.

*2-(1-Phenanthren-9-yl-ethylidene)-malononitrile (**2c**):* **(**83%, yellowish crystal 130-132 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, *J*=8.4 Hz, 1H,ArH ,), 8.71 (d, *J*=8.4 Hz, 1H, ArH), 7.94 (d, *J*=1.1 Hz, 1H, ArH), 7.78-7.63 (m, 6H, ArH), 2.78 (s, 3H, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 178.13, 133.72, 131.30, 131.12, 130.48, 129.67, 129.34, 128.77, 127.96, 127.80, 127.63, 126.48, 125.00, 123.93, 122.98, 112.18, 111.87, 88.60, 25.86. IR (KBr film): 3058, 2980, 2232, 1585, 1493, 1370,1261, 1057, 898.

*2-(2-bromo-1-(phenanthren-9-yl)ethylidene)malononitrile (**3c**):* (79% ; orange crystal m.p: 179-180 °C).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J=8.8 Hz, 1H, ArH), 8.72 (d, J=8.4 Hz, 1H, ArH), 7.98 (d, *J*=8.4 Hz, 1H, ArH), 7.81-7.67 (m, 5H, ArH), 7.59 (d, *J*=8.8 Hz, 1H, ArH), 4.81 (d, *J*=9,53 Hz 1H, CH_2Br), 4.59 (d, *J*=9,17 Hz 1H, CH_2Br diasteretop proton). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.90, 133.44, 132.94,132.06, 131.71, 131.52, 131.24, 131.12, 130.94, 129.85, 129.67, 126.54, 125.85, 124.78, 113.18, 112.88, 93.50, 31.43. IR (KBr film): 3040, 2890, 2235, 1627, 1580, 1449, 1241, 1118, 1041, 892.

*2-amino-4-(naphthalen-1-yl)-1-(1-phenylethyl)-1H-pyrrole-3-carbonitrile (**4a**):*^{1}H-NMR (400 MHz): δ 8.23-8.20 (m, 1H, ArH), 7.90-7.87 (m, 1H, ArH), 7.82 (d, 1H, ArH *J*=8.1Hz), 7.57-7.33 (m, 7H, ArH), 7.20 (d, 2H, *J*=7.2Hz, ArH), 6.63 (s, 1H, ArH), 5.29 (q, 1H, *J*=7.0Hz, CH), 3.76 (bs, 2H, NH_2), 1.85 (d, 1H, *J*=6.9Hz, CH_3) ^{13}C-NMR (100 MHz): δ 145.36, 141.42, 134.23, 132.48, 131.50, 129.59, 128.63, 128.47, 127.93, 127.57, 126.32, 126.02, 126.00,125.69,121.94, 117.37, 112.55, 55.25, 22.01 MS(CI) m/z: (M^+) 337/338/339. IR: 3434, 3335, 3230, 3057, 2980, 2201, 1631, 1551, 1507, 1484, 1451, 1297, 1265, 1156. UV $\lambda(\varepsilon_{max})$: 230 nm.

*2-amino-4-(naphthalen-2-yl)-1-(1-phenylethyl)-1H-pyrrole-3-carbonitrile (**4b**):* (71%, Light brown amorphous solid). ^{1}H-NMR (400 MHz): δ 8.17 (s, 1H, ArH), 7.89-7.73 (m, 4H, ArH), 7.50-7.34 (m, 5H, ArH), 7.18 (d, 2H, *J*=7.3Hz, ArH), 6.79 (s, 1H, ArH), 5.25 (q, 1H, *J*=7.0Hz, CH), 3.78 (bs, 2H, NH_2), 1.86 (d, 3H, CH_3 *J*=7.0Hz). ^{13}C-NMR (100 MHz): δ 146.38, 141.18, 134.02, 132.59, 131.01, 129.59, 128.54, 128.51, 128.27, 127.82, 126.45, 125.96, 125.77, 124.72, 124.1, 123.15, 117.92, 110.56, 55.33, 21.95. MS(CI) m/z: (M^+) 337/338/339. IR: 3444, 3342, 3225, 3025, 2976, 2928, 2199, 1642, 1600, 1549, 1451, 1379, 1274, 1221, 1155. UV $\lambda(\varepsilon_{max})$: 228 nm.

2-amino-4-(phenanthren-9-yl)-1-(1-phenylethyl)-1H-pyrrole-3-carbonitrile ***(4c)****:*(82%, Colorless crystal, mp: 102-104 ºC). ^{1}H-NMR (400 MHz): δ 8.77–8.69 (m, 2H, ArH), 8.26- 8.24 (m, 1H, ArH), 7.92-7.90 (m, 1H, ArH), 7.82 (s, 1H, ArH), 7.69-7.60 (m, 4H, ArH), 7.45-7.35 (m, 2H, ArH), 7.23-7.21 (m, 2H, ArH), 6.69 (s, 1H, ArH), 5.30 (q, 1H, *J*=7.3Hz, CH), 3.77 (bs, 2H, NH_2), 1.86 (d, 3H, *J*=7,0 Hz, CH_3). ^{13}C-NMR (100 MHz):δ 145.19, 141.43, 131.86, 131.37, 131.00, 130.29, 130.11, 129.61, 128.88, 128.50, 128.34, 126.96, 126.85, 126.82, 126.75, 125.97, 123.19, 122.73, 122.08, 117.16, 112.69, 55.33, 22.02. MS(CI) m/z: (M^+) 387/388/389. IR: 3427, 3337, 3229, 3061, 2964, 2201, 1708, 1626, 1551, 1492, 1449, 1263, 1157, 1027. UV λ(ε_{max}): 256 nm.

2-amino-4-(phenanthren-3-yl)-1-(1-phenylethyl)-1H-pyrrole-3-carbonitrile ***(4d)****:*(88%, Dark brown amorphous solid). ^{1}H-NMR (400 MHz): δ 9.05 (s, 1H, ArH), 8.79 (d, 1H, ArH, J=8.4Hz), 7.90-7.83 (d, 3H, ArH), 7.74-7.58 (m, 4H, ArH), 7.42-7.31 (m, 3H, ArH), 7.19 (d, 2H, *J*=7.3Hz, ArH), 6.86 (s, 1H, ArH), 5.26 (q, 1H, *J*=7.0Hz, CH), 3.79 (bs, 2H, NH_2), 1.88 (d, 3H, *J*=7,0Hz, CH_3). ^{13}C-NMR (100 MHz): δ 146.49, 141.18, 132.55, 131.77,131.07, 130.95, 130.62, 129.60, 129.16, 128.75, 128.52, 126.94, 126.89, 126.85, 126.77, 125.97, 124.83, 123.49, 123.24, 119.54, 118.13, 110.54, 55.38, 21.97. MS(CI) m/z: (M^+) 387/388/389. IR: 3433, 3337, 3229, 2981, 2198, 1711, 1618, 1550, 1482, 1453,1223, 1157, 1027. UV λ(ε_{max}): 256 nm.

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Supporting Information

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References

[1] Fischer, H. 2,4-dimethyl-3,5-dicarbethoxypyrrole. *Org. Syn. Coll.* **1943,** *2*, 202-202.
[2] Battersby, A. R. Nature's pathways to the pigments of life. *Nat. Prod. Rep*. **1987,** *4*, 77-87.
[3] Wamhoff, H; Wehling, B. Heterocyclische β-enaminoester; 18[1]. Zur synthese von 2-aminopyrrol-3-carbonsäure-derivaten. *Synthesis* **1976,** *1*, 51-51.
[4] Laks, J.A.S.; Ross, J.R.; Bayomi, S.M.; Sowell, J.W. Synthesis of N-1-substituted 2-amino-3-*tert*-butoxycarbonyl-4,5-dimethylpyrroles. *Synthesis* **1985,** *3*, 291-293.
[5] Pichler, H.; Folker, G.; Roth, H.J.; Eger, K. Synthesis of 7-unsubstituted 7h-pyrrolo[2,3-D]pyrimidines. *Liebigs Ann. Chem.* **1986,** *9*, 1485-1505.
[6] Ross, J.R.; Vishwakarma, J.W.; Sowell, J.W. A facile synthesis of pyrrolo[1,2-A]pyrimidines and pyrrolo[1,2-A]Imidazoles. *J. Heterocycl. Chem.* **1987,** *24*, 661-665.
[7] Demir, A.S.; Emrullahoglu M. An effective new synthesis of 2-aminopyrrole-4-carboxylates. *Tetrahedron* **2005,** *61*, 10482-10489.
[8] Joule J. A.; Mills K.; Smith G. F. Pyrroles: Reactions and Synthesis. *Heterocyclic Chemistry*, **1995**, 3rd ed.; Chapman and Hall: London

[9] a) Pantoş, G.D.; Rodriguez-Morgade, M.S.; Torres, T.; Lynch, V.M.; Sessler J.L. 2-amino-3,4-diethylpyrrole derivatives: New building blocks for coiled structures. *Chem. Commun*. **2006,** *20*, 2132-2134. b) Mohamed, M.S.; El-Domany, R.A.; El-Hameed, R.H.A. Synthesis of certain pyrrole derivates as antimicrobial agent. *Acta Pharm.* **2009**, *59*, 145-158.

[10] Dede, B. Önemli bir beş-üyeli heteroaromatik bileşik: Pirol. *Erciyes Üniv. Fen Bilim. Enst. Der.* **2006**, *22 (1-2)*, 121-141.

[11] a) Huisgen, R.; Laschtuvka, E. Eine neue synthese von derivaten des pyrrols. *Chem. Ber*. **1960**, *93*, 65-81. b)Ghorab, M.M.; Heiba, H.I.; Khalil, A.I.; Abou El Ella, D.A.; Noeman, E. Computer-based ligand design and synthesis of some new sulfonamides bearin pyrrole or pyrrolopyrimidine moieties having potential antitumor and radioprotective activities. *Phosphor., Sulfur Sil. Relat. Elem.* **2008**, *183*, 90-104.

[12] Sonoda, M.; Kuriyama, N.; Tomioka, Y.; Yamazaki, M. Studies on heterocyclic enaminonitriles. I. Synthesis and aromatization of 2-Amino-3-cyano-1-ethoxycarbonyl-4, 5-dihydropyrroles. *Chem. Pharm. Bull.* **1982**, *30*, 2357-2363.

[13] Tümer, F.; Ekinci, D.; Zilbeyaz, K.; Demir, Ü. An efficient synthesis of substituted 4-aryl-3-cyano-2-amino thiophenes by a stepwise Gewald reaction. *Turkish J. Chem*. **2004**, *28 (4)*, 395-404.