Gas-Phase Synthesis of Pyrazolo[3,4-b]pyridin-4-ones

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Abstract: Flash vacuum pyrolysis (FVP) at 500–600 °C of 1-substituted pyrazolylaminomethylene derivatives of Meldrum's acid provides 1-substituted pyrazolo[3,4-*b*]pyridin-4-ones in high yields. If the 1-substituent is a *tert*-butyl group, FVP at 750–850 °C causes elimination of 2-methyl-1-propene to give the parent pyrazolo[3,4-*b*]pyridin-4-one.

Key words: gas-phase reactions, pericyclic reactions, heterocycles, Meldrum's acid, medicinal chemistry

There are very few references to 1-unsubstituted pyrazolo[3,4-*b*]pyridin-4-ones **1** in the literature[2] and all known derivatives except the parent compound **1** (R = R′ = H) have a substituent in the 6-position. Potential functionalization of the 4-position (e.g., via the triflate or the 4-chloro compound) would provide 4-substituted pyrazolo[3,4-*b*]pyridines **2** (Figure 1), which have shown diverse application in medicinal chemistry.[3] On the other hand, substitution at the 1-position generally results in loss of biological activity due to the disruption of the hydrogen bonding regime.[4]

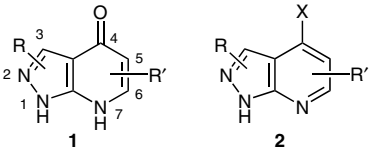
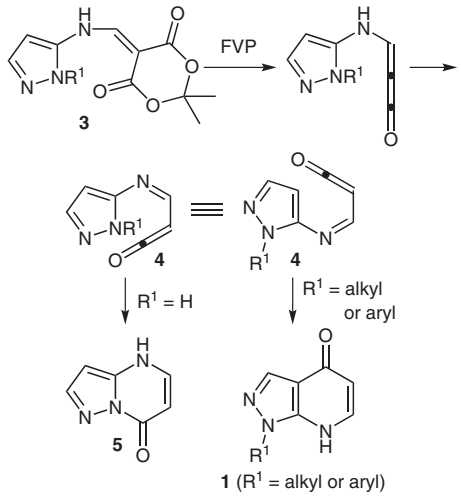


Figure 1 1-Unsubstituted pyrazolo[3,4-*b*]pyridin-4-ones **1** and 4-substituted pyrazolo[3,4-*b*]pyridines **2**

In earlier work, we explored a potential route to **1** by flash vacuum pyrolysis (FVP) of Meldrum's acid derivatives [e.g., **3** (R^1 = H)], but cyclization of the imidoylketene intermediate **4** (R^1 = H) occurred exclusively at the adjacent nitrogen atom to provide a useful route to the pyrazolo[1,5-*a*]pyrimidine system **5** (Scheme 1).[5] Clearly this route must be blocked to provide pyrazolo[3,4-*b*]pyridin-4-ones.

The present work therefore had a range of objectives. First, **3** (R^1 = alkyl or aryl) were synthesized and pyrolyzed to ensure that, in the absence of the pyrazole NH, cyclization onto the adjacent carbon atom to give **1** (R = 1-alkyl or 1-aryl) would take place (Scheme 1), as observed in many related systems.[6] Second, we explored the



Scheme 1

design of a thermal N-protecting group, which would remain at low furnace temperatures, but be selectively removed at higher furnace temperatures to provide N-unsubstituted pyrazolopyridinones **1** (R^1 = H). If the previous stages were successful, we aimed finally to functionalize the 4-position of the pyrazolo[3,4-*b*]pyridin-4-ones to establish that the route has significant potential for the synthesis of pyrazolo[3,4-*b*]pyridines **2**.

The 1-substituted and 1,3-disubstituted 3-aminopyrazoles **6a**–**f** (Figure 2) were either commercially available or were synthesized by known methods. Compounds **6c**,[7] **6e**,[8] and **6f**[9a] are known only in patents or are formed in poor yield;[9b] their full characterization data are given here. Compound **6c** was formed as a 5:1 mixture of **6c** and its 1-*tert*-butyl-3-amino isomer, which was taken on to the next stage without purification. Reaction of **6a**–**f** with methoxymethylene Meldrum's acid in acetonitrile gave the aminomethylene derivatives **3a**–**f** (Figure 2) in 89–99% yield and (generally) high purity. Compound **3c** was purified by recrystallization before pyrolysis.

FVP of **3a** and **3b** at 600 °C (0.03 Torr) gave 1-methylpyrazolo[3,4-*b*]pyridin-4-one (**1aa**) (92%) and its 3-methyl-1-phenyl analogue **1ba** (95%), respectively, as involatile solids that crystallized at the exit point of the furnace. It is clear, therefore, that blocking the 1-position of the pyrazole has the effect of diverting the cyclization to the adjacent carbon atom to provide the target pyrazolopyridinones.

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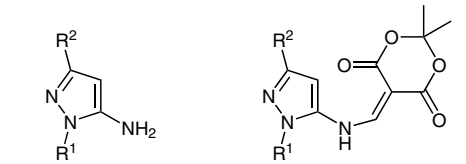
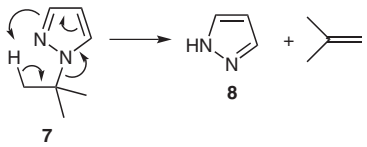


6a R^1 = Me, R^2 = H
6b R^1 = Ph, R^2 = Me
6c R^1 = *t*-Bu, R^2 = H
6d R^1 = *t*-Bu, R^2 = Me
6e R^1 = *t*-Bu, R^2 = Ph
6f R^1 = R^2 = *t*-Bu

3a R^1 = Me, R^2 = H
3b R^1 = Ph, R^2 = Me
3c R^1 = *t*-Bu, R^2 = H
3d R^1 = *t*-Bu, R^2 = Me
3e R^1 = *t*-Bu, R^2 = Ph
3f R^1 = R^2 = *t*-Bu

Figure 2 1,3-Disubstituted 3-aminopyrazoles **6** and aminomethylene derivatives **3**

In order to access the 1-unsubstituted pyrazolo[3,4-*b*]pyridines **1** (R^1 = H), a thermally removable N-protecting group was required. If a retro-ene reaction is possible, an *N*-*tert*-butyl group is ideal because the only co-product is 2-methyl-1-propene. We have exploited this in the pyridazin-3-one series[10] and it is also known that *N*-*tert*-butylpyrazole (**7**) loses 2-methyl-1-propene at high temperatures (Scheme 2).[11] A temperature profile of this reaction (Figure 3) shows that, in our apparatus, at temperatures below 600 °C the *N*-alkyl product **7** is formed exclusively whereas at temperatures above 850 °C, only the deprotected product **8** was formed. It was therefore anticipated that FVP of **3c**–**f** in the range 500–600 °C should provide the *N*-*tert*-butyl products **1** (R^1 = *t*-Bu) whereas FVP in the range 750–850 °C should provide the deprotected products **1** (R^1 = H).



7 **8**

Scheme 2

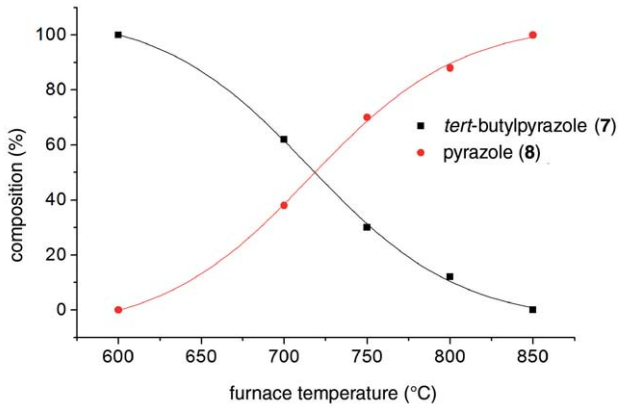
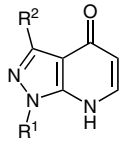


Figure 3 Temperature-conversion plot for FVP of **7**

These predictions were borne out in practice. FVP of **3c**–**f** at 500 °C gave the pyrazolopyridinones **1ca**, **1da**, **1ea**, and **1fa** (Figure 4) in 83–97% yields and at 750–850 °C gave the deprotected products **1cb** and **1db** in 67–82% yields whilst the more highly substituted derivatives **1eb** and **1fb** were obtained as more complex mixtures.[12] N-Unsubstituted pyrazolopyridinones show exceptionally broad peaks in their NMR spectra due to tautomerization, but the two NH resonances at ca. δ_H = 12.8–13.8 and 11.5–11.8 are characteristic, as previously reported.[2a]



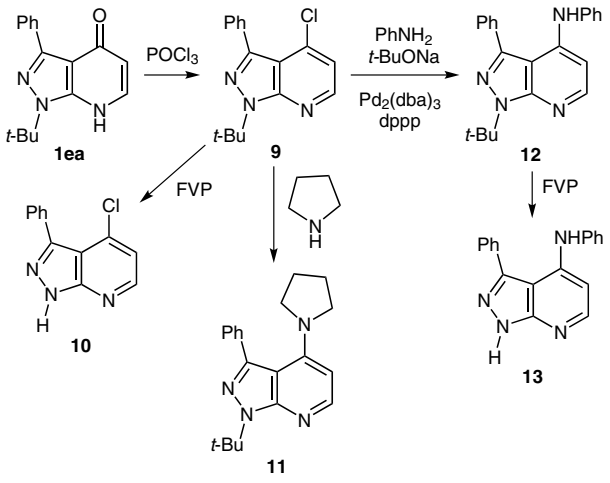
1aa R^1 = Me, R^2 = H
1ba R^1 = Ph, R^2 = Me
1ca R^1 = *t*-Bu, R^2 = H
1da R^1 = *t*-Bu, R^2 = Me
1ea R^1 = *t*-Bu, R^2 = Ph
1fa R^1 = R^2 = *t*-Bu

1cb R^1 = H, R^2 = H
1db R^1 = H, R^2 = Me
1eb R^1 = H, R^2 = Ph
1fb R^1 = H, R^2 = *t*-Bu

Figure 4 Pyrazolopyridinones **1**

As an alternative to the one-pass cyclization-deprotection described above, the protecting group can be retained prior to functionalization of the 4-oxo substituent. This strategy is illustrated for the 3-phenyl series **1e**, which was chosen as it might prove unreactive owing to *peri* interactions with the 3-substituent.

Thus, treatment of **1ea** with phosphoryl chloride gave the 4-chloro compound **9** (99%), which could either be thermally deprotected to **10** (87%), or reacted further. For example, reaction of **9** with pyrrolidine in the absence of a catalyst provided a low yield of the pyrrolidino compound **11** (37%); alternatively, reaction with aniline under Buchwald–Hartwig conditions gave the anilino compound **12** (87%), which could be thermally deprotected to **13** (72%) (Scheme 3).



Scheme 3

In conclusion, the work described here has provided a flexible gas-phase route to pyrazolo[3,4-*b*]pyridin-4-ones

and pyrazolo[3,4-*b*]pyridines. An important feature of the strategy is the use of an *N*-*tert*-butyl group, which may be retained at low furnace temperatures (allowing functionalization of the 4-oxo group) or removed at high furnace temperatures to provide a one-pass route to N-unsubstituted analogues.

^{1}H and ^{13}C NMR spectra were recorded at 500 or 250 MHz and 125 or 63 MHz, respectively, unless otherwise stated. Chemical shifts are given in ppm relative to TMS. Mass spectra were recorded under electron impact conditions.

5-Amino-1-*tert*-butyl-1*H*-pyrazole (6c)[7]
tert-Butylhydrazine hydrochloride (5.99 g, 48.1 mmol) was added to EtOH (60 mL) to form a slurry. To this was added NaOAc (7.93 g, 96.7 mmol) and 2-chloroacrylonitrile (5 mL, 62.6 mmol). The solution was heated to 80 °C for 18 h, cooled, and the solvent removed in vacuo. The residue was slowly diluted with distilled H_2O (35 mL) and partitioned between sat. aq $NaHCO_3$ (40 mL) and EtOAc (40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$), and the solvent removed in vacuo to afford a red oil; yield: 7.95 g (91%); bp 93–94 °C/0.9 Torr (yellow liquid). The product was a 5:1 mixture of the title compound **6c** and its 1-*tert*-butyl-3-amino isomer. The crude product was used to prepare the Meldrum's acid derivative **3c**, which was purified by recrystallization (see below).

^{1}H NMR ($CDCl_3$): δ = 7.21 (d, ^3J = 1.8 Hz, 1 H), 5.57 (d, ^3J = 1.8 Hz, 1 H), 3.60 (br s, 2 H), 1.65 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 144.5 (C_q), 136.6 (CH), 94.1 (CH), 58.5 (C_q), 29.3 (3 CH_3).

MS: *m*/*z* (%) = 139 (M^+, 45), 83 (M – C_4H_{10}, 100).

HRMS: *m*/*z* calcd for $C_7H_{13}N_3$ (M^+): 139.1104; found: 139.1103.

5-Amino-1-*tert*-butyl-3-phenyl-1*H*-pyrazole (6e)[8]
A solution of 3-oxo-3-phenylpropanenitrile (1.5 g, 10.3 mmol) in EtOH (10 mL) was added to a slurry of *tert*-butylhydrazine hydrochloride (2.6 g, 20.7 mmol) in EtOH (35 mL) and the solution was heated to reflux with stirring for 18 h. The solution was cooled, concentrated and the residue was partitioned between sat. aq $NaHCO_3$ (30 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$), and the solvent removed in vacuo to give **6e** as a pale yellow solid; yield: 2.2 g (97%); mp 100–102 °C.

^{1}H NMR (DMSO-d_6): δ = 7.64 (d, ^3J = 7.4 Hz, 2 H), 7.33 (t, ^3J = 7.4 Hz, 2 H), 7.22 (t, ^3J = 7.4 Hz, 1 H), 5.79 (s, 1 H), 4.97 (s, 2 H), 1.58 (s, 9 H).

^{13}C NMR (DMSO-d_6): δ = 148.1 (C_q), 146.1 (C_q), 135.0 (C_q), 128.8 (2 CH), 127.1 (CH), 125.0 (2 CH) 89.2 (CH), 58.3 (C_q), 40.1 (3 CH_3).

MS: *m*/*z* (%) = 215 (M^+, 25), 159 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{17}N_3$ (M^+): 215.1417; found: 215.1416.

5-Amino-1,3-di-*tert*-butyl-1*H*-pyrazole (6f)[9]
A solution of 4,4-dimethyl-3-oxovaleronitrile (1.75 g, 14.0 mmol) in EtOH (10 mL) was added to a slurry of *tert*-butylhydrazine hydrochloride (3.5 g. 28.1 mmol) in EtOH (35 mL) and the solution was heated to reflux with stirring for 18 h. The solution was cooled, concentrated, and the residue was partitioned between sat. aq $NaHCO_3$ (30 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$), and the solvent removed to give **6f** as a pale orange solid; yield: 1.8 g (66%); mp 67–69 °C (Lit.[9a] mp 64–66 °C).

^{1}H NMR ($CDCl_3$): δ = 5.48 (s, 1 H), 3.46 (s, 2 H), 1.27 (s, 18 H).

^{13}C NMR ($CDCl_3$): δ = 157.8 (C_q), 144.1 (C_q), 90.2 (CH), 58.2 (C_q), 44.7 (C_q), 30.4 (3 CH_3), 29.5 (3 CH_3).

Spectra differ significantly from those reported,[9b] but were recorded in a different solvent.

MS: *m*/*z* (%) = 195 (M^+, 29), 139 (63), 124 (100).

HRMS: *m*/*z* calcd for $C_{11}H_{21}N_3$ (M^+): 195.1730; found: 175.1728.

Meldrum's Acid Derivatives; General Procedure
5-(Methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.5 g, 2.9 mmol) was added to a stirred solution of the 5-aminopyrazole **6** (2.9 mmol) in MeCN (10 mL). After stirring for 1 h, the solvent was removed in vacuo to complete the precipitation of the product.

5-(1-Methyl-1*H*-pyrazol-5-ylaminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (3a)
Treatment of **6a** using the general procedure gave **3a**; yield: 0.71 g (98%); yellow solid; mp 144 °C (MeOH).

^{1}H NMR ($CDCl_3$): δ = 11.28 (d, ^3J = 13.3 Hz, 1 H), 8.34 (d, ^3J = 13.3 Hz, 1 H), 7.34 (d, ^3J = 2.1 Hz, 1 H), 6.18 (d, ^3J = 2.1 Hz, 1 H), 3.85 (s, 3 H), 1.75 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 165.7 (C_q), 162.6 (C_q), 154.7 (CH), 139.1 (CH), 138.0 (C_q), 105.6 (C_q), 95.3 (CH), 88.9 (C_q), 35.4 (CH_3), 27.1 (2 CH_3).

MS: *m*/*z* (%) = 251 (M^+, 16), 193 (100), 149 (14), 122 (40).

Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.6; H, 5.2; N, 16.75. Found: C, 52.65; H, 5.35; N, 16.8.

5-(3-Methyl-1-phenyl-1*H*-pyrazol-5-ylaminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (3b)
Treatment of **6b** using the general procedure gave **3b**; yield: 0.90 g (95%); yellow solid; mp 167 °C (MeOH).

^{1}H NMR ($CDCl_3$): δ = 11.45 (d, ^3J = 13.4 Hz, 1 H), 8.38 (d, ^3J = 13.4 Hz, 1 H), 7.56–7.42 (m, 5 H), 6.17 (s, 1 H), 2.34 (s, 3 H), 1.71 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 165.3 (C_q), 162.7 (C_q), 153.1 (CH), 150.1 (C_q), 138.3 (C_q), 136.8 (C_q), 130.0 (2 CH), 128.8 (CH), 124.8 (2 CH), 105.5 (C_q), 94.3 (CH), 88.8 (C_q), 27.1 (2 CH_3), 14.0 (CH_3).

MS: *m*/*z* (%) = 327 (M^+, 23), 269 (100), 225 (22), 184 (74), 156 (22).

Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.4; H, 5.25; N, 12.85. Found: C, 62.3; H, 5.15; N, 12.75.

5-(1-*tert*-Butyl-1*H*-pyrazol-5-ylamino)methylene-2,2-dimethyl-1,3-dioxane-5,6-dione (3c)
Treatment of **6c** using the general procedure gave **3c**; yield: 0.985 g (97%); yellow solid; mp 84 °C.

^{1}H NMR ($CDCl_3$): δ = 11.53 (d, ^3J = 13.4 Hz, 1 H), 8.33 (d, ^3J = 13.4 Hz, 1 H), 7.41 (d, ^3J = 1.9 Hz, 1 H), 6.23 (d, ^3J = 1.9 Hz, 1 H), 1.77 (s, 6 H), 1.70 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 165.6 (C_q), 162.9 (C_q), 154.7 (CH), 137.5 (C_q), 137.3 (CH), 105.6 (C_q), 97.8 (CH), 88.4 (C_q), 60.3 (C_q), 29.8 (3 CH_3), 27.3 (2 CH_3).

MS: *m*/*z* (%) = 293 (M^+, 21), 235 (47), 179 (59), 161 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{19}N_3O_4$ (M^+): 293.1381; found: 293.1384.

5-(1-*tert*-Butyl-3-methyl-1*H*-pyrazol-5-ylamine)-2,2-dimethyl-1,3-dioxane-4,6-dione (3d)
Treatment of **6d** using the general procedure gave **3d**; yield: 0.88 g (99%); yellow solid; mp 82 °C.

^{1}H NMR ($CDCl_3$): δ = 11.47 (br d, ^3J = 13.4 Hz, 1 H), 8.29 (d, ^3J = 13.4 Hz, 1 H), 6.00 (s, 1 H), 2.23 (s, 3 H), 1.75 (s, 6 H), 1.66 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 165.9 (C_q), 162.9 (C_q), 154.4 (CH), 146.2 (C_q), 137.7 (C_q), 105.5 (C_q), 97.1 (CH), 88.1 (C_q), 59.7 (C_q), 29.8 (3 CH_3), 27.1 (2 CH_3), 13.9 (CH_3).

MS: *m*/*z* (%) = 307 (M^+, 21), 249 (100), 175 (68).

HRMS: *m*/*z* calcd for $C_{15}H_{21}N_3O_4$ (M^+): 307.1527; found: 307.1533.

5-(1-*tert*-Butyl-3-phenyl-1*H*-pyrazol-5-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (3e)
Treatment of **6e** using the general procedure gave **3e**; yield: 0.97 g (98%); yellow solid; mp 152 °C.

^{1}H NMR ($CDCl_3$): δ = 11.59 (d, ^3J = 13.4 Hz, 1 H), 8.43 (d, ^3J = 13.4 Hz, 1 H), 7.80 (d, ^3J = 7.3 Hz, 2 H), 7.44 (t, ^3J = 7.3 Hz, 2 H), 7.35 (t, ^3J = 7.3 Hz, 1 H), 6.75 (s, 1 H), 1.81 (s, 6 H), 1.77 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 166.0 (C_q), 162.9 (C_q), 154.4 (CH), 148.5 (C_q), 138.8 (C_q), 132.8 (C_q), 128.7 (2 CH), 128.1 (CH), 125.3 (2 CH), 105.7 (C_q), 94.5 (CH), 88.5 (C_q), 60.6 (C_q), 29.9 (3 CH_3), 27.2 (2 CH_3).

MS: *m*/*z* (%) = 369 (M^+, 33), 311 (100), 237 (58), 211 (57), 183 (44), 108 (45).

HRMS: *m*/*z* calcd for $C_{20}H_{23}N_3O_4$ (M^+): 369.1683; found: 369.1690.

5-(1,3-Di-*tert*-butyl-1*H*-pyrazol-5-ylamino)methylene-2,2-dimethyl-1,3-dioxane-5,6-dione (3f)
Treatment of **6f** using the general procedure gave **3f**, yield: 0.83 g (89%); yellow solid; mp 105 °C.

^{1}H NMR ($CDCl_3$): δ = 11.47 (d, ^3J = 13.1 Hz, 1 H), 8.35 (d, ^3J = 13.1 Hz, 1 H), 6.08 (s, 1 H), 1.78 (s, 6 H), 1.67 (s, 9 H), 1.28 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 165.9 (C_q), 163.1 (C_q), 158.9 (C_q), 154.6 (CH), 137.0 (C_q), 105.5 (C_q), 94.0 (CH), 87.8 (C_q), 59.8 (C_q), 32.3 (C_q), 30.3 (3 CH_3), 29.9 (3 CH_3), 27.1 (2 CH_3).

MS: *m*/*z* (%) = 349 (M^+, 24), 291 (100), 217 (27), 202 (45), 176 (56).

HRMS: *m*/*z* calcd for $C_{18}H_{27}N_3O_4$ (M^+): 349.1996; found: 349.2000.

FVP Reactions
Flash vacuum pyrolysis reactions were carried out by distillation of the substrate in vacuo through an electrically heated silica furnace tube (35 × 2.5 cm). Products were trapped in a U-tube situated at the exit point of the furnace and cooled with liquid N_2. Conditions were first established on a small scale (20 mg) where the product(s) were dissolved in a deuterated solvent and analyzed directly by ^{1}H NMR spectroscopy. Larger-scale pyrolyses, involving 0.1 g or more of substrate, were usually removed from the trap by solution in CH_2Cl_2 (30 mL). The precursors and pyrolysis conditions [quantity of precursor, inlet temperature (T_i), furnace temperature (T_f), pressure range (*P*), and pyrolysis time (*t*)] and yields are stated.

FVP of 1-*tert*-Butylpyrazole (7)
This compound was too volatile for normal inlet conditions. It was therefore cooled in an acetone-dry ice bath, which was slowly removed to allow sublimation (20 mg, T_i acetone/dry ice bath, T_f 600–850 °C, *P* 0.03 Torr, *t* 15 min).

1-Methyl-1,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (1aa)
FVP of **3a** (recrystallized from MeOH, 203 mg, 0.81 mmol, T_i 199 °C, T_f 600 °C, *P* 0.03 Torr, *t* 30 min) gave **1aa**; yield: 111 mg (92%); off-white solid; mp 164 °C (Lit.[13] mp 165–168 °C).

^{1}H NMR (DMSO-d_6): δ = 8.37 (d, ^3J = 4.0 Hz, 1 H), 8.30 (s, 1 H), 6.65 (br s, 1 H), 4.22 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 162.4 (br C_q), 150.7 (br C_q), 148.1 (br CH), 130.6 (CH), 107.9 (br C_q), 104.4 (CH), 33.9 (CH_3).

MS: *m*/*z* (%) = 149 (M^+, 100), 95 (12), 78 (14), 63 (13).

HRMS: *m*/*z* calcd for $C_7H_7N_3O$ (M^+): 149.0584; found: 149.0584.

3-Methyl-1,7-dihydro-1-phenylpyrazolo[3,4-*b*]pyridin-4-one (1ba)
FVP of **3b** (recrystallized from MeOH, 195 mg, 0.60 mmol, T_i 170 °C, T_f 600 °C, *P* 0.03 Torr, *t* 45 min) gave **1ba**; yield: 0.129 mg (95%); off-white solid; mp 195 °C.

^{1}H NMR (DMSO-d_6): δ = 11.76 (s, 1 H), 8.31 (br m, 3 H), 7.57 (app t, ^3J = 7.8 Hz, 2 H), 7.32 (d, ^3J = 7.3 Hz, 1 H), 6.66 (br s, 1 H), 2.68 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 160.6 (C_q), 153.1 (C_q), 150.9 (CH), 142.0 (C_q), 139.5 (C_q), 128.9 (2 CH), 124.9 (CH), 119.7 (2 CH), 107.4 (C_q), 103.2 (CH), 14.3 (CH_3).

MS: *m*/*z* (%) = 226 (M^+, 30), 225 (100), 79 (15), 78 (39).

HRMS: *m*/*z* calcd for $C_{13}H_{11}N_3O$ (M^+): 225.0897; found: 225.0896.

1-*tert*-Butyl-1,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (1ca)
FVP of **3c** (recrystallized from cyclohexane, 300 mg, 1.02 mmol, T_i 210 °C, T_f 500 °C, *P* 0.03 Torr, *t* 0.5 h) gave **1ca**; yield: 185 mg (95%); yellow solid; mp 189–191 °C.

^{1}H NMR (DMSO-d_6): δ = 11.40 (s, 1 H), 8.12 (br s, 1 H), 8.02 (s, 1 H), 6.49 (br s, 1 H), 1.74 (s, 9 H). ^{13}C NMR (DMSO-d_6): δ = 159.3 (C_q), 152.9 (C_q), 149.7 (CH), 128.5 (CH), 108.9 (C_q), 102.2 (CH), 59.6 (C_q), 29.2 (3 CH_3).

MS: *m*/*z* (%) = 191 (M^+, 24), 135 (56).

HRMS: *m*/*z* calcd for $C_{10}H_{13}N_3O$ (M^+): 191.1064; found: 191.1060.

1,7-Dihydropyrazolo[3,4-*b*]pyridin-4-one (1cb)
FVP of **3c** (recrystallized from cyclohexane, 50 mg, 0.17 mmol, T_i 210 °C, T_f 750 °C, *P* 0.03 Torr, *t* 0.5 h) was followed by distillation of CH_2Cl_2 into the U-tube trap. The solvent was removed in vacuo to afford a yellow solid, which was triturated with Et_2O and filtered under vacuum. The filtrate was further washed with Et_2O to yield **1cb**; yield: 24 mg (67%); pale brown solid; mp 327–330 °C (Lit.[2d] mp 328–330 °C).

^{1}H NMR (DMSO-d_6): δ (major tautomer) = 13.54 (s, 1 H), 11.71 (s, 1 H), 8.28 (br s, 1 H), 7.62 (br s, 1 H), 5.66 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ (major tautomer) = 177.1 (C_q), 151.2 (C_q), 139.2 (CH), 125.8 (CH), 113.4 (C_q), 107.3 (CH).

MS: *m*/*z* (%) = 135 (M^+, 100).

1-*tert*-Butyl-1,7-dihydro-3-methylpyrazolo[3,4-*b*]pyridin-4-one (1da)
FVP of **3d** (125 mg, 0.41 mmol, T_i 160 °C, T_f 500 °C, *P* 0.03 Torr, *t* 1 h) gave **1da**; yield: 0.70 g (83%); off-white solid; mp 158 °C.

^{1}H NMR (DMSO-d_6): δ = 11.17 (br s, 1 H), 8.01 (d, ^3J = 4.7 Hz, 1 H), 6.34 (d, ^3J = 4.7 Hz, 1 H), 2.45 (s, 3 H), 1.63 (s, 9 H).

^{13}C NMR (DMSO-d_6): δ = 160.7 (br C_q), 152.2 (br C_q), 147.5 (CH), 137.4 (br C_q), 107.2 (br C_q), 101.5 (CH), 58.5 (C_q), 28.8 (3 CH_3), 14.3 (CH_3).

MS: *m*/*z* (%) = 205 (M^+, 48), 150, (22), 149 (100), 148 (26).

HRMS: *m*/*z* calcd for $C_{11}H_{15}N_3O$ (M^+): 205.1210; found: 205.1210.

3-Methyl-1,7-dihydropyrazolo[3,4-*b*]pyridin-3-one (1db)
FVP of **3d** (100 mg, 0.33 mmol, T_i 160 °C, T_f 850 °C, *P* 0.03 Torr, *t* 45 min) gave **1db**; yield: 0.40 g (82%); off-white solid; mp 254 °C.

^{1}H NMR (DMSO-d_6): δ (major tautomer) = 13.11 (s, 1 H), 11.51 (s, 1 H), 7.50 (t, ^3J = 6.3 Hz, 1 H), 5.55 (d, ^3J = 6.3 Hz, 1 H), 2.53 (s, 3 H).

^{13}C NMR (DMSO-d_6, 600 MHz): δ (major tautomer) = 178.1 (br C_q), 151.5 (br C_q), 141.5 (br C_q), 138.6 (CH), 110.2 (C_q), 107.1 (CH), 11.0 (CH_3).

MS: *m*/*z* (%) = 149 (M^+, 80), 78 (100).

HRMS: *m*/*z* calcd for $C_7H_7N_3O$ (M^+): 149.0584; found: 149.0583.

1-*tert*-Butyl-1,7-dihydro-3-phenylpyrazolo[3,4-*b*]pyridin-4-one (1ea)
FVP of **3e** (500 mg, 1.36 mmol, T_i 220 °C, T_f 500 °C, P 0.03 Torr, t 0.5 h) gave **1ea**; yield: 358 mg (96%); yellow solid; mp 295–298 °C.

^{1}H NMR ($CDCl_3$): δ = 11.51 (s, 1 H), 8.23 (d, ^3J = 5.4 Hz, 1 H), 8.00 (d, ^3J = 7.3 Hz, 2 H), 7.45 (t, ^3J = 7.3 Hz, 2 H), 7.36 (t, ^3J = 7.3 Hz, 1 H), 6.60 (d, ^3J = 5.4 Hz, 1 H), 1.80 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 160.0 (C_q), 154.1 (C_q), 149.6 (CH), 140.7 (C_q), 134.1 (C_q), 129.0 (2 CH), 128.4 (2 CH), 128.0 (CH), 105.8 (C_q), 102.6 (CH), 59.9 (C_q), 29.2 (3 CH_3).

MS: *m*/*z* (%) = 267 (M^+, 33), 211 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{17}N_3O$ (M^+): 267.1366; found: 267.1367.

1,7-Dihydro-3-phenylpyrazolo[3,4-*b*]pyridin-4-one (1eb)
FVP of **3e** (500 mg, 1.36 mmol, T_i 220 °C, T_f 750 °C, P 0.03 Torr, t 0.5 h) was followed by distillation of CH_2Cl_2 into the U-tube trap. The solution was removed and the insoluble product filtered under vacuum to give **1eb**; yield: 275 mg (96% mix[12]); off-white solid; mp 298 °C.

^{1}H NMR (DMSO-d_6): δ (major tautomer) = 13.85 (br s, 1 H), 11.74 (br s, 1 H), 8.29 (br s, 1 H), 8.05 (br d, ^3J = 4.9 Hz, 1 H), 7.63 (m, 2 H), 7.47 (m, 2 H), 5.71 (br s, 1 H).

MS: *m*/*z* (%) = 211 (M^+, 34), 183 (100).

HRMS: *m*/*z* calcd for $C_{12}H_9N_3O$ (M^+): 211.0751; found: 211.0751.

1,3-Di-*tert*-butyl-1,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (1fa)
FVP of **3f** (500 mg, 1.43 mmol, T_i 200 °C, T_f 500 °C, P 0.03 Torr, t 0.5 h) was followed by distillation of CH_2Cl_2 into the U-tube trap. The solution was removed and solvent removed in vacuo to afford **1fa**; yield: 345 mg (97%); yellow solid; mp 264–266 °C.

^{1}H NMR ($CDCl_3$): δ = 11.39 (s, 1 H), 8.13 (d, ^3J = 4.7 Hz, 1 H), 6.50 (d, ^3J = 4.7 Hz, 1 H), 1.71 (s, 9 H), 1.43 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 159.3 (C_q), 154.4 (C_q), 148.9 (CH), 139.4 (C_q), 105.7 (C_q), 101.9 (CH), 59.0 (C_q), 33.7 (C_q), 29.1 (3 CH_3), 26.1 (3 CH_3).

MS: *m*/*z* (%) = 247 (M^+, 29), 232 (54), 232 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{21}N_3O$ (M^+): 247.1685; found: 247.1690.

3-*tert*-Butyl-1,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (1fb)
FVP of **3f** (500 mg, 1.43 mmol, T_i 200 °C, T_f 750 °C, P 0.03 Torr, t 0.5 h) was followed by distillation of CH_2Cl_2 into the U-tube trap. The solution was removed and the insoluble product **1fb** was filtered under vacuum; yield: 374 mg (95% mix[12]); off-white solid; mp 265–266 °C.

^{1}H NMR (DMSO-d_6): δ (major tautomer) = 12.88 (br s, 1 H), 11.56 (br s, 1 H), 7.59 (br s, 1 H), 5.63 (br s, 1 H), 1.44 (s, 9 H).

MS: *m*/*z* (%) = 191 (M^+, 28), 176 (100), 149 (27).

HRMS: *m*/*z* calcd for $C_{10}H_{13}N_3O$ (M^+): 191.1059; found: 191.1063.

1-*tert*-Butyl-4-chloro-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (9)
Compound **1ea** (1.00 g, 3.74 mmol) was dissolved in $POCl_3$ (18 mL, 197 mmol) and heated to reflux for 4 h. The solution was cooled, and the volume reduced in vacuo. H_2O (40 mL) was added slowly to the dark residue followed by sat. aq $NaHCO_3$ (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and the solvent removed in vacuo to afford **9**; yield: 1.06 g (99%); brown solid; mp 123–125 °C.

^{1}H NMR ($CDCl_3$): δ = 8.41 (d, ^3J = 5.0 Hz, 1 H), 7.77 (m, 2 H), 7.48 (m, 3 H), 7.14 (d, ^3J = 5.0 Hz, 1 H), 1.91 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 151.9 (C_q), 147.3 (CH), 141.6 (C_q), 137.7 (C_q), 133.1 (C_q), 130.5 (2 CH), 128.2 (CH), 127.9 (2 CH), 117.2 (CH), 113.5 (C_q), 60.7 (C_q), 29.2 (3 CH_3).

MS: *m*/*z* (%) = 287 [M^+ (^{37}Cl), 10], 285 [M^+ (^{35}Cl), 31], 231 (32), 229 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{16}{}^{35}ClN_3$ (M^+): 285.1038; found: 285.1039.

4-Chloro-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (10)
FVP of **9** (50 mg, 0.18 mmol, T_i 300 °C, T_f 750 °C, P 0.033 Torr, t 0.5 h) was followed by distillation of CH_2Cl_2 into the U-tube trap. The solvent was removed in vacuo to afford **10**; yield: 35 mg (87%); pale brown solid; mp 274–277 °C.

^{1}H NMR ($CDCl_3$): δ (major tautomer) = 12.85 (s, 1 H), 8.57 (d, ^3J = 5.2 Hz, 1 H), 7.81 (d, ^3J = 6.2 Hz, 2 H), 7.52 (m, 3 H), 7.26 (d, ^3J = 5.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ (major tautomer) = 153.7 (C_q), 149.1 (CH), 145.8 (C_q), 139.2 (C_q), 132.4 (C_q), 130.3 (2 CH), 128.7 (CH), 128.1 (2 CH), 118.3 (CH), 112.4 (C_q).

MS: *m*/*z* (%) = 231 [M^+ (^{37}Cl), 30], 229 [M^+(^{35}Cl), 100], 166 (50).

HRMS: *m*/*z* calcd for $C_{12}H_8{}^{35}ClN_3$ (M^+): 229.0412; found: 229.0414.

1-*tert*-Butyl-3-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (11)
Pyrrolidine (1.0 mL, 11 mmol) was added to a solution of **9** (250 mg, 0.877 mmol) in 1,2-dimethoxyethane (15 mL) and the mixture was heated at reflux with stirring for 18 h. The solvent was removed and the residue was partitioned between sat. aq $NaHCO_3$ (25 mL) and EtOAc (25 mL). The organic layer was separated and the solvent removed in vacuo to yield an orange residue, which was purified by dry flash chromatography eluting with hexane–EtOAc (20:1). Product containing fractions were combined and solvent removed in vacuo to give **11** as a yellow gum, which crystallized on standing; yield: 87 mg (37%); mp 122–123 °C.

^{1}H NMR ($CDCl_3$): δ = 8.18 (d, ^3J = 5.5 Hz, 1 H), 7.66 (d, ^3J = 6.9 Hz, 2 H), 7.42 (t, ^3J = 7.6 Hz, 2 H), 7.35 (t, ^3J = 8.6 Hz, 1 H), 6.28 (d, ^3J = 5.5 Hz, 1 H), 3.06 (t, ^3J = 6.5 Hz, 4 H), 1.89 (s, 9 H), 1.73 (t, ^3J = 6.5 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 153.3 (C_q), 151.5 (C_q), 147.4 (CH), 141.8 (C_q), 136.7 (C_q), 129.2 (2 CH), 128.4 (2 CH), 127.6 (CH), 106.0 (C_q), 99.6 (CH), 59.7 (C_q), 51.5 (2 CH_2), 29.1 (3 CH_3), 25.2 (2 CH_2).

MS: *m*/*z* (%) = 320 (M^+, 54), 264 (100), 263 (M – C_3H_6O, 38).

HRMS: *m*/*z* calc for $C_{20}H_{24}N_4$ (M^+): 320.2007; found: 320.2005.

4-Anilino-1-*tert*-butyl-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (12)
A solution of **9** (285 mg, 1.00 mmol), aniline (0.1 mL, 1.1 mmol), $Pd_2(dba)_3$ (18 mg, 0.02 mmol), dppp (16 mg, 0.04 mmol), and *t*-BuONa (134 mg, 1.4 mmol) in toluene (10 mL) contained in an oven-dried flask purged with N_2, was heated to 70 °C for 72 h. The mixture was cooled, taken up in Et_2O (10 mL), washed with brine (3 × 5 mL), and concentrated in vacuo to give the crude product, which was purified by dry flash chromatography eluting with hexane–EtOAc (20:1). Product containing fractions were combined and solvent removed in vacuo to afford **12** as a yellow gum, which crystallized on standing; yield: 280 mg (87%); mp 116–118 °C.

^{1}H NMR ($CDCl_3$): δ = 8.23 (d, ^3J = 5.5 Hz, 1 H), 7.68 (d, ^3J = 6.9 Hz, 2 H), 7.77 (t, ^3J = 7.5 Hz, 2 H), 7.55 (t, ^3J = 7.4 Hz, 1 H), 7.38 (dd, ^3J = 8.4, 7.4 Hz, 2 H)Hz,), 7.17 (m, 3 H), 6.72 (d, ^3J = 5.5 Hz, 1 H), 6.62 (br s, 1 H), 1.91 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 152.8 (C_q), 148.8 (CH), 145.9 (C_q), 140.5 (C_q), 139.2 (C_q), 134.9 (C_q), 129.5 (2 CH), 129.3 (2 CH), 129.1 (2 CH), 128.6 (CH), 124.5 (CH), 122.3 (2 CH), 104.5 (C_q), 97.7 (CH), 60.0 (C_q), 29.2 (3 CH_3).

MS: *m*/*z* (%) = 342 (M^+, 42), 286 (100).

HRMS: *m*/*z* calcd for $C_{22}H_{22}N_4$ (M^+): 342.1850; found: 342.1852.

4-Anilino-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (13)
FVP of **12** (30 mg, 0.88 mmol, T_i 235 °C, T_f 750 °C, P 0.03 Torr, t 0.5 h) was followed by distillation of CH_2Cl_2 into the U-tube trap. The solvent was removed in vacuo to afford **13**; yield: 18 mg (72%); pale yellow solid; mp 216–217 °C.

^{1}H NMR ($CDCl_3$): δ (major tautomer) = 12.92 (br s, 1 H), 8.33 (d, ^3J = 5.7 Hz, 1 H), 7.81 (d, ^3J = 7.3 Hz, 2 H), 7.58 (t, ^3J = 7.4 Hz, 2 H), 7.52 (t, ^3J = 7.4 Hz, 1 H), 7.41 (t, ^3J = 7.9 Hz, 2 H), 7.23 (m, 3 H), 6.76 (d, ^3J = 5.7 Hz, 1 H), 6.74 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ (major tautomer) = 154.7 (C_q), 150.3 (C_q), 146.8 (CH), 144.5 (C_q) 138.7 (C_q), 134.4 (C_q), 129.6 (2 CH), 129.3 (2 CH), 129.0 (2 CH), 128.9 (CH), 125.1 (CH), 122.8 (2 CH), 102.8 (C_q), 98.3 (CH).

MS: m/z (%) = 286 (M^+, 100), 285 (58), 258 (58).

HRMS: m/z calcd for $C_{18}H_{14}N_4$ (M^+): 286.1224; found: 286.1218.

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