HETEROCYCLES, Vol. 103, No. 1, 2021, pp. 476 - 483. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 13th April, 2020, Accepted, 8th May, 2020, Published online, 13th May, 2020
DOI: 10.3987/COM-20-S(K)11

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

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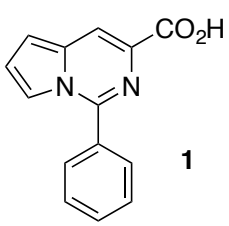
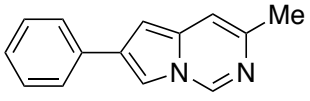
This paper is dedicated to Professor. Yasuyuki Kita on the occasion of his 77th birthday.

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]



1



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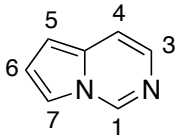

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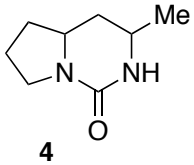
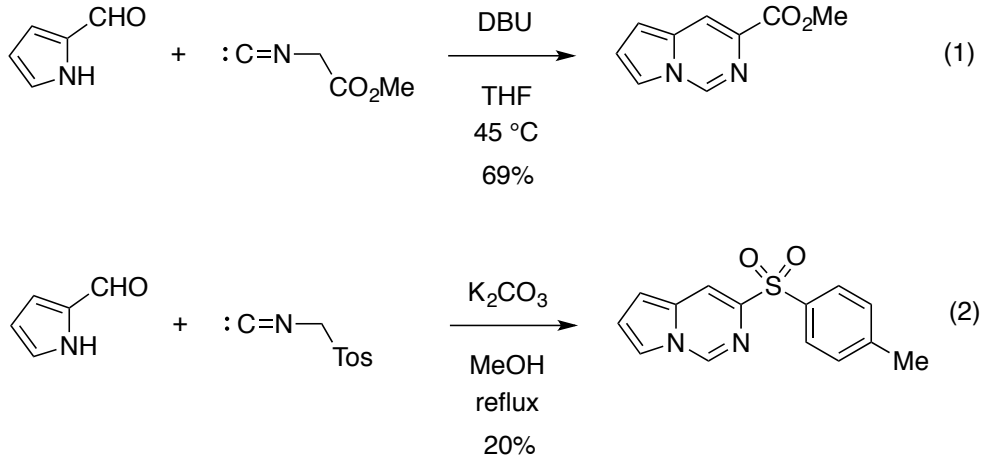


4

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.

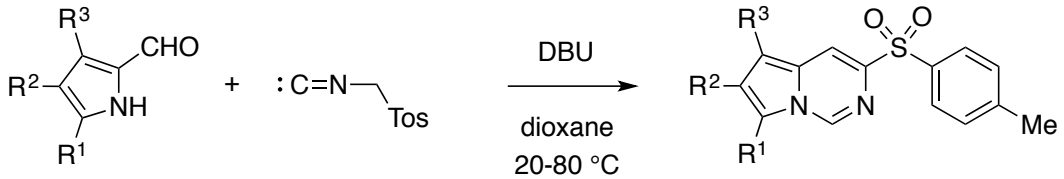


Scheme 1

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 K_2CO_3 originally used by Kitagawa, and gave cleaner products. Other solvents (THF,

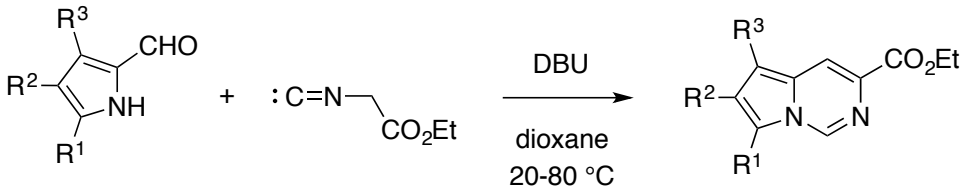
diethyl ether) gave some unidentified byproducts. We have confirmed the structure of **8** by X-ray crystallography.[14]



5, $R^1 = R^2 = R^3 = H$
7, $R^1 = Cl$, $R^2 = R^3 = H$
9, $R^1 = R^3 = Me$, $R^2 = H$
11, $R^1 = R^2 = Br$, $R^3 = H$

6, $R^1 = R^2 = R^3 = H$
8, $R^1 = Cl$, $R^2 = R^3 = H$
10, $R^1 = R^3 = Me$, $R^2 = H$
12, $R^1 = R^2 = Br$, $R^3 = H$

Scheme 2

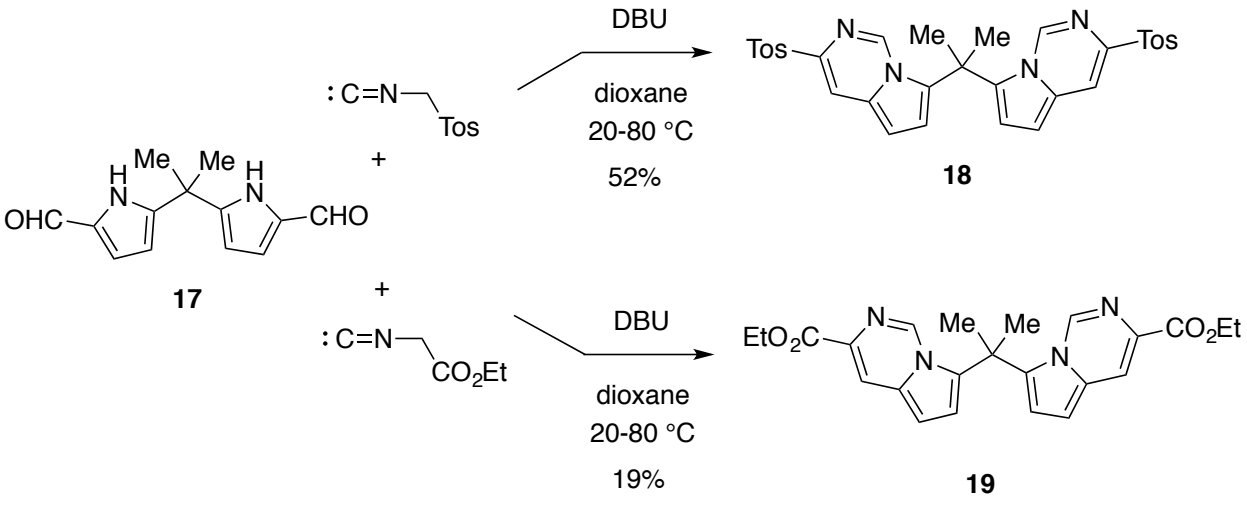


5, $R^1 = R^2 = R^3 = H$
7, $R^1 = Cl$, $R^2 = R^3 = H$
9, $R^1 = R^3 = Me$, $R^2 = H$
11, $R^1 = R^2 = Br$, $R^3 = H$

13, $R^1 = R^2 = R^3 = H$
14, $R^1 = Cl$, $R^2 = R^3 = H$
15, $R^1 = R^3 = Me$, $R^2 = H$
16, $R^1 = R^2 = Br$, $R^3 = H$

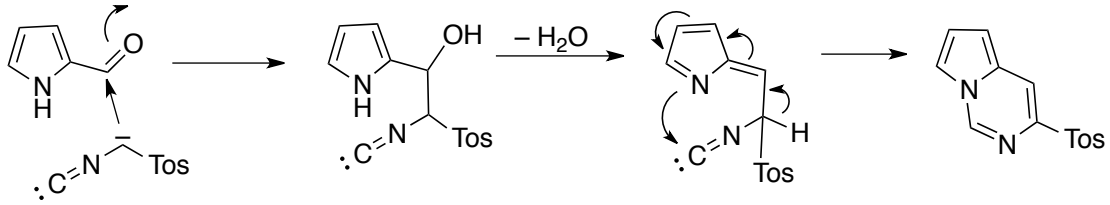
Scheme 3

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 compound[16] 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-pyrroyl)oxazole.[11]



Scheme 5. An abbreviated mechanism proposed by Kitagawa[11]

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 ^{1}H NMR spectra at 300 MHz were taken on a Varian XL-300 Fourier transform NMR spectrometer and ^{1}H NMR spectra at 500 MHz were taken either on a Varian Inova 500 MHz or Bruker Avance III 500 MHz NMR spectrometer. ^{13}C 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 ($CDCl_3$: 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.

1*H*-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]; ^{1}H NMR (300 MHz, $CDCl_3$) 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-1*H*-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]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (br, NH), 9.40 (s, 1H), 6.92 (m, 1H), 6.23 (m, 1H).

4,5-Dibromo-1*H*-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]; ^{1}H NMR (300 MHz, $CDCl_3$) 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 described[17] and this was acylated according to the method of Farhanullah and Ram[16] 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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 isocyanoacetate (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 of DCM, washed with 1M HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4), 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]; ^{1}H NMR (500 MHz, $CDCl_3$) 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; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{12}N_2O_2SCl$: 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{16}H_{17}N_2O_2S$: 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; ^{1}H NMR (500[1] MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{11}N_2O_2SBr_2$: 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]; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{10}H_{10}N_2O_2Cl$: 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{12}H_{15}N_2O_2$: 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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{10}H_9N_2O_2Br_2$: 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.); ^{1}H NMR (300 MHz, $CDCl_3$) 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 $C_{31}H_{29}N_4O_4S_2$: 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 gave **19** in 19% yield as a colorless solid: mp 114-116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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.

ACKNOWLEDGEMENTS

We thank Dartmouth College for support of this work and Drs. Evans Onyango and Qi-Xian Lin for technical assistance.

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