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 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. 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.

In earlier work, we explored a potential route to 1 by flash vacuum pyrolysis (FVP) of Meldrum’s acid derivatives [e.g., 3 (R1 = H)], but cyclization of the imidoylketene intermediate 4 (R1 = H) occurred exclusively at the adjacent nitrogen atom to provide a useful route to the pyrazolo[1,5-a]pyrimidine system 5 (Scheme 1). Clearly this route must be blocked to provide pyrazolo[3,4-b]pyridin-4-ones.

Scheme 1

The present work therefore had a range of objectives. First, 3 (R1 = 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. Second, we explored the 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 (R1 = 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 6f9a 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-aminoo isomer, which was taken on to the next stage without purification. Reaction of 3 butyl-3-amino isomer, which was taken on to the next stage without purification.

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.

In order to access the 1-unsubstituted pyrazolo[3,4-b]pyridines 1 (R1 = 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 series10 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 (R1 = t-Bu) whereas FVP in the range 750–850 °C should provide the deprotected products 1 (R1 = H).

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. δH = 12.8–13.8 and 11.5–11.8 are characteristic, as previously reported.2a

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]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.

1H and 13C 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-1H-pyrazole (6c)

tert-Butylhydrazine hydrochloride (5.99 g, 48.1 mmol) was added to EOH (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 H2O (35 mL) and partitioned between sat. aq NaHCO3 (30 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 (MgSO4), 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).

HRMS: m/z calcld for C11H13N3O4: 201.1730; found: 201.1744. Spectra differ significantly from those reported,9b but were recorded in a different solvent.

MS: m/z (%) = 195 (M, 14%), 139 (63), 124 (100).

1H NMR (DMSO-d6): δ = 7.64 (d, J = 7.4 Hz, 2 H), 7.33 (t, J = 7.4 Hz, 2 H), 7.22 (t, J = 7.4 Hz, 1 H), 5.79 (s, 1 H), 4.97 (s, 2 H), 1.58 (s, 9 H).

13C NMR (DMSO-d6): δ = 148.1 (Cq), 146.1 (Cq), 135.0 (Cq), 128.8 (2 CH), 127.1 (CH), 125.0 (2 CH) 89.2 (CH), 58.3 (Cq), 40.1 (3 CH3).

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


5-Amino-1,3-di-tert-butyl-1H-pyrazole (6f)

A solution of 4,4-dimethyl-3-oxovaleronitrile (1.75 g, 14.0 mmol) in EOH (10 mL) was added to a slurry of tert-butylhydrazine hydrochloride (3.5 g, 28.1 mmol) in EOH (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 NaHCO3 (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 (MgSO4), 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).

HRMS: m/z (%) = 195 (M, 14%), 139 (63), 124 (100).

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-aminoazopyrazole 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-1H-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).

HRMS: m/z (%) = 195 (M, 14%), 139 (63), 124 (100).

MS: m/z (%) = 215 (M*, 16), 193 (100), 149 (14), 122 (40).

Ana. Calcld for C10H13N3O4: C, 52.6; H, 5.2; N, 16.75. Found: C, 52.65; H, 5.35; N, 16.8.
5-(3-Methyl-1-phenyl-1H-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).

1H NMR (CDCl3): δ = 11.45 (d, J = 13.4 Hz, 1 H), 8.38 (d, J = 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).

13C NMR (CDCl3): δ = 165.3 (Cq), 162.7 (Cq), 153.1 (CH), 150.1 (Cq), 138.3 (Cq), 136.8 (Cq), 130.0 (2 CH), 128.8 (CH), 124.8 (2 CH), 105.5 (Cq), 94.3 (CH), 88.8 (Cq), 27.1 (2 CH3), 14.0 (CH3).

MS: m/z (%) = 293 (M+, 24), 291 (100), 217 (27), 202 (45), 176 (56).

HRMS: m/z calc'd for C18H17N3O5 (M+) = 294.1151; found: 294.1153.

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 N2. Conditions were first established on a small scale (20 mg) where the product(s) were dissolved in a deuterated solvent and analyzed directly by 1H NMR spectroscopy. Larger-scale pyrolyses, involving 0.1 g or more of substrate, were usually removed from the trap by solution in CH2Cl2 (30 mL). The precursors and pyrolysis conditions [quantity of precursor, inlet temperature (Ti), furnace temperature (Tf), 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, Tf acetone/dry ice bath, 70–80 °C, P = 0.03 Torr, t = 15 min).

1-Methyl-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (1a)

FVP of 3a (recrystallized from MeOH, 203 mg, 0.81 mmol, Tf 199 °C, Tf 600 °C, P = 0.03 Torr, t = 30 min) gave 1a; yield: 111 mg (92%); off-white solid; mp 164 °C (Lit.13 mp 160–168 °C).

1H NMR (DMSO-d6): δ = 8.37 (d, J = 4.0 Hz, 1 H), 8.30 (s, 1 H), 6.65 (br s, 1 H), 4.22 (s, 3 H).

13C NMR (DMSO-d6): δ = 162.4 (br Cq), 150.7 (br Cq), 148.1 (br CH), 130.6 (CH), 107.9 (br Cq), 104.4 (CH), 33.9 (CH3).

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

HRMS: m/z calc'd for C6H11N3O3 (M+): 149.0584; found: 149.0584.

3-Methyl-1,7-dihydro-1-phenylpyrazolo[3,4-b]pyridin-4-one (1b)

FVP of 3b (recrystallized from MeOH, 195 mg, 0.60 mmol, Tf 170 °C, Tf 600 °C, P = 0.03 Torr, t = 45 min) gave 1b; yield: 0.129 mg (95%); off-white solid; mp 195 °C.

1H NMR (DMSO-d6): δ = 11.76 (s, 1 H), 8.31 (br m, 3 H), 7.57 (app t, J = 7.8 Hz, 2 H), 7.32 (d, J = 7.3 Hz, 1 H), 6.66 (br s, 1 H), 2.68 (s, 3 H).

13C NMR (DMSO-d6): δ = 160.6 (Cq), 151.3 (Cq), 150.9 (CH), 142.0 (Cq), 139.5 (Cq), 128.9 (2 CH), 124.9 (CH), 119.7 (2 CH), 107.4 (Cq), 103.2 (CH), 14.3 (CH3).

MS: m/z (%) = 226 (M+, 30), 225 (100), 79 (15), 38 (79).

HRMS: m/z calc'd for C13H11N3O3 (M+): 225.0897; found: 225.0896.

1-tet-Butyl-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (1ca)

FVP of 3c (recrystallized from cyclohexane, 300 mg, 1.02 mmol, Tf 210 °C, Tf 500 °C, P = 0.03 Torr, t = 0.5 h) gave 1ca; yield: 185 mg (95%); yellow solid; mp 189–191 °C.
1H NMR (DMSO-d$_6$): $\delta$ = 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). 13C NMR (DMSO-d$_6$): $\delta$ = 159.3 (C$_q$), 152.9 (C$_q$), 149.7 (CH), 128.5 (CH), 108.9 (C$_q$), 102.2 (CH), 95.6 (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$_3$O (M$^+$): 191.0646; found: 191.0646.

1.7-Dihydropyrazolo[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$_2$Cl$_2$ into the U-tube trap. The solvent was removed and the insoluble product filtered under vacuum to give 1eb; yield: 275 mg (96% mix$_{12}$); off-white solid; mp 298 °C.

1H NMR (DMSO-d$_6$): $\delta$ (major tautomer) = 13.85 (br s, 1 H), 11.74 (br s, 1 H), 8.29 (br s, 1 H), 8.05 (br d, $J$ = 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$_{16}$H$_{17}$N$_3$O (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$_f$ 750 °C, P 0.03 Torr, t 0.5 h) was followed by distillation of CH$_2$Cl$_2$ into the U-tube trap. The solvent was removed and the insoluble product filtered under vacuum to afford 1fa; yield: 345 mg (97%); yellow solid; mp 264–266 °C.

1H NMR (CDCl$_3$): $\delta$ = 11.39 (s, 1 H), 8.13 (d, $J$ = 4.7 Hz, 1 H), 6.50 (d, $J$ = 4.7 Hz, 1 H), 1.71 (s, 9 H), 1.43 (s, 9 H).

13C NMR (CDCl$_3$): $\delta$ = 153.3 (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$_{16}$H$_{17}$N$_3$O (M$^+$): 247.1685; found: 247.1690.

1.7-Dihydro-3-phenylpyrazolo[3,4-b]pyridin-4-one (1fa)

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$_2$Cl$_2$ into the U-tube trap. The solvent was removed and the insoluble product filtered under vacuum to give 1fa; yield: 275 mg (96% mix$_{12}$); off-white solid; mp 298 °C.

1H NMR (DMSO-d$_6$): $\delta$ (major tautomer) = 13.85 (br s, 1 H), 11.74 (br s, 1 H), 8.29 (br s, 1 H), 8.05 (br d, $J$ = 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$_{16}$H$_{17}$N$_3$O (M$^+$): 211.0751; found: 211.0751.
1H NMR (CDCl3): δ (major tautomter) = 12.85 (s, 1 H), 8.57 (d, J = 5.2 Hz, 1 H), 7.81 (d, J = 6.2 Hz, 2 H), 7.52 (m, 3 H), 7.26 (d, J = 5.2 Hz, 1 H).

13C NMR (CDCl3): δ (major tautomter) = 153.7 (Cq), 149.1 (CH), 145.8 (Cq), 139.2 (Cq), 132.4 (Cq), 130.3 (2 CH), 128.7 (CH), 128.1 (2 CH), 118.3 (CH), 112.4 (Cq).

MS: m/z (%) = 231 [M+13C], 30, 229 [M+13C], 100, 166 (50).

HRMS: m/z calc for C12H8Cl3N3 (M+): 229.0412; found: 229.0414.

1-tert-Butyl-3-phenyl-4-(pyrrolidin-1-yl)-1H-pyrazolo[3,4-b]pyridine (11)

Pyridoline (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. NaHCO3 (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.

1H NMR (CDCl3): δ = 8.18 (d, J = 5.5 Hz, 1 H), 7.66 (d, J = 6.9 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.35 (t, J = 8.6 Hz, 1 H), 6.28 (d, J = 5.5 Hz, 1 H), 3.06 (t, J = 6.5 Hz, 4 H), 1.89 (s, 9 H), 1.73 (t, J = 6.5 Hz, 4 H).

13C NMR (CDCl3): δ = 153.1 (Cq), 151.5 (Cq), 147.4 (CH), 141.8 (Cq), 136.7 (Cq), 129.2 (2 CH), 128.4 (2 CH), 127.6 (CH), 106.0 (Cq), 99.6 (CH), 59.7 (Cq), 51.5 (2 CH), 29.2 (2 CH), 25.2 (2 CH).

MS: m/z (%) = 320 (M+, 54), 264 (100), 263 (M–C3H6O, 38).

HRMS: m/z calc for C18H14N4 (M+): 286.1224; found: 286.1218.

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References

(1) Deceased.


(12) For 1eb and 1fb, the product was contaminated with unreacted starting material as well as the pyrazolo[1,5-a]pyrimidine isomer, indicating competing N-tert-butyl deprotection prior to ring formation, and hence cyclization via pathway 4 to 5 in Scheme 1 rather than 4 to 1.