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Facile Synthesis of 1-Substituted 2-Amino-3-cyanopyrroles: New Synthetic Precursors for 5,6-Unsubstituted Pyrrolo[2,3-*d*]pyrimidines

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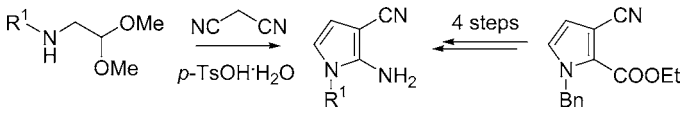
ABSTRACT



1-Benzyl-3-cyanopyrrole-2-carbonyl azide (5) underwent a Curtius rearrangement followed by quenching with alcohols to form the corresponding carbamates (6a–c). The carbamates 6a,b were unblocked to give the desired 2-amino-1-benzyl-3-cyanopyrrole (1a). A more facile procedure was subsequently developed for the synthesis of 1-substituted 2-amino-3-cyanopyrroles. *N*-Substituted aminoacetaldehyde dimethyl acetals (7a–c) were condensed with malononitrile in the presence of *p*-toluenesulfonic acid monohydrate to afford the corresponding 1-substituted 2-amino-3-cyanopyrroles (1a–c).

Aromatic or heteroaromatic compounds with *o*-aminocyano groups[1] are versatile building blocks for the synthesis of fused [*d*]pyrimidines and [*c*]pyrazoles. Our group has a longstanding interest in the synthesis of 5:6 fused [*d*]pyrimidines such as purines,[2−7] pyrazolo[3,4-*d*]pyrimidines,[8−12] and pyrrolo-[2,3-*d*]pyrimidines.[13−17] These heterocycles represent the aglycons of the more common bicyclic nucleosides, and these

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(1) Taylor, E. C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles*; Wiley: New York, 1970.
(2) Rousseau, R. J.; Townsend, L. B.; Robins, R. K. *Chem. Commun.* **1966**, 265−266.
(3) Rousseau, R. J.; Townsend, L. B. *J. Org. Chem.* **1968**, *33*, 2828−2830.
(4) Rousseau, R. J.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1968**, *90*, 2661−2668.
(5) Rousseau, R. J.; Panzica, R. P.; Reddick, S. M.; Robins, R. K.; Townsend, L. B. *J. Org. Chem.* **1970**, *35*, 631−635.
(6) Groziak, M. P.; Chern, J. W.; Townsend, L. B. *J. Org. Chem.* **1986**, *51*, 1065−1069.
(7) Chern, J. W.; Lin, G. S.; Chen, C. S.; Townsend, L. B. *J. Org. Chem.* **1991**, *56*, 4213−4218.
(8) Long, R. A.; Gerster, J. F.; Townsend, L. B. *J. Heterocycl. Chem.* **1970**, *7*, 863−869.
(9) Revankar, G. R.; Townsend, L. B. *J. Chem. Soc. C* **1971**, 2440−2442.
(10) Long, R. A.; Lewis, A. F.; Robins, R. K.; Townsend, L. B. *J. Chem. Soc. C* **1971**, 2443−2446.
(11) Townsend, L. B.; Long, R. A.; McGraw, J. P.; Miles, D. W.; Robins, R. K.; Eyring, H. *J. Org. Chem.* **1974**, *39*, 2023−2027.
(12) Earl, R. A.; Pugmire, R. J.; Revankar, G. R.; Townsend, L. B. *J. Org. Chem.* **1975**, *40*, 1822−1828.
(13) Tolman, R. L.; Robins, R. K.; Townsend, L. B. *J. Heterocycl. Chem.* **1967**, *4*, 230−238.
(14) Swayze, E. E.; Shannon, W. M.; Buckheit, R. W.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *Nucleosides Nucleotides* **1992**, *11*, 1507−1527.
(15) Krawczyk, S. H.; Nassiri, M. R.; Kucera, L. S.; Kern, E. R.; Ptak, R. G.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1995**, *38*, 4106−4114.
(16) Renau, T. E.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1996**, *39*, 873−880.
(17) Porcari, A. R.; Townsend, L. B. *Synth. Comm.* **1998**, *28*, 3835−3843.

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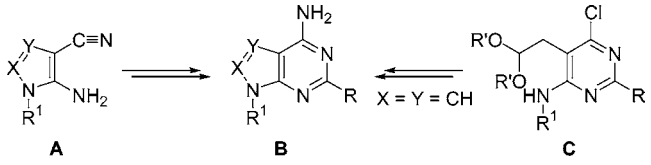
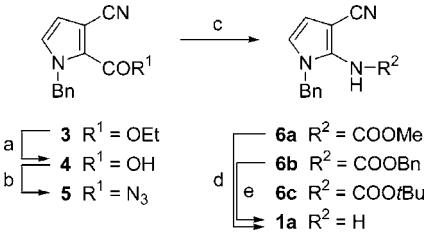
Scheme 1



1,2,3-triazole: X = Y = N
imidazole: Y = N, X = CH, CMe
pyrazole: X = N, Y = CH, CMe, CPh, C-CN
pyrrole: X = Y = CPh
X = Y = CMe
X = CH, Y = CMe, CPh, C-CN
X = C-SMe, Y = C-CN
X = CBr, Y = C-CN
Y = CH, X = CPh
X = Y = CH

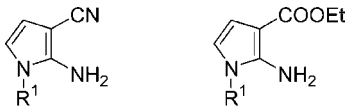
Scheme 2[a]



[a] Reagents and conditions: (a) (i) KOH, EtOH, reflux, 90 min; (ii) H^+, >95%. (b) Diphenylphosphoryl azide, Et_3N, DMF, 0 °C to rt. (c) MeOH, BnOH or *t*-BuOH, heat (**6a**, 59% from **4**; **6b**, 86% from **4**; **6c**, 74% from **4**). (d) 10% Pd/C, 40 psi H_2, MeOH, rt, 90 min, 75%. (e) KOH, ethylene glycol, 115 °C, 90 min, 59%.

heteroaromatic aglycons have been shown to possess a variety of biological activities. The conventional synthesis of 5:6 [*d*]-fused 4-aminopyrimidines (**B**) is based on the annulation of five-membered-ring *o*-aminonitriles. The *o*-aminocyano-azoles (**A**) react with isocyanate equivalents followed by a base-promoted cyclization or react with aldehyde equivalents followed by an amination-cyclization to afford the [*d*]-fused 4-aminopyrimidines, e.g., purines, pyrazolo[3,4-*d*]pyrimidines, and pyrrolo[2,3-*d*]pyrimidines. (Scheme 1)

However, there is one major exception, i.e., the 5,6-unsubstituted pyrrolo[2,3-*d*]pyrimidines (**B**, X = Y = CH). This 5:6 fused [*d*]pyrimidine ring system (Scheme 1) has in general been synthesized from the appropriate pyrimidines (**C**)[18,19] instead of pyrroles, because of the lack of viable pyrrole precursors, e.g., **1** and **2**.



A perusal of the literature revealed that only a few synthetic routes had been reported for the synthesis of 2-aminopyrrole-3-carbonitriles (**1**) and the corresponding 3-carboxylates (**2**). Toja et al. has reported the synthesis of ethyl 2-aminopyrrole-3-carboxylate, which is currently the most feasible route toward this rather unstable pyrrole derivative.[20] 2-Aminopyrrole-3-carbonitriles were anticipated to be more stable because of the strong electron-withdrawing effect of the 3-cyano group. However, the only routes for preparing 2-aminopyrrole-3-carbonitriles were limited to special orientations and required multistep elaboration from commercially available materials.[21,22] These restrictions prompted us to initiate studies designed to provide a facile and practical synthesis for the preparation of 1-substituted 2-aminopyrrole-3-carbonitriles.

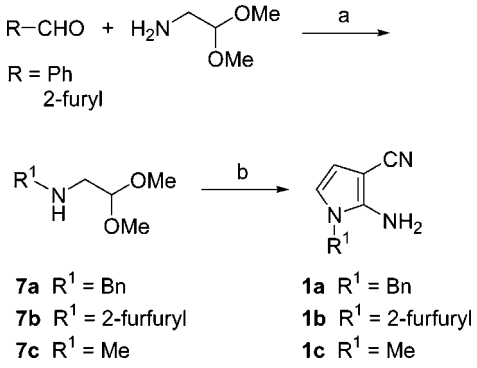
Our first approach was based on functional group manipulations from existing pyrrole derivatives. Ethyl 1-benzyl-3-cyanopyrrole-2-carboxylate[21] (**3**) was saponified to the corresponding acid (**4**).[21] The acid was reacted with diphenylphosphoryl azide to afford the acyl azide (**5**), which then underwent a Curtius rearrangement in the presence of an excess amount of alcohols to give the corresponding carbamates[23] (**6a**−**c**). Carbamates are widely used protecting groups for amines, and a removal of the carbamates should give the desired 1-benzyl-2-amino-3-cyanopyrrole (**1a**).[24] The desired product **1a**[25] was obtained from either a base hydrolysis of **6a** or a catalytic hydrogenolysis of the Cbz-masked precursor **6b**. (Scheme 2)

A direct synthesis of 2-amino-3-cyanopyrroles from acyclic precursors was also explored. Attempts to prepare the

(18) Winkeler, H. D.; Seela, F. *Chem. Ber.* **1980**, *113*, 2069−2080.
(19) Duffy, T. D.; Wibberley, D. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1921−1929.
(20) Toja, E.; Tarzia, G.; Ferrari, P.; Tuan, G. *J. Heterocycl. Chem.* **1986**, *23*, 1555−1560.
(21) Huisgen, R.; Laschtuvka, E. *Chem. Ber.* **1960**, *93*, 65−81.
(22) Sonoda, M.; Kuriyama, N.; Tomioka, Y.; Yamazaki, M. *Chem. Pharm. Bull.* **1982**, *30*, 2357−2363.

(23) **1-Benzyl-2-methoxycarbonylamino-3-cyanopyrrole (6a).** To a solution of 1-benzyl-3-cyanopyrrole-2-carboxylic acid[21] (**4**, 7.04 g, 31.12 mmol) in *N*,*N*-dimethylformamide (75 mL) at 0 °C was added diphenylphosphoryl azide (DPPA, 7.65 mL, 9.72 g, 35.30 mmol, 1.1 equiv), and triethylamine (4.75 mL, 3.42 g, 33.80 mmol, 1.1 equiv). The solution was allowed to stir at room temperature for 6 h. Methanol (7 mL) was added, and the reaction mixture was heated at 65 °C for 8 h. The solvents were evaporated in vacuo, and then the resulting residue was dissolved in EtOAc (140 mL). The solution was extracted with 1 N aqueous HCl solution (3 × 80 mL), washed with saturated aqueous $NaHCO_3$ solution (3 × 80 mL), dried over anhydrous $MgSO_4$, and then concentrated to dryness. The residue was recrystallized from ethanol to give **6a** (4.695 g, 18.39 mmol, 59%): mp 140−142 °C (EtOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.57 (bs, 1 H, NH), 7.36−7.28 (m, 3 H), 7.16−7.15 (m, 2 H), 6.87 (d, 1 H, J = 2.9 Hz), 6.46 (d, 1 H, J = 3.3 Hz), 5.05 (s, 2 H), 3.63 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 155.8, 137.6, 133.6, 129.4 (CH), 128.5 (CH), 128.2 (CH), 121.3 (CH), 116.7, 110.4 (CH), 89.0, 53.3 (CH_3), 50.0 (CH_2); IR (KBr, cm^{-1}) 3281, 3141, 3125, 2226, 1735, 1679, 1570, 1507. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.94; H, 5.08; N, 16.30.
(24) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 503−550 (7. Protection for the Amino Group−Carbamates).
(25) **2-Amino-1-benzyl-3-cyanopyrrole (1a).** Purified by flash column chromatography (Hex/EtOAc = 7:3, R_f = 0.27) and recrystallized from Hex/EtOAc: mp 104−106 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.32 (m, 3H), 7.13−7.11 (m, 2 H), 6.24 (d, 1 H, J = 3.4 Hz), 6.17 (d, 1 H, J = 3.4 Hz), 4.95 (s, 2 H), 3.84 (bs, 2 H, NH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.1, 136.2, 129.6 (CH), 128.6 (CH), 127.1 (CH), 118.1, 116.7 (CH), 108.6 (CH), 76.1, 50.0 (CH_2); IR (KBr, cm^{-1}) 3375, 3325, 2187, 1636, 1548, 1505; MS (EI/70 eV) *m*/*z* 91 (100), 197 (41) (M^+); HRMS calcd for $C_{12}H_{11}N_3$ (M^+) 197.0953, found 197.0952. Anal. Calcd for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30. Found: C, 73.00; H, 5.58; N, 21.47.

Scheme 3[a]

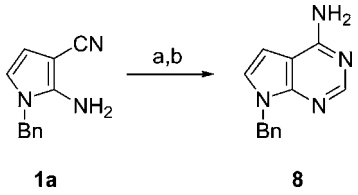


[a] Reagents and conditions: (a) (i) benzene, reflux, Dean−Stark apparatus; (ii) $NaBH_4$, EtOH, rt. (b) Malononitrile, 2 equiv of *p*-TsOH·H_2O, CH_2Cl_2, rt (**1a**, 35% from benzaldehyde; **1b**, 19% from 2-furaldehyde; **1c**, 12% from **7c**).

2-amino-3-cyanopyrroles by methods analogous to Toja's approach[20] were unsuccessful. The versatile 2,2-diethoxyethylmalononitrile[18,26] has been used previously as an important building block for the preparation of pyrrolo[2,3-*d*]pyrimidines[26] and was considered as a possible precursor for our synthesis. A variety of acidic conditions including *p*-toluenesulfonic acid and anhydrous and aqueous hydrochloric acid have been employed for the reaction of 2,2-diethoxyethylmalononitrile with benzylamine. However, formation of the desired 2-amino-3-cyanopyrrole or the possible imine adduct was not observed in our studies. It was of considerable interest that the reaction of 2,2-diethoxyethylmalononitrile with ammonium chloride in the presence of hydrochloric acid produced only 2-chloro-3-cyanopyrrole instead of the desired 2-amino-3-cyanopyrrole. This result is consistent with previous observations from other groups.[27,28]

An alternative route from *N*-substituted aminoacetaldehyde dimethyl acetals was subsequently investigated. When commercially available methylaminoacetaldehyde dimethyl acetal (**7c**) was treated with malononitrile in the presence of *p*-toluenesulfonic acid monohydrate in dichloromethane, 2-amino-3-cyano-1-methylpyrrole (**1c**) was obtained as the only product. To test the generality of this approach, other *N*-substituted aminoacetaldehyde dimethyl acetals were studied. Compounds **7a,b** were prepared from the corresponding aldehydes with aminoacetaldehyde dimethyl acetal by a reductive amination[29,30] and were subsequently treated with malononitrile under the same conditions to afford the desired 1-substituted 2-amino-3-cyanopyrroles (**1a,b**).[31] (Scheme 3)

Scheme 4[a]



[a] Reagents and conditions: (a) diethoxymethyl acetate, cat. Bu_4NHSO_4, CH_3CN, reflux, 3 h. (b) NH_3/MeOH, 60 °C, 4 h, 56% from **1a**.

The synthesis of 7-substituted 5,6-unsubstituted pyrrolo[2,3-*d*]pyrimidines can then be accomplished by conventional methods from 1-substituted 2-amino-3-cyanopyrroles. For instance, 2-amino-1-benzyl-3-cyanopyrrole (**1a**) was treated with triethyl orthoformate or diethoxymethyl acetate[32] to form the corresponding imidate, which was followed by an amination-cyclization to afford 4-amino-7-benzylpyrrolo[2,3-*d*]pyrimidine[33] (**8**) in 56% yield. (Scheme 4)

In conclusion, our investigation has successfully provided a direct and facile synthesis of 1-substituted 2-amino-3-cyanopyrroles that are amenable to the preparation of a variety of pyrrole derivatives. This study also established a new strategy for the synthesis of 7-substituted 5,6-unsubstituted pyrrolo[2,3-*d*]pyrimidines.

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Supporting Information Available: Experimental procedures and characterization for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049207D

(26) Davoll, J. *J. Chem. Soc.* **1960**, 131−138.
(27) Zepeda, L. G.; Rojasgardida, M.; Moralesrios, M. S.; Josephnathan, P. *Tetrahedron* **1989**, *45*, 6439−6448.
(28) Lowen, G. T. U. S. Patent 5,041,556, 1991.
(29) Boisbrun, M.; Jeannin, L.; Toupet, L.; Laronze, J.-Y. *Eur. J. Org. Chem.* **2000**, 3051−3057.
(30) Kaye, I. A.; Minsky, I. *J. Am. Chem. Soc.* **1949**, *71*, 2272−2273.
(31) **General Procedure for Reaction of *N*-Substituted Aminoaldehyde Dimethyl Acetals with Malononitrile.** To a mixture of the appropriate *N*-substituted aminoacetaldehyde dimethyl acetal (10 mmol; **7c**, commercially available; **7a,b**, prepared from aminoacetaldehyde dimethyl acetal and aldehyde without purification) and malononitrile (10 mmol, 1 equiv) in dichloromethane (100 mL) was added *p*-toluenesulfonic acid monohydrate (20 mmol, 2 equiv). The reaction mixture was stirred at room temperature. After the reaction was completed, the solvent was evaporated under reduced pressure. The resulting residue was dissolved in EtOAc, washed with saturated aqueous Na_2CO_3 solution and saturated aqueous NaCl solution, and dried over anhydrous Na_2SO_4, and then the solvent was evaporated under reduced pressure. The resulting oil was purified by flash column chromatography.
(32) Beaudet, I.; Duchene, A.; Parrain, J. L.; Quintard, J. P. *J. Organomet. Chem.* **1992**, *427*, 201−212.
(33) Montgomery, J. A.; Hewson, K. *J. Med. Chem.* **1967**, *10*, 665−667.