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An Efficient Synthesis of Pyrrolo[2,3-*d*]pyrimidines via Inverse Electron Demand Diels−Alder Reactions of 2-Amino-4-cyanopyrroles with 1,3,5-Triazines

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Abstract: The scope of the inverse electron demand Diels−Alder reaction of 2-amino-4-cyanopyrroles (**3a**−**e**) with 1,3,5-triazines (**1**, **2**) is reported. This methodology is suitable for one-pot syntheses of highly substituted and highly functionalized pyrrolo[2,3-*d*]pyrimidines that are the central heterocyclic nucleus of various nucleoside natural products such as toyocamycin, sangivamycin, and tubercidin.

Pyrrolo[2,3-*d*]pyrimidines (7-deazapurines) closely resemble purines and are the central nucleus of many natural products. Their frequent natural occurrence and unusual biological properties have promoted ample studies toward their synthesis[1] and biological evaluation.[2] For example, tubercidin, toyocamycin, and sangivamycin are naturally occurring antibacterials and their synthetic analogues show intriguing biological activities: e.g. GP649 is a potent inhibitor of adenosine kinase (IC_{50} = 0.2 nM) and has in vivo antiseizure activities (ED_{50} = 4.2 mg/kg) in the rat, Figure 1.[3]

As part of our ongoing interest in developing efficient synthetic methods for the preparation of purine analogues,[4] we have introduced 5-aminopyrazoles[5,7] and

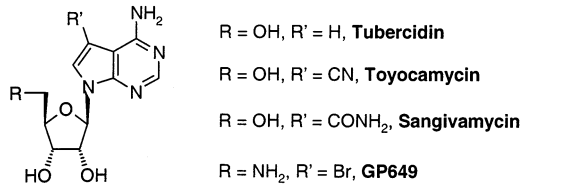
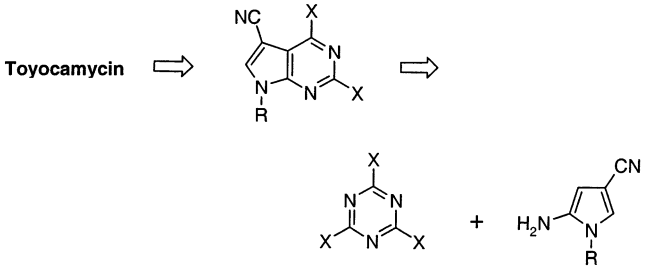


FIGURE 1. Naturally occurring and synthetic pyrrolo[2,3-*d*]-pyrimidines.

SCHEME 1



5-aminoimidazoles[6] as dienophiles for the inverse electron demand Diels−Alder (IDA) reactions of various 1,3,5-triazines. These reactions are useful for the one-pot synthesis of various pyrazolo[3,4-*d*]pyrimidines and purine analogues. Moreover, it is particularly encouraging that purine nucleosides were prepared in one pot from 1-ribosylated 5-aminoimidazoles via IDA reactions, thus avoiding the often troublesome glycosylation reactions. These results prompted us to investigate 2-aminopyrroles as potential dienophiles in IDA reactions with 1,3,5-triazines,[8] which may be a feasible methodology toward the synthesis of toyocamycin and related analogues (Scheme 1). Herein, we report studies of the IDA reactions of 1,3,5-triazines (**1**, **2**)[9] with various 2-amino-4-cyanopyrroles (**3a**−**e**). This method enables the efficient construction of the heterocyclic nucleus of toyocamycin.

2-Amino-4-cyanopyrroles (**3a**−**e**) were readily prepared using procedures reported by Brodrick and Wibberley.[10] When treated with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**1**), *remarkablely, **3a** underwent IDA reaction at room temperature in just 2 h to efficiently generate pyrrolo[2,3-d]pyrimidine **4a** in high yield*. This observation of high reactivity exhibited by pyrrole **3a** is very unusual compared to other IDA reactions since most uncatalyzed IDA reactions were conducted under thermal conditions and sometimes required prolonged heating at elevated temperatures.[11] The scope of this reaction was subsequently studied and results are summarized in Table 1 (see eq 1).

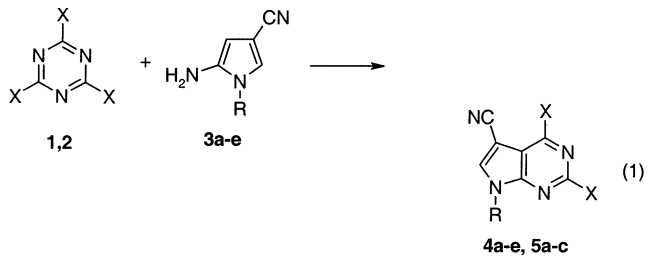


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TABLE 1. IDA Reactions of Pyrroles 3a−e with 1,3,5-Triazines 1 and 2

entry	diene	dienophile	conditions[a]	method[b]	product	yield, %
1	**1**	**3a**	DMSO, 25 °C, 2 h	**A**	**4a**	84
2	**1**	**3a**	DMSO, 25 °C, 2 h	**B**	**4a**	96
3	**1**	**3b**	DMSO, 25 °C, 2 h	**B**	**4b**	95
4	**1**	**3c**	DMSO, 25 °C, 2 h	**B**	**4c**	92
5	**1**	**3d**	DMSO, 25 °C, 2 h	**B**	**4d**	92
6	**1**	**3e**	DMSO, 25 °C, 2 h	**B**	**4e**	93
7	**2**	**3a**	DMSO, 95 °C, 2 h	**A**	**5a**	57
8	**2**	**3a**	DMSO, 95 °C, 2 h	**B**	**5a**	92
9	**2**	**3b**	DMSO, 95 °C, 2 h	**B**	**5b**	90
10	**2**	**3c**	DMSO, 95 °C, 2 h	**A**	**5c**	66

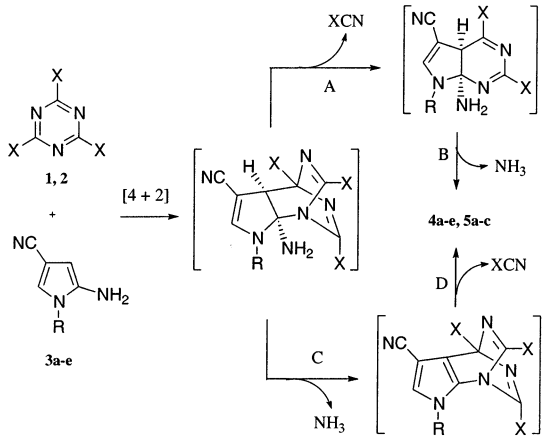
[a] Reactions were conducted under nitrogen. [b] Method A: pyrroles **3a**−**e** were the limiting reagents. Method B: 1,3,5-triazines **1** and **2** were the limiting reagents.

Pyrroles **3b**−**e** were proved to be effective dienophiles for this facile reaction with 1,3,5-triazine **1** and generated various pyrrolo[2,3-*d*]pyrimidines (**4b**−**e**) in very good yields after only 2 h at room temperature, entries 1−6, Table 1. It is noted that various groups are tolerated at the N1 position, e.g. alkyl, cycloalkyl, arylalkyl, and sulfide containing groups. The shorter time and lower temperature required for IDA reactions between pyrroles **3a**−**e** and 1,3,5-triazine **1**, compared to 5-aminopyrazole,[5] indicate that pyrroles **3a**−**e** are much more reactive dienophiles, entries 1−6, Table 1. As evident from Table 1, when 1,3,5-triazines were used as the limiting reagents (method B), excellent yields of pyrrolo[2,3-*d*]pyrimidine derivatives (**4a**−**e**) were obtained, entries 2 and 8, Table 1. However, when pyrroles **3a**−**e** were used as the limiting reagents (method A), lower yields were observed, entries 1 and 7, Table 1. This observation may be attributed to the instability of these pyrroles, since they are highly electron-rich species and are known to be unstable in their free base forms.

Encouraged by these results, the less reactive 1,3,5-triazine **2** was investigated under the current reaction conditions. The 1,3,5-triazine **2** was found to be less reactive compared to 1,3,5-triazine **1** and required moderate heating, entries 7−10, Table 1, which is consistent with our previous observations.[6] Nevertheless, pyrrolo-[2,3-*d*]pyrimidines **5a**−**c** were also generated in good to excellent yields.

It is envisioned that pyrroles **3a**−**e** should serve as dienophiles in a similar manner as 5-aminopyrazoles[5] and 5-aminoimidazoles.[6] Our previous calculations suggest that the initial [4 + 2] cycloaddition reaction is a stepwise reaction,[12] but the subsequent reactions may proceed in two different pathways, Scheme 2. In one path, a retro Diels−Alder (RDA) reaction (step A) of the [4 + 2] cycloadduct (with the loss of XCN) followed by elimination of ammonia or ammonium chloride (step B) produces **4a**−**e** or **5a**−**c** in a regioselective manner. In another path, elimination of ammonia or ammonium chloride (step C) from the [4 + 2] cycloadduct followed by a RDA reaction (step D) also gives **4a**−**e** or **5a**−**c**. The detailed mechanism of this type of cascade reaction is the subject of various theoretical studies and results will be reported in due course.

SCHEME 2



In conclusion, 2-amino-4-cyanopyrroles (**3a**−**e**) were shown to be efficient dienophiles for the IDA reaction of 1,3,5-triazines (**1**, **2**). When 1,3,5-triazine **1** was used, pyrroles **3a**−**e** were proved to be remarkably reactive permitting the cascade reaction to proceed at room temperature. This methodology is suitable for one-step syntheses of highly substituted and highly functionalized pyrrolo[2,3-*d*]pyrimidines that are the central heterocyclic nucleus of various natural products such as toyocamycin, sangivamycin, and tubercidin.

Experimental Section

General. ^{1}H NMR (200 MHz) and proton-decoupled ^{13}C NMR spectra (50 MHz) were recorded in either $CDCl_3$ or DMSO-d_6 with tetramethylsilane as the internal standard. Melting points were uncorrected. High-resolution mass spectra (HRMS) electrospray ionization (ESI) were obtained at Mass Consortium (San Diego, CA 92121). Microanalyses and Infrared spectroscopy analyses were carried out at Robertson Microlit Laboratories (29 Samson Ave., P.O. Box 927, Madison, NJ 07940). All anhydrous reactions were carried out using oven-dried flasks, and anhydrous solvents (such as DMSO, ethanol, etc.) were purchased from chemical suppliers and used as received. Analytical TLC was conducted on silica gel 60 F_{254} plates (Merck) and flash chromatography was carried out using silica gel 60, 230−400 mesh (Merck).

Pyrroles **3a**−**e** were prepared according to Brodrick and Wibberley's procedures.[10]

2-Amino-1-benzyl-4-cyanopyrrole HCl salt (3a): tan solid. MS calcd for $C_{12}H_{11}N_3$ $[MH]^+$ 198, found 198.

2-Amino-4-cyano-1-neopentylpyrrole HCl salt (3b): Red solid. MS calcd for $C_{10}H_{15}N_3$ $[MH]^+$ 178, found 178.

2-Amino-4-cyano-1-propylpyrrole HCl salt (3c): Red foam. MS calcd for $C_8H_{11}N_3$ $[MH]^+$ 150, found 150.

2-Amino-4-cyano-1-cyclopentylpyrrole HCl salt (3d): Red solid. MS calcd for $C_{10}H_{13}N_3$ $[MH]^+$ 176, found 176.

2-Amino-4-cyano-1-[1-(2-methylthio)ethyl]pyrrole HCl salt (3e): Red solid. MS calcd for $C_8H_{11}N_3S$ $[M + Na]^+$ 204, found 204.

General Procedures for IDA Reactions of 2-Aminopyrroles with 1,3,5-Triazines. Method A: Synthesis of 7-Ben-

(8) Diels−Alder reactions between tetrazines and pyrroles were reported by Seitz and co-workers: Seitz, G.; Mohr, R.; Hoferichter, R. *Chem.-Ztg.* **1988**, *112*, 17. Seitz, G.; Kampchen, T. *Arch. Pharm.* **1978**, *311*, 728. Seitz, G.; Kampchen, T. *Chem.-Ztg.* **1975**, *99*, 292.

(9) 3,5-Triazine **2** was purchased from chemical suppliers and used as received, while 1,3,5-triazine **1** was prepared according to Ott's procedure: Ott, E. *Chem Ber.* **1919**, *52*, 656.

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zyl-2,4-bis(ethoxycarbonyl)-5-cyanopyrrolo[2,3-*d*]pyrimidine (4a). A mixture of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**1**, 121 mg, 0.41 mmol, 2.1 equiv) and 2-amino-1-benzyl-4-cyanopyrrole hydrogen chloride salt (**3a**, 44 mg, 0.19 mmol) in anhydrous DMSO (2.0 mL) was stirred at 25 °C under nitrogen for 2 h. The crude reaction mixture was evaporated to dryness, and the crude material was purified by flash chromatography (SiO_2, 1 × 15 cm, 50% ethyl acetate−hexane) to give pure **4a** (62 mg, 84%) as a white solid: mp 132−135 °C; ^{1}H NMR (DMSO-d_6, 200 MHz, ppm) δ 9.14 (1H, s), 7.34 (5H, br s), 5.62 (2H, s), 4.50 (4H, 2 × q, J = 7.1 Hz), 1.40 (6H, 2 × t, J = 7.1 Hz); IR (KBr) 3075, 2980, 2229, 1748, 1732, 1246, 1224 cm^{-1}. MS calcd for $C_{20}H_{18}N_4O_4$ [MH]$^+$ 379, found 379. Anal. Calcd for $C_{20}H_{18}N_4O_4 + 0.5H_2O$: C, 62.01; H, 4.94; N, 14.46. Found: C, 62.08; H, 4.82; N, 14.67.

Method B: Synthesis of 2,4-Bis(ethoxycarbonyl)-5-cyano-7-neopentylpyrrolo[2,3-*d*]pyrimidine (4b). A suspension of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**1**, 100 mg, 0.336 mmol) and 2-amino-1-neopentyl-4-cyanopyrrole hydrogen chloride (**3b**, 143 mg, 0.672 mmol, 2.0 equiv) in anhydrous DMSO (2 mL) was stirred at 25 °C under nitrogen for 2 h. The crude reaction mixture was diluted with ethyl acetate (35 mL), washed with saturated sodium bicarbonate (15 mL), water (3 × 25 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated to dryness and the crude material was purified by flash chromatography (SiO_2, 2 × 15 cm, 30% ethyl acetate−hexane) to give pure **4b** (117 mg, 97%) as a pinkish solid: mp 138−139 °C (EtOAc−hexane, off-white needles); ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.09 (1H, s), 4.68 (2H, q, J = 7.2 Hz), 4.55 (2H, q, J = 7.2 Hz), 4.30 (2H, s), 1.52 (3H, t, J = 7.2 Hz), 1.48 (3H, t, J = 7.2 Hz), 1.01 (9H, s); MS calcd for $C_{18}H_{22}N_4O_4$ [MH]$^+$ 359, found 359. Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.50; H, 6.12; N, 15.61.

2,4-Bis(ethoxycarbonyl)-5-cyano-7-propylpyrrolo[2,3-*d*]pyrimidine (4c). Method A: white needles (EtOAc−hexane), mp 133−134 °C; ^{1}H NMR (DMSO-d_6, 200 MHz, ppm) δ 9.07 (1H, s), 4.52 (2H, q, J = 7.2 Hz), 4.43 (2H, q, J = 7.2 Hz), 4.35 (2H, t, J = 7.0 Hz), 1.89 (2H, m), 1.41 (3H, t, J = 7.0 Hz), 1.36 (3H, t, J = 7.0 Hz), 0.85 (3H, t, J = 7.7 Hz). Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 57.90; H, 5.47; N, 16.90.

2,4-Bis(ethoxycarbonyl)-5-cyano-7-cyclopentylpyrrolo-[2,3-*d*]pyrimidine (4d). Method B: Off-white needles (EtOAc−hexane), mp 141−142 °C; ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.19 (1H, s), 5.49 (1H, m), 4.66 (2H, q, J = 7 Hz), 4.56 (2H, q, J = 7 Hz), 2.39−1.83 (8H, m), 1.52 (3H, t, J = 7 Hz), 1.49 (3H, t, J = 7 Hz). MS calcd for $C_{18}H_{20}N_4O_4$ [MH]$^+$ 357, found 357. Anal. Calcd for $C_{18}H_{20}N_4O_4$: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.53; H, 5.74; N, 15.65.

2,4-Bis(ethoxycarbonyl)-5-cyano-7-[1-(2-methylthio)-ethyl]pyrrolo[2,3-*d*]pyrimidine (4e). Method B: white needles (EtOAc−hexane), mp 182−186 °C; ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.24 (1H, s), 4.68 (2H, t, J = 6.6 Hz), 4.67 (2H, q, J = 6.8 Hz), 4.55 (2H, q, J = 7.2 Hz), 3.00 (2H, t), 2.12 (3H, s), 1.51 (3H, t, J = 6.8 Hz), 1.48 (3H, t, J = 6.8 Hz); IR (KBr) 3075, 2980, 2231, 1742, 1728, 1307, 1225, 1219 cm^{-1}. MS calcd for $C_{16}H_{18}N_4O_4S$ [MH]$^+$ 363, found 363. Anal. Calcd for $C_{16}H_{18}N_4O_4S$: C, 53.03; H, 5.01; N, 15.46. Found: C, 53.20; H, 4.93; N, 15.37.

7-Benzyl-5-cyanopyrrolo[2,3-*d*]pyrimidine (5a). Method A: off-white needles (EtOAc−hexane), mp 148−150 °C; ^{1}H NMR (DMSO-d_6, 200 MHz, ppm) δ 8.09 (1H, s), 4.68 (2H, q, J = 7.2 Hz), 4.55 (2H, q, J = 7.2 Hz), 4.30 (2H, s), 1.52 (3H, t, J = 7.2 Hz), 1.48 (3H, t, J = 7.2 Hz), 1.01 (9H, s); IR (KBr), 3096, 3047, 2227, 1592, 1567, 1440, 11420, 1168, 629 cm^{-1}. MS calcd for $C_{14}H_{10}N_4$ [MH]$^+$ 235, found 235. Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.54; H, 3.99; N, 23.99.

5-Cyano-7-neopentylpyrrolo[2,3-*d*]pyrimidine (5b). Method B: off-white needles (EtOAc−hexane), mp 150−151 °C; ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.09 (1H, s), 4.68 (2H, q, J = 7.2 Hz), 4.55 (2H, q, J = 7.2 Hz), 4.30 (2H, s), 1.52 (3H, t, J = 7.2 Hz), 1.48 (3H, t, J = 7.2 Hz), 1.01 (9H, s). MS calcd for $C_{12}H_{14}N_4$ [MH]$^+$ 215, found 215. Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 67.20; H, 6.49; N, 26.13.

5-Cyano-7-propylpyrrolo[2,3-*d*]pyrimidine (5c). Method A: off-white needles (EtOAc−hexane), mp 78−81 °C; ^{1}H NMR (DMSO-d_6, 200 MHz, ppm) δ 9.23 (1H, s), 9.00 (1H, s), 8.68 (1H, s), 4.27 (2H, t, J = 7.3 Hz), 1.84 (1H, m), 0.82 (3H, t, J = 7.3 Hz); IR (KBr), 3096, 3053, 2980, 2228, 1592, 1565, 1526, 1355, 1157 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.22; H, 5.21; N, 30.08.

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