

SYNTHESIS OF PYRROLO[1,2-*c*]PYRIMIDINES

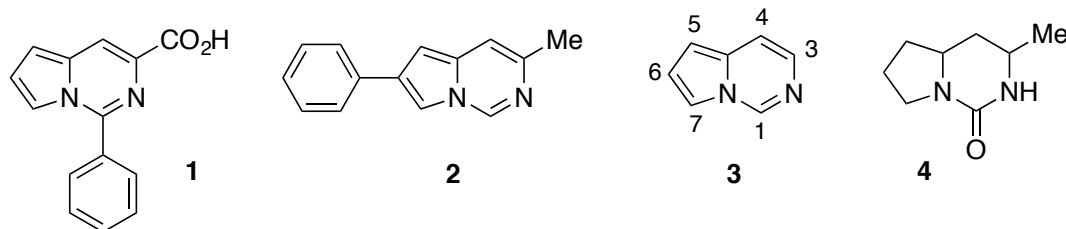
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Abstract – The synthesis of several new pyrrolo[1,2-*c*]pyrimidines from the base-induced condensation of pyrrolo-2-carbaldehydes with either TosMIC (toluenesulfonylmethyl isocyanide) or ethyl isocyanoacetate is described, along with the preparation of novel bis(pyrrolo[1,2-*c*]pyrimidines).

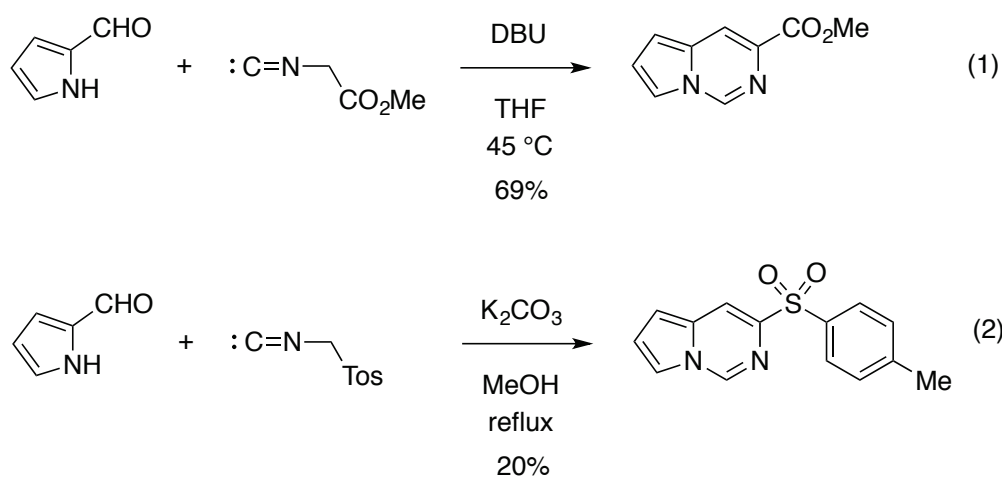
The pyrrolo[1,2-*c*]pyrimidine ring system has an interesting history. In 1949 Herz inadvertently synthesized 1-phenylpyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid (**1**), the first example of this ring system, in a reinvestigation of the reaction between pyrrole-2-carbaldehyde and hippuric acid.¹ In 1963 Boekelheide achieved the first targeted synthesis of this ring system with the preparation of 3-methyl-6-phenylpyrrolo[1,2-*c*]pyrimidine (**2**) via a classical Chichibabin reaction.² The parent molecule **3**, which was found to be aromatic though oxidatively labile, was prepared by Rapoport in 1965 via the cyclization of 3-(4-pyrimidyl)-1-propanol (or its tosylate) and subsequent dehydrogenation.³ Rapoport also isolated 3-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]pyrimidin-1-one (**4**) as a chemical degradation product of the toxic shellfish poison, saxitoxin.⁴ More recently, variants of Boekelheide's Chichibabin approach to pyrrolo[1,2-*c*]pyrimidine **2** have been implemented in syntheses of this ring system,⁵ and the synthesis of all of the isomeric pyrrolopyrimidines has been reviewed.⁶



The interest in the pyrrolo[1,2-*c*]pyrimidine ring system as a biological scaffold was sparked by the pyridopyrrolo[1,2-*c*]pyrimidine marine alkaloid variolin B and several related fused derivatives that display antitumor and other biological activity.⁷ Furthermore, the electrochemical properties of pyrrolo[1,2-*c*]pyrimidines have been investigated with a view to employing this highly fluorescent ring

system in electrochemical sensors.⁸ The biological activity of each isomeric pyrrolopyrimidine has been reviewed recently.⁹

Independently, and by serendipity, two groups discovered a new, more powerful construction of the pyrrolo[1,2-*c*]pyrimidine ring system. Suzuki found in 1976 that methyl isocyanoacetate reacts with pyrrole-2-carbaldehydes to give pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid esters (equation 1),¹⁰ and Kitagawa discovered in 1979 the matching reaction between tosylmethyl isocyanide (TosMIC) and pyrrole-2-carbaldehydes to afford 3-tosylpyrrolo[1,2-*c*]pyrimidines (equation 2) (Scheme 1).¹¹ Interestingly, other heteroaromatic aldehydes (furyl, thienyl, pyridyl) react with TosMIC to give the expected oxazoles.

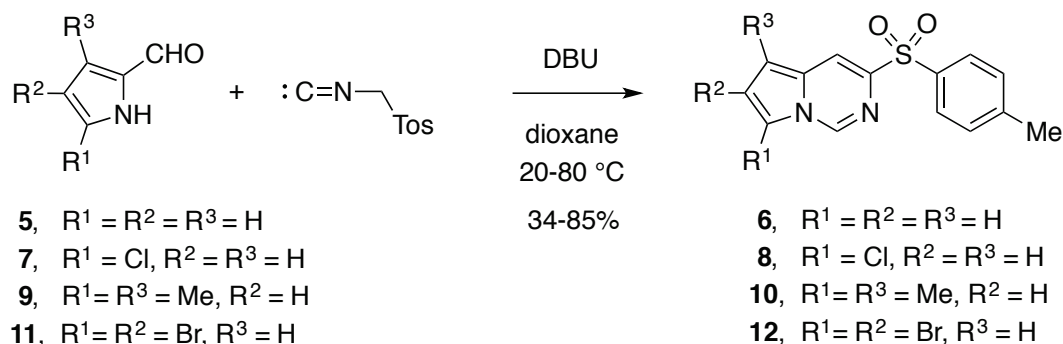


Scheme 1

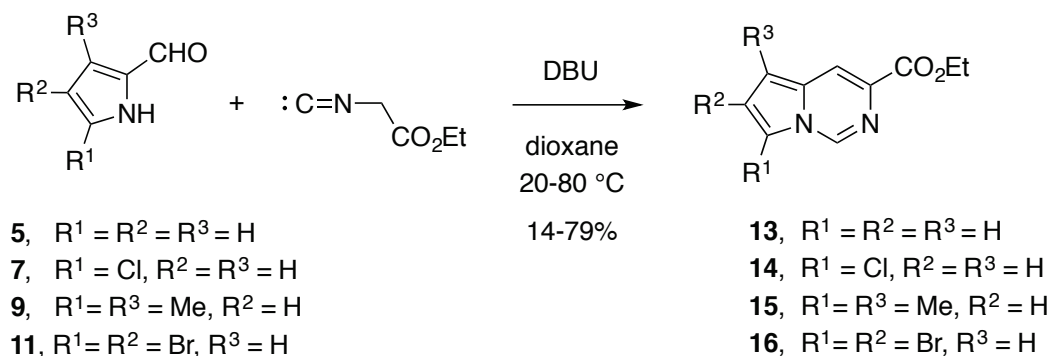
The group of Alvarez-Builla has used both the Suzuki and Kitagawa reactions to prepare many new pyrrolo[1,2-*c*]pyrimidines,¹² and Baxendale has customized the Suzuki reaction for a flow synthesis of pyrrolo[1,2-*c*]pyrimidines.¹³

In connection with another project in our laboratory, we desired several previously unknown substituted pyrrolo[1,2-*c*]pyrimidines, including examples of “bis(pyrrolo[1,2-*c*]pyrimidines)” that could be fashioned from the appropriate bis(pyrrole-2-carbaldehydes). Such bis(pyrrolo[1,2-*c*]pyrimidines) appear to be unknown. Our reactions between pyrrole-2-carbaldehydes (**5**, **7**, **9**, **11**) and TosMIC to give the respective pyrrolo[1,2-*c*]pyrimidines (**6**, **8**, **10**, **12**) are shown in Scheme 2. Likewise, the similar reactions between pyrrole-2-carbaldehydes (**5**, **7**, **9**, **11**) and ethyl isocyanoacetate to give the respective pyrrolo[1,2-*c*]pyrimidines (**13-16**) are shown in Scheme 3. Of these pyrrolo[1,2-*c*]pyrimidines, **6** and **13** are known.^{11a,12} For both reactions we found that the nucleophilic base DBU in dioxane was somewhat superior to K₂CO₃ originally used by Kitagawa, and gave cleaner products. Other solvents (THF,

diethyl ether) gave some unidentified byproducts. We have confirmed the structure of **8** by X-ray crystallography.¹⁴

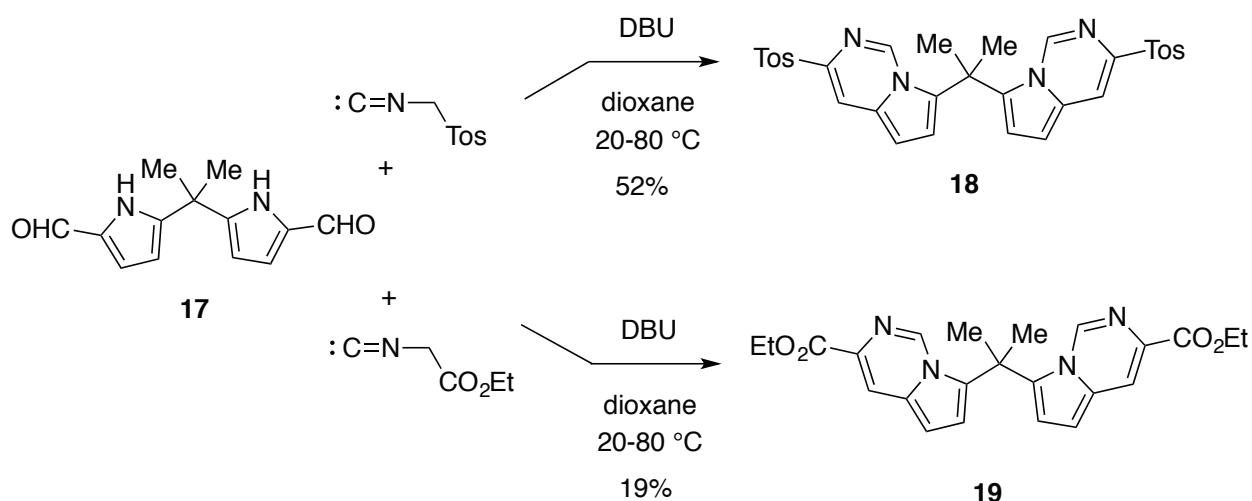


Scheme 2



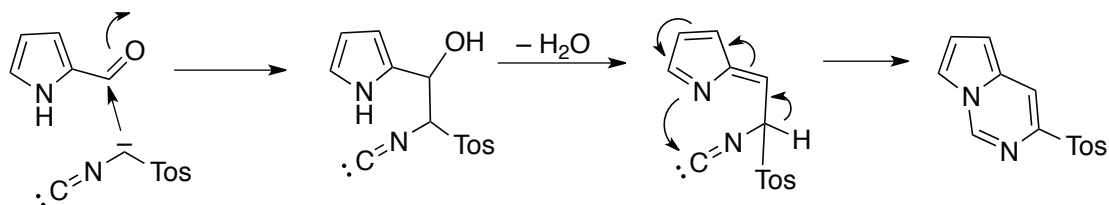
Scheme 3

We prepared the known 5,5'-(propane-2,2-diyl)bis(1*H*-pyrrole-2-carbaldehyde) (**17**)¹⁵ according to a literature acylation procedure for a related compound¹⁶ via 2,2'-(propane-2,2-diyl)bis(1*H*-pyrrole).¹⁷ Dialdehyde **17** undergoes the usual reactions with TosMIC and ethyl isocyanoacetate to give the products **18** and **19**, respectively (Scheme 4). It will be noted that the reaction yields with TosMIC are consistently higher than those with ethyl isocyanoacetate.



Scheme 4

An abbreviated mechanism as proposed by Kitagawa for the formation of the pyrrolo[1,2-*c*]pyrimidine ring system is shown in Scheme 5.¹¹ Pyrroles lacking an NH, for example, 1-methylpyrrole-2-carbaldehyde, undergo cyclization via the carbonyl oxygen to form 5-(1-methyl-2-pyrrolyl)oxazole.¹¹



Scheme 5. An abbreviated mechanism proposed by Kitagawa¹¹

In conclusion, we have synthesized several new pyrrolo[1,2-*c*]pyrimidines that bear substituents (Br, Cl, Me) amenable for metalation and cross-coupling reactions. In addition we describe the first examples of bis(pyrrolo[1,2-*c*]pyrimidines).

EXPERIMENTAL

All ¹H NMR spectra at 300 MHz were taken on a Varian XL-300 Fourier transform NMR spectrometer and ¹H NMR spectra at 500 MHz were taken either on a Varian Inova 500 MHz or Bruker Avance III 500 MHz NMR spectrometer. ¹³C NMR were taken as proton decoupled spectra on a Bruker 500 MHz NMR spectrometer. Chemical shifts (δ) are reported in ppm using the residual solvent proton or carbon signal (CDCl₃: δ_{H} 7.27, δ_{C} 77.23). Multiplicities are indicated as the following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Melting points were determined using open capillary tubes with a Laboratory Devices Mel Temp and are uncorrected. High-resolution mass spectrometry (HRMS) was performed at the University of Illinois Urbana-Champaign, SCS, Mass Spectrometry laboratory. All reactions were performed under positive nitrogen pressure unless noted otherwise. Reactions were monitored by thin layer chromatography (TLC) visualized under shortwave UV light at 254 nm.

1H-Pyrrole-2-carbaldehyde [5]. This compound was prepared as previously described.¹⁸ The crude product was purified by flash chromatography using 4:1 hexanes: EtOAc; mp 42-43 °C [lit.¹⁸ 44-45 °C]; ¹H NMR (300 MHz, CDCl₃) δ 10.01 (br, NH), 9.53 (d, J = 1 Hz, 1H), 7.17 (d, J = 1 Hz, 1H), 7.01 (m, 1H), 6.36 (m, 1H).

5-Chloro-1H-pyrrole-2-carbaldehyde [7]. This compound was prepared as previously described.¹⁹ The crude product was purified by flash chromatography using 8:1 hexanes: EtOAc; mp 103-105 °C [lit.¹⁹ mp 110-111 °C]; ¹H NMR (300 MHz, CDCl₃) δ 9.72 (br, NH), 9.40 (s, 1H), 6.92 (m, 1H), 6.23 (m, 1H).

4,5-Dibromo-1H-pyrrole-2-carbaldehyde [11]. This compound was prepared as previously

described.²⁰ The crude product was purified by flash chromatography using 8:1 hexanes: EtOAc; mp 148-150 °C [lit.²¹ mp 155-156 °C]; ¹H NMR (300 MHz, CDCl₃) δ 9.67 (br, NH), 9.37 (s, 1H), 6.96 (d, *J* = 3 Hz, 1H).

5,5'-(Propane-2,2-diyl)bis(1*H*-pyrrole-2-carbaldehyde) [17]. The known 2,2'-(propane-2,2-diyl)bis(1*H*-pyrrole) was prepared as previously described¹⁷ and this was acylated according to the method of Farhanullah and Ram¹⁶ to afford **17**. The crude product was purified by flash chromatography using 8:1 hexanes: EtOAc to afford the known **17** as colorless crystals: mp 181-182 °C; ¹H NMR (300 MHz, CDCl₃) δ 10.76 (br, 2NH), 9.26 (s, 2H), 6.87 (t, *J* = 3 Hz, 2H), 6.23 (t, *J* = 3 Hz, 2H), 1.77 (s, 6H). For a different acylation of 2,2'-(propane-2,2-diyl)bis(1*H*-pyrrole) to afford **17**, see Beer *et al.*¹⁵

Pyrrolo[1,2-*c*]pyrimidines. General Procedure. To an ice bath cooled solution of pyrrole-2-carbaldehyde (50 mg, 1 equivalent) in dioxane (10 mL) were added either TosMIC or ethyl isocynoacetate (1.3 equivalents) and DBU (1.3 equivalents). The solution was stirred for 2-48 h at 20-80 °C, as followed by TLC, and quenched with aq. 1M HCl. The product was extracted with EtOAc or DCM, washed with 1M HCl (20 mL), saturated aqueous NaHCO₃ (20 mL), and brine (20 mL). The organic layer was dried (Na₂SO₄), filtered through glass wool and concentrated *in vacuo*. The crude product was purified by flash chromatography using 3:1 hexanes: EtOAc to give the described pyrrolo[1,2-*c*]pyrimidines.

3-Tosylpyrrolo[1,2-*c*]pyrimidine [6].¹² A reaction of pyrrole-2-carbaldehyde (**5**) with TosMIC afforded **35** in 85% yield as a light yellow-green solid product: mp 197-199 °C [lit.¹² mp 200-202 °C]; ¹H NMR (500 MHz, CDCl₃) δ 8.74 (s, 1H), 8.25 (s, 1H), 7.94 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 2 Hz, 1H), 7.32 (d, *J* = 8 Hz, 2H), 7.03 (dd, *J* = 4, 2 Hz, 1H), 6.82 (d, *J* = 4 Hz, 1H), 2.41 (s, 3H).

7-Chloro-3-tosylpyrrolo[1,2-*c*]pyrimidine [8]. A reaction of 5-chloropyrrole-2-carbaldehyde (**7**) with TosMIC afforded **8** in 66% yield as a light yellow solid: mp 181-184 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.77 (s, 1H), 8.24 (d, *J* = 1 Hz, 1H), 7.95 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 6.92 (d, *J* = 4 Hz, 1H), 6.84 (d, *J* = 4 Hz, 1H), 2.42 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 144.8, 141.2, 136.4, 135.9, 130.0, 129.6, 128.9, 116.9, 115.0, 110.7, 106.2, 21.9; HRMS *m/z* Calcd for C₁₄H₁₂N₂O₂SCl: 307.0308. Found: 307.0303.

5,7-Dimethyl-3-tosylpyrrolo[1,2-*c*]pyrimidine [10]. A reaction of 3,5-dimethylpyrrole-2-carbaldehyde (**9**) (Aldrich) with TosMIC afforded **10** in 58% yield as a yellow solid: mp 183-185 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.46 (s, 1H), 8.17 (s, 1H), 7.95 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 6.62 (s, 1H), 2.50 (s, 3H), 2.41 (s, 3H), 2.38 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 144.3, 137.9, 137.2, 136.1, 129.8, 128.6, 126.7, 122.6, 119.5, 116.1, 114.2, 21.8, 11.3, 10.4; HRMS *m/z* Calcd for C₁₆H₁₇N₂O₂S: 301.1011. Found: 301.1007.

6,7-Dibromo-3-tosylpyrrolo[1,2-*c*]pyrimidine [12]. A reaction of 4,5-dibromopyrrole-2-carbaldehyde

(**11**) with TosMIC afforded **12** in 34% yield as a light yellow solid: mp 178-180 °C; ¹H NMR (500¹ MHz, CDCl₃) δ 8.74 (s, 1H), 8.16 (s, 1H), 7.94 (d, *J* = 8 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 6.98 (s, 1H), 2.43 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 145.1, 142.7, 137.1, 136.0, 131.5, 130.0, 129.0, 113.3, 112.0, 108.9, 98.0, 21.9; HRMS *m/z* Calcd for C₁₄H₁₁N₂O₂SBr₂: 428.8908, found: 428.8906.

Ethyl pyrrolo[1,2-*c*]pyrimidine-3-carboxylate [13].^{12b} A reaction of pyrrole-2-carbaldehyde (**5**) with ethyl isocyanoacetate afforded **13** in 79% yield as a light yellow solid: mp 61-63 °C [lit.^{12b} mp 69-71 °C]; ¹H NMR (500 MHz, CDCl₃) δ 8.85 (s, 1H), 8.22 (s, 1H), 7.53 (s, 1H), 6.98 (d, *J* = 3 Hz, 1H), 6.76 (d, *J* = 3 Hz, 1H), 4.64 (q, *J* = 7 Hz, 2H), 1.43 (t, *J* = 7 Hz, 3H).

Ethyl 7-chloropyrrolo[1,2-*c*]pyrimidine-3-carboxylate [14]. A reaction of 5-chloropyrrole-2-carbaldehyde (**7**) with ethyl isocyanoacetate afforded **14** in 52% yield as a light yellow-orange solid: 90-92 °C (dec); ¹H NMR (300 MHz, CDCl₃) δ 8.61 (s, 1H), 8.20 (d, *J* = 1 Hz, 1H), 6.90 (d, *J* = 4 Hz, 1H), 6.79 (d, *J* = 4 Hz, 1H), 4.46 (q, *J* = 7 Hz, 2H), 1.44 (t, *J* = 7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.0, 135.1, 130.6, 117.6, 116.5, 105.4, 62.0, 14.6 (2 missing peaks); HRMS *m/z* Calcd for C₁₀H₁₀N₂O₂Cl: 225.0431. Found: 225.0429.

Ethyl 5,7-dimethylpyrrolo[1,2-*c*]pyrimidine-3-carboxylate [15]. A reaction of 3,5-dimethylpyrrole-2-carbaldehyde (**9**) (Aldrich) with ethyl isocyanoacetate afforded **15** in 33% yield as a yellow-orange solid: mp 89-91 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (s, 1H), 8.17 (s, 1H), 6.61 (s, 1H), 4.46 (q, *J* = 7 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 1.45 (t, *J* = 7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.4, 135.5, 127.7, 127.0, 122.6, 119.4, 116.7, 115.6, 61.6, 14.7, 11.4, 10.5; HRMS *m/z* Calcd for C₁₂H₁₅N₂O₂: 219.1134. Found: 219.1127.

Ethyl 6,7-dibromopyrrolo[1,2-*c*]pyrimidine-3-carboxylate [16]. A reaction of 4,5-dibromopyrrole-2-carbaldehyde (**11**) with ethyl isocyanoacetate afforded **16** in 14% yield along with 40% of starting material; the product as a light yellow-orange solid: 134-137 °C (dec); ¹H NMR (300 MHz, CDCl₃) δ 8.27 (s, 1H), 8.13 (d, *J* = 1 Hz, 1H), 6.94 (d, *J* = 1 Hz, 1H), 4.47 (q, *J* = 7 Hz, 2H), 1.45 (t, *J* = 7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 164.7, 136.2, 132.4, 132.0, 116.0, 111.4, 107.9, 97.3, 62.1, 14.6; HRMS *m/z* Calcd for C₁₀H₉N₂O₂Br₂: 346.9031, found: 346.0930.

3-Tosyl-7-(2-(3-tosylpyrrolo[1,2-*c*]pyrimidin-7-yl)propan-2-yl)pyrrolo[1,2-*c*]pyrimidine [18]. A reaction of 5,5'-(propane-2,2-diyl)bis(1*H*-pyrrole-2-carbaldehyde) (**17**) with TosMIC afforded **18** in 52% yield as a colorless solid: 168-170 °C (dec.); ¹H NMR (300 MHz, CDCl₃) δ 8.18 (s, 2H), 8.13 (s, 2H), 7.84 (d, *J* = 8 Hz, 4H), 7.27 (d, *J* = 8 Hz, 4H), 2.37 (s, 6H), 1.89 (s, 6H); HRMS *m/z* Calcd for C₃₁H₂₉N₄O₄S₂: 585.1622. Found: 585.1630.

Diethyl 7,7'-(propane-2,2-diyl)bis(pyrrolo[1,2-*c*]pyrimidine-3-carboxylate) [19]. A reaction of 5,5'-(propane-2,2-diyl)bis(1*H*-pyrrole-2-carbaldehyde) (**17**) with ethyl isocyanoacetate afforded **19** in 19% yield as a colorless solid: mp 114-116 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.15 (d, *J* = 9 Hz, 4H),

7.14 (d, $J = 4$ Hz, 2H), 6.83 (d, $J = 4$ Hz, 2H), 4.36 (q, $J = 7$ Hz, 4H), 1.98 (s, 6H), 1.36 (t, $J = 7$ Hz, 6H); HRMS m/z Calcd for $C_{23}H_{25}N_4O_4$: 421.1876. Found: 421.1869.

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