The Hemetsberger–Knittel Synthesis of Substituted 5-, 6-, and 7-Azaindoles

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Abstract: A series of substituted 5-, 6-, and 7-azaindoles were prepared via the Hemetsberger–Knittel reaction. In general, better yields were obtained at higher temperatures and shorter reaction times than required for the formation of the analogous indoles, and in some cases, only decomposition occurred below a minimum temperature. The resulting templates offer up to five sites for subsequent functionalization to allow a wide range of chemical diversity.

Key words: Hemetsberger–Knittel reaction, azaindoles, thermolysis, cyclization, template

Indoles are very important heterocycles omnipresent in a large variety of natural products and pharmaceuticals, and their synthesis is well documented.[1] Lately, more attention has been paid to their isosteric analogues, the azaindoles.[2] Recently, during the course of a medicinal chemistry investigation, we sought to gain rapid access to functionalized azaindole templates **1**–**3** (Figure 1) shown below as replacements of the indole nucleus.

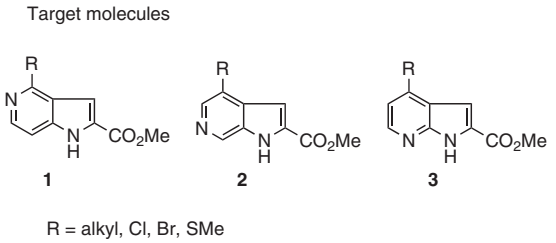
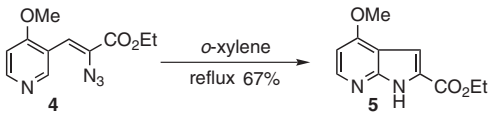


Figure 1

Although numerous methods exist for the synthesis of 2-ester substituted indoles, relatively little has been published on the analogous azaindoles.[3] One such route is the Hemetsberger–Knittel reaction[4] recently employed by Fresneda and Molina[5] (Equation 1) where they effected thermolysis of the 2-azido-3-pyridine acrylate **4** in xylene at reflux. To our knowledge, this is the only instance of its application to the synthesis of azaindoles.



Equation 1 The Hemetsberger–Knittel reaction

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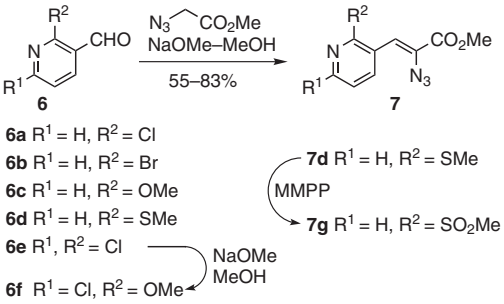
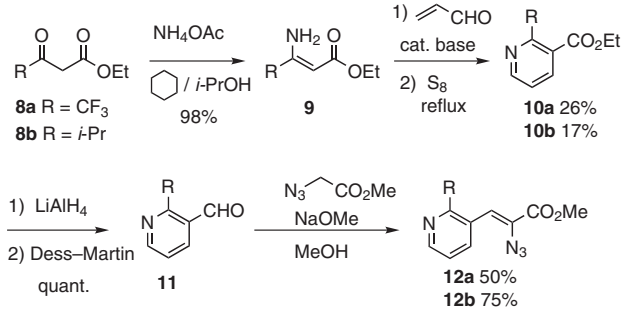
Therefore we were interested in studying the generality of this reaction for the preparation of a series of substituted 5-, 6-, and 7-azaindoles.

The synthesis began with the preparation of the intermediate 2-azido-3-pyridineacrylates **7** as shown in Scheme 1. The corresponding pyridine carboxaldehydes **6** were prepared using known procedures[6] or were commercially available (**6a**, **6b**). The methyl ether **6c** and methyl thioether **6d** were prepared by treating **6a** with NaOMe or NaSMe, respectively.[7] Treatment of **6e** with NaOMe in MeOH at room temperature gave **6f**. Methylsulfone **7g** was obtained by MMPP oxidation of **7d** in 73% yield.



Scheme 1 Synthesis of 5-azaindole precursors

Scheme 2 shows the preparation of two alkyl substituted azidopyridine acrylates via the construction of the pyridine ring **10**.[8] Keto ester **8** was condensed with NH_4OAc to give enamine **9**, which was treated with acrolein and catalytic piperidine to give the partially saturated pyridine. Oxidation with elemental sulfur then provided pyridine ester **10**. Reduction/oxidation gave the aldehyde **11** which was carried through to the azidopyridine acrylate **12**.



Scheme 2 Alkyl-substituted 5-azaindole precursors

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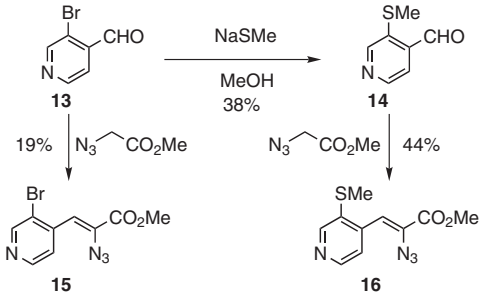
The preparation of two precursors for the synthesis of 6-azaindoles is shown in Scheme 3.[9] Yields for all steps were lower compared to those for the analogous reactions in Scheme 1.



Scheme 3 Synthesis of 6-azaindole precursors

The 7-azaindole precursors **17** and **18** were prepared from 4-chloropyridine in a similar fashion to Scheme 3, and for comparison purposes, the unsubstituted precursors **19**–**21** were prepared from the commercially available pyridine carboxaldehydes (see Figure 2).

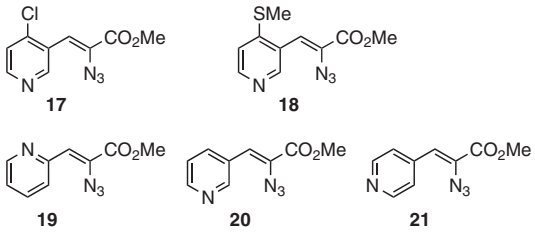
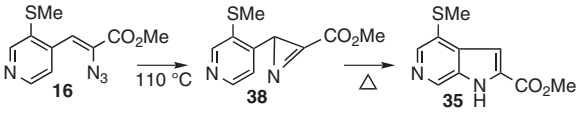


Figure 2

The cyclization was initially studied with the unsubstituted azidopyridine acrylates, the results of which can be seen in entries 1–3 of Table 1. Heating a solution of **19** in xylene at 110 °C or 140 °C for 60 minutes led only to the formation of methyl pyrazolo[1,5-*a*]pyridine-2-carboxylate (**22**), a known reaction.[10] At 110 °C, substrate **20** gave very little product whereas at 160 °C we obtained selectively the 7-azaindole **23** in modest yield. The *para*-substituted substrate **21** gave only decomposition products at 110 °C or 140 °C. These results are not surprising in light of the fact that the pyridine ring is electron poor with respect to the phenyl analogues which react smoothly in refluxing xylene.[4] The electron poor nature of the ring could therefore hinder insertion of the nitrene into the C–H bond. Also, in **19** and **21**, cyclization onto the position *meta* to the ring nitrogen appears to be even further disfavored. These results suggested that the choice of temperature could be critical for the outcome of the thermolysis reaction, as is further exemplified for the two substrates leading to 6-azaindoles (entries 13 and 14). In these cases, no product was obtained using the standard procedure A (160 °C). Subsequent experiments led us to suspect that this was below the temperature threshold for the nitrene insertion to give the 6-azaindole nucleus. For instance, in the case of the SMe containing precursor **16**, clean formation of the intermediate aziridine **38** was noted by NMR at approximately 110 °C (see Equation 2). However, when the solution of **38** was heated to 140 °C no azaindole formation was seen by NMR, only gradual decomposition with time. Separate experiments with increasingly higher temperatures indicated that refluxing decalin (191 °C, procedure C) was required to obtain an acceptable yield (51%) of the desired product. A minimum temperature is therefore required to effect the desired cyclization of the intermediate, below which only side reactions occur.



Equation 2

Standard procedure A was also applied to the synthesis of two 4-substituted 7-azaindoles (**36** and **37**) in modest yields (40% and 56%, respectively).

Our best results were obtained in the synthesis of 5-azaindoles. Entries 4–12 in Table 1 show the outcomes for substituted 5-azaindole formation. In general, the thermolysis reaction appears to proceed smoothly at 160 °C with halogen, ether, thioether, methylsulfone, and alkyl substituents on the pyridine ring, giving good to very good yields (66–93%) of the corresponding azaindoles with the exception of the methoxychloro-substituted entry 12 (32%).

Also noteworthy is that the thermolysis reaction was tolerant of various solvents, and was carried out equally well in refluxing diglyme, DMF (microwave conditions), and *o*-dichlorobenzene. However, the resulting azaindoles are soluble in these solvents and for ease of isolation on medium scale, mesitylene allowed for a simple crystallization and filtration.

In summary, we have demonstrated a facile, general method for the synthesis of 2-ester substituted 5-, 6-, and 7-azaindole templates which offer up to five different sites for functionalization with the potential to give a wide range of chemical diversity. It has been shown that the temperature is critical, and the use of refluxing mesitylene for the thermolysis of the azidopyridine acrylates attains or exceeds the temperature threshold for cyclization for the majority of the substrates, while also allowing for easy isolation of the product by filtration.

Flash chromatography was carried out with EM Science Silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 500 or AMX 500 NMR Spectrometer, with chemical shifts reported in ppm relative to the residual deuterated solvent. Analytical analyses were carried out by Prevalere Life Sciences Inc. in Whitesboro, NY. HRMS analysis was carried out by the Biomedical Mass Spectrometry Unit of McGill University under FAB+ conditions.

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Table 1 Thermolysis of 2-Azido-3-pyridine Acrylates

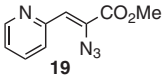
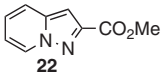
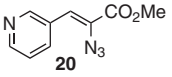
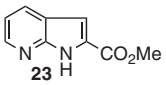
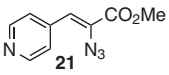
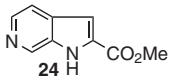
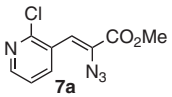
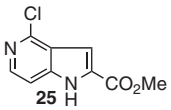
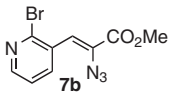
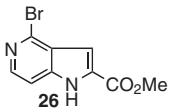
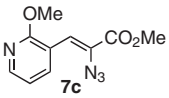
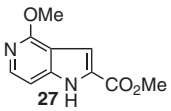
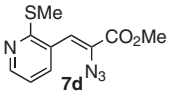
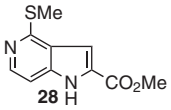
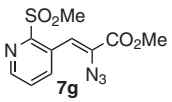
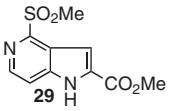
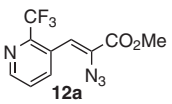
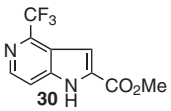
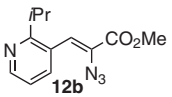
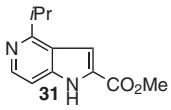
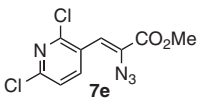
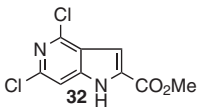
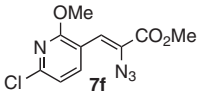
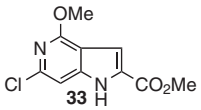
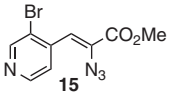
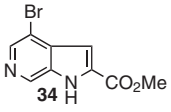
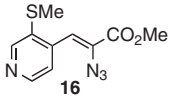
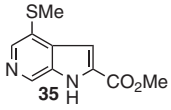
Entry	Azidopyridine acrylate	Yield (%)[a]	Product	Procedure	Yield (%)
1	 **19**	52	 **22**	B	67
2	 **20**	56	 **23**	B	25
3	 **21**	7	 **24**	B	0
4	 **7a**	63	 **25**	B	72
5	 **7b**	55	 **26**	A	78
6	 **7c**	66	 **27**	A	93
7	 **7d**	68	 **28**	A	84
8	 **7g**	73 from **7d**	 **29**	A	69
9	 **12a**	26	 **30**	B	66
10	 **12b**	53	 **31**	B	75
11	 **7e**	64	 **32**	A	77
12	 **7f**	83	 **33**	A	32
13	 **15**	19	 **34**	C	44
14	 **16**	44	 **35**	C	51

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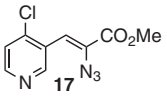
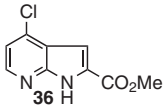
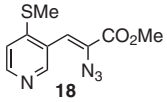
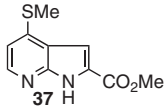
Table 1 Thermolysis of 2-Azido-3-pyridine Acrylates (continued)

Entry	Azidopyridine acrylate	Yield (%)[a]	Product	Procedure	Yield (%)
15	 **17**	41	 **36**	A	40
16	 **18**	60	 **37**	B	56

[a] Yields for the conversion of pyridine carboxaldehyde **6** to azidopyridineacrylate **7** with the exception of **7g**.

Preparation of Azidopyridine Acrylates; General Procedure (Figure 3)

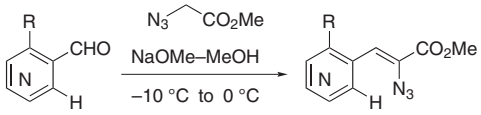


Figure 3

To a solution of the pyridine carboxaldehyde (41 mmol) and methyl azidoacetate (9.4 mL, 102 mmol) in MeOH (65 mL) at –10 °C to –15 °C (internal temperature probe) was added, over 30 min, a 25 weight% solution of NaOMe in MeOH (4.37 M, 23.4 mL, 102 mmol). The addition was (and must be) carried out slowly to allow the resulting heat (from the exothermic reaction) to dissipate and maintain the internal temperature at ca –10 °C. When the addition was completed, the reaction was allowed to warm slowly to 0 °C, where it was maintained for 2 h. During this time a fine precipitate (the product) generally started to form and bubbles were often observed. The flask was then fitted with a bubbler and the reaction was stirred overnight in an ice bath in the cold-room. The suspension was then poured onto a mixture of ice (ca 200 g) and solid NH_4Cl, stirred until all the ice had melted (pH should be neutral), and the product was collected by filtration[11] and was washed with cold water. After vacuum drying, the solid was dissolved in CH_2Cl_2 and $MgSO_4$ was added. The suspension was filtered through a small plug of silica gel, and washed with CH_2Cl_2. This process ensured that no NH_4Cl or water remained in the product. Removal of solvent then yielded the desired azidopyridine acrylate.

Methyl (2*Z*)-2-Azido-3-pyridin-3-ylacrylate (20)
Synthesized following the general procedure to give the product as a pale brown solid (yield: 56%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.91 (d, *J* = 2.1 Hz, 1 H), 8.52 (dd, *J* = 1.6, 4.8 Hz, 1 H), 8.39 (m, 1 H), 7.41 (dd, *J* = 4.8, 8.1 Hz, 1 H), 6.94 (s, 1 H), 3.91 (s, 3 H).

^{13}C NMR (500 MHz, acetone-d_6): δ = 164.82, 153.19, 151.45, 138.10, 130.96, 129.25, 124.99, 122.65, 54.24.

Methyl (2*Z*)-2-Azido-3-pyridin-4-ylacrylate (21)
Synthesized following the general procedure to give the product as a pale brown solid (yield: 56%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.61–8.66 (m, 2 H), 7.75–7.80 (m, 2 H), 6.89 (s, 1 H), 3.95 (s, 3 H).

Methyl (2*Z*)-2-Azido-3-(2-chloropyridin-3-yl)acrylate (7a)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 63%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.61 (dd, *J* = 1.8, 7.9 Hz, 1 H), 8.34 (dd, *J* = 1.8, 4.7 Hz, 1 H), 7.47 (dd, *J* = 4.7, 7.9 Hz, 1 H), 7.12 (s, 1 H), 3.94 (s, 3 H).

Methyl (2*Z*)-2-Azido-3-(2 bromopyridin-3-yl)acrylate (7b)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 55%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.53 (m, 1 H), 8.31 (m, 1 H), 7.49 (m, 1 H), 7.08 (s, 1 H), 3.94 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 168.03, 154.86, 148.75, 144.32, 135.60, 134.63, 128.19, 125.16, 58.00.

Methyl (2*Z*)-2-Azido-3-(2-methoxypyridin-3-yl)acrylate (7c)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 55%). Note: after stirring overnight at 0 °C the reaction mixture turned into a thick paste.

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.54 (m, 1 H), 8.13 (m, 1 H), 7.17 (s, 1 H), 7.02 (m, 1 H), 3.95 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 168.48, 166.24, 152.76, 143.70, 132.13, 122.07, 122.02, 121.32, 58.32, 57.66.

Methyl (2*Z*)-2-Azido-3-[2-(methylthio)pyridin-3-yl]acrylate (7d)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 68%). Note: after stirring overnight at 0 °C the reaction mixture turned into a thick paste.

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.40 (m, 1 H), 8.28 (m, 1 H), 7.16 (m, 1 H), 7.02 (s, 1 H), 3.93 (s, 3 H), 2.55 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 164.70, 160.38, 150.76, 138.20, 130.26, 128.30, 120.54, 119.65, 54.38, 14.00.

Methyl (2*Z*)-2-Azido-3-[2-(methylsulfonyl)pyridin-3-yl]acrylate (7g)
To a solution of **7d** (76 mg, 0.305 mmol) in MeOH (2 mL) and CH_2Cl_2 (5 mL) at 0 °C was added MMPP (377 mg, 0.61 mmol). The mixture was stirred at 0 °C for 1 h, followed by 4 h at r.t. The solvent was then removed under vacuum, and the residue was partitioned between EtOAc and sat. Na_2CO_3 solution. The organic layer was washed with H_2O and brine, and then dried ($MgSO_4$), filtered, and evaporated. The crude was purified by preparative TLC, eluting with EtOAc–hexane (2:1) to give the title compound as an off-white solid (yield: 63 mg, 73%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.70 (dd, *J* = 0.88, 8.07 Hz, 1 H), 8.60 (m, 1 H), 7.74 (m, 1 H), 7.70 (s, 1 H), 3.92 (s, 3 H), 3.37 (s, 3 H).

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^{13}C NMR (125 MHz, acetone-d_6): δ = 164.54, 158.01, 149.59, 141.94, 131.56, 128.51, 128.43, 118.03, 54.52, 41.42.

Methyl (2*Z*)-2-Azido-3-[2-(trifluoromethyl)pyridin-3-yl]acrylate (12a)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 26%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.67 (d, *J* = 4.3 Hz, 1 H), 8.63 (d, *J* = 8.1 Hz, 1 H), 7.77 (dd, *J* = 4.7, 8.1 Hz, 1 H), 7.14 (d, *J* = 2.0 Hz, 1 H), 3.97 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 163.58, 149.40 145.48 (q, *J* = 32.4 Hz), 140.34, 131.31, 128.79, 127.44, 123.03 (q, *J* = 274.8 Hz), 117.33 (d, *J* = 2.1 Hz), 53.79.

Methyl (2*Z*)-2-Azido-3-(2-isopropylpyridin-3-yl)acrylate (12b)
Prepared according to the general procedure except that the reaction was stirred for 3.5 h at 0 °C before being poured onto NH_4Cl–ice mixture. The product was then extracted with hexane–EtOAc (1:1), and the organic layer was dried (Na_2SO_4), filtered, evaporated, and co-evaporated with toluene to give the product as a yellow oil (yield: 53%). The crude material was used as such for the thermolysis.

Methyl (2*Z*)-2-Azido-3-(2,6-dichloropyridin-3-yl)acrylate (7e)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 64%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.69 (d, *J* = 8.3 Hz, 1 H), 7.56 (d, *J* = 8.3 Hz, 1 H), 7.06 (s, 1 H), 3.94 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 164.38, 150.86, 150.60, 143.47, 131.79, 128.81, 124.99, 117.81, 54.58.

Methyl (2*Z*)-2-Azido-3-(6-chloro-2-methoxypyridin-3-yl)acrylate (7f)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 83%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.60 (d, *J* = 8.6 Hz, 1 H), 7.11 (s, 1 H), 6.85 (d, *J* = 8.6 Hz, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 164.82, 164.81, 149.93, 143.40, 128.59, 122.13, 119.82, 111.17, 55.39, 54.33.

Methyl (2*Z*)-2-Azido-3-(3-bromopyridin-4-yl)acrylate (15)
Prepared following the general procedure except that the reaction mixture was stirred at 0 °C for 40 h since little precipitate had formed after 16 h, and mini-workup/NMR indicated incomplete reaction. A pale yellow solid was obtained (yield: 19%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.80 (s, 1 H), 8.60 (m, 1 H), 8.14 (m, 1 H), 7.07 (s, 1 H), 3.98 (s, 3 H).

Methyl (2*Z*)-2-Azido-3-[3-(methylthio)pyridin-4-yl]acrylate (16)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 44%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.61 (s, 1 H), 8.47 (m, 1 H), 7.93 (m, 1 H), 7.18 (s, 1 H), 3.97 (s, 3 H), 2.60 (s, 3 H).

Methyl (2*Z*)-2-Azido-3-(4-chloropyridin-3-yl)acrylate (17)
Synthesized following the general procedure to give the product as a pale yellow solid (yield: 41%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 9.28 (s, 1 H), 8.47 (d, *J* = 5.3 Hz, 1 H), 7.54 (d, *J* = 5.3 Hz, 1 H), 7.09 (s, 1 H), 3.94 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 164.52, 153.32, 151.93, 144.30, 131.01, 129.53, 126.04, 117.81, 54.51.

Methyl (2*Z*)-2-Azido-3-[4-(methylthio)pyridin-3-yl]acrylate (18)
Synthesized following the general procedure to give the product as an off-white solid (yield: 60%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.95 (s, 1 H), 8.39 (m, 1 H), 7.31 (m, 1 H), 7.00 (s, 1 H), 3.95 (s, 3 H), 2.60 (s, 3 H).

Small-Scale Thermolysis; Standard Procedure A (Figure 4)

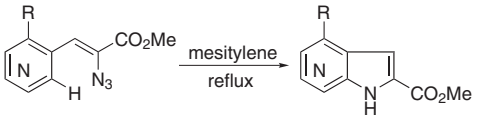

Figure 4

A 0.1 M solution of the azidopyridine acrylate in mesytilene was brought to reflux under N_2 for 1 h. The solvent was then removed by bulb-to-bulb distillation, and the azaindole was purified by flash chromatography, eluting with EtOAc–hexane.

Medium-Scale Thermolysis (> 0.5 g); Standard Procedure B
A 0.1 M solution of the azidopyridine acrylate in mesytilene was brought to reflux for 1 h, and was then allowed to cool to r.t., and finally to 0 °C for 1 h. The crystalline product was collected by filtration, and was then stirred overnight with EtOAc–hexane (1:20) to give the final product.

Synthesis of 6-Azaindoles; Standard Procedure C
To a refluxing solution of decalin was added the azidopyridine acrylate (2 g/500 mL). After 10 min at reflux, the mixture was allowed to cool to r.t., and then to 0 °C. The product was then collected by filtration and washed with hexane to give the corresponding 6-azaindole.

Methyl 1*H*-Pyrrolo[2,3-*b*]pyridine-2-carboxylate (23)
Prepared following the standard thermolysis procedure A to give the product as an off-white solid (yield: 25%); mp 200–201 °C.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.38 (m, 1 H), 8.12 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.19 (s, 1 H), 7.17 (m, 1 H), 3.94 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.44, 148.81, 146.76, 130.78, 127.52, 118.99, 116.84, 106.62, 52.00.

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.33; H, 4.38; N, 15.67.

Methyl 4-Chloro-1*H*-pyrrolo[3,2-c]pyridine-2-carboxylate (25)
Prepared following the standard thermolysis procedure B to give the product as an off-white solid (yield: 72%); mp 213–216 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.77 (s, 1 H), 8.09 (d, *J* = 5.8 Hz, 1 H), 7.42 (d, *J* = 5.7 Hz, 1 H), 7.17 (s, 1 H), 3.91 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.70, 145.12, 142.71, 142.38, 130.00, 122.95, 108.74, 106.84, 53.17, 40.88, 40.71, 40.55, 40.38, 40.21.

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.14; H, 3.19; N, 13.28.

Methyl 4-Bromo-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (26)
Prepared following the standard thermolysis procedure A to give the product as an off-white solid (yield: 78%); mp 197–200 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.80 (s, 1 H), 8.05 (d, *J* = 5.7 Hz, 1 H), 7.44 (d, *J* = 5.7 Hz, 1 H), 7.06 (s, 1 H), 3.89 (s, 3 H).

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^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.85, 142.32, 140.6, 135.90, 129.04, 124.88, 108.18, 107.24, 52.36.

Anal. Calcd for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.77; H, 2.72; N, 10.95.

Methyl 4-Methoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (27)

Prepared following the standard thermolysis procedure A to give the product as an off-white solid (yield: 93%); mp 172–174 °C (dec.).

^{1}H NMR (500 MHz, acetone-d_6): δ = 11.32 (br, 1 H, NH), 7.86 (d, *J* = 6.0 Hz, 1 H), 7.18 (d, *J* = 1.2 Hz, 1 H), 7.08 (m, 1 H), 4.01 (s, 3 H), 3.88 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 165.89, 160.67, 144.30, 142.35, 128.51, 113.96, 107.69, 104.30, 54.11, 52.97.

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.09; H, 4.90; N, 13.40.

Methyl 4-(methylthio)-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (28)

Prepared following the standard thermolysis procedure A to give the product as an off-white solid (yield: 84%); mp 195–197 °C.

^{1}H NMR (500 MHz, acetone-d_6): δ = 11.35 (br, 1 H, NH), 8.18 (d, *J* = 5.9 Hz, 1 H), 7.21 (m, 1 H), 7.16 (d, *J* = 1.1 Hz, 1 H), 3.90 (s, 3 H), 2.64 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 162.79, 155.96, 144.25, 141.26, 129.27, 123.33, 107.47, 105.72, 53.11.

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.93; H, 4.69; N, 12.57.

Methyl 4-(Methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (29)

Prepared following the standard thermolysis procedure A to give the product as an off-white solid (yield: 69%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 11.81 (br, 1 H, NH), 8.44 (d, *J* = 5.7 Hz, 1 H), 7.79 (m, 1 H), 7.68 (d, *J* = 1.0 Hz, 1 H), 3.96 (s, 3 H), 3.33 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 162.58, 154.23, 144.40, 143.13, 132.71, 121.36, 112.77, 108.12, 53.54, 41.10.

Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02; S, 12.61. Found: C, 47.42; H, 4.14; N, 10.91; S, 12.42.

Methyl 4-(Trifluoromethyl)-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (30)

Prepared following the standard thermolysis procedure B to give the product as an off-white solid (yield: 66%); mp 204–205 °C.

^{1}H NMR (500 MHz, acetone-d_6): δ = 11.81 (br s, 1 H), 8.48 (d, *J* = 5.7 Hz, 1 H), 7.78 (d, *J* = 5.7 Hz, 1 H), 7.37 (s, 1 H), 3.98 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 161.29, 142.49, 142.28 (q, *J* = 34.8 Hz), 142.26, 131.30, 122.87 (q, *J* = 273.6 Hz), 120.77, 110.99, 105.63 (d, *J* = 1.75 Hz), 52.25.

Anal. Calcd for $C_{10}H_7F_3N_2O_2$: C, 49.19; H, 2.89; N, 11.47. Found: C, 49.52; H, 2.97; N, 11.29.

Methyl 4-Isopropyl-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (31)

Prepared following the standard thermolysis procedure B to give the product as a pale yellow solid (yield: 75%); mp 129–130 °C.

^{1}H NMR (500 MHz, acetone-d_6): δ = 11.36 (s, 1 H), 8.27 (d, *J* = 5.8 Hz, 1 H), 7.41 (s, 1 H), 7.30 (d, *J* = 5.8 Hz, 1 H), 3.93 (s, 3 H), 3.59 (m, 1 H), 1.39 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 162.92, 161.86, 142.98, 141.35, 128.15, 122.37, 107.10, 105.68, 51.77, 33.58, 21.83.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.02; H, 6.51; N, 13.11.

Methyl 4,6-Dichloro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (32)

Prepared following the standard thermolysis procedure A to give the product as an off-white solid (yield: 69%); mp 216–220 °C (dec.).

^{1}H NMR (500 MHz, acetone-d_6): δ = 11.79 (br, 1 H, NH), 7.51 (s, 1 H), 7.22 (s, 1 H), 3.94 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 162.26, 145.13, 144.76, 144.34, 132.31, 124.03, 108.36, 107.85, 53.54.

HRMS (FAB+): *m*/*z* calcd for $C_9H_6Cl_2N_2O_2H^+$: 244.98838; found: 244.988458.

Methyl 6-Chloro-4-methoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (33)

Prepared following the standard thermolysis procedure A to give the product as an off-white solid (yield: 32%); mp 196–208 °C (dec.).

^{1}H NMR (400 MHz, acetone-d_6): δ = 11.24 (br, 1 H, NH), 7.16 (m, 1 H), 6.75 (m, 1 H), 3.933 (s, 3 H), 3.929 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 162.57, 162.45, 146.84, 143.27, 130.96, 120.82, 107.88, 90.75, 55.48, 53.21.

Anal. Calcd for $C_{10}H_9ClN_2O_3$: C, 49.91; H, 3.77; N, 11.64. Found: C, 49.97; H, 3.78; N, 11.30.

Methyl 4-Bromo-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylate (34)

Prepared following the standard thermolysis procedure C to give the product as an off-white solid (yield: 44%); mp 222–224 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.93 (br s, 1 H), 8.83 (s, 1 H), 8.34 (s, 1 H), 7.09 (s, 1 H), 3.94 (s, 3 H).

^{13}C NMR (125 MHz, DMSO): δ = 161.77, 139.85, 136.38, 134.82, 132.31, 132.04, 113.36, 106.37, 53.39.

Anal. Calcd for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.29; H, 2.69; N, 10.92.

Methyl 4-(Methylthio)-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylate (35)

Prepared following the standard thermolysis procedure C to give the product as an off-white solid (yield: 51%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 11.55 (br s, 1 H), 8.78 (s, 1 H), 8.13 (s, 1 H), 7.20 (s, 1 H), 3.97 (s, 3 H), 2.66 (s, 3 H).

Methyl 4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (36)

Prepared following the standard thermolysis procedure A to give the product as an off-white solid (yield: 40%); mp 217–218 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.36 (d, *J* = 5.1 Hz, 1 H), 7.31 (d, *J* = 5.1 Hz, 1 H), 7.13 (s, 1 H), 3.88 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.00, 149.24, 147.35, 136.41, 128.46, 118.14, 116.68, 104.01, 52.27.

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.04; H, 3.20; N, 13.13.

Methyl 4-(Methylthio)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (37)

Prepared following the standard thermolysis procedure B to give the product as an off-white solid (yield: 56%); mp 213–216 °C (dec.).

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^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.65 (s, 1 H), 8.29 (d, *J* = 5.0 Hz, 1 H), 7.07 (s, 1 H), 7.00 (d, *J* = 5.1 Hz, 1 H), 3.88 (s, 3 H), 2.61 (s, 3 H).

^{13}C NMR (125 MHz, DMSO): δ = 162.06, 148.42, 147.59, 144.95, 127.46, 117.43, 111.82, 105.19, 52.86, 13.73.

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(11) Azidopyridine acrylate **12b** was isolated by extraction with EtOAc–hexane (1:1) since it is an oil.

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