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 literature2 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 (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).5 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.6 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 pyrazolo[3,4-b]pyridinones 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.

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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, 6e, and 6f are known only in patents or are formed in poor yield; 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.

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 series and it is also known that 3-substituted 3-phenyl series 12a

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. 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).

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.

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-Butyldihyrazine 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 H2O (35 mL) and 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 in vacuo to afford a red oil; yield: 0.71 g (87%); bp 67–69 °C (Lit.9a mp 64–66 °C).

MS: m/z calcd for C11H13N3O4: C, 52.6; H, 5.2; N, 16.75. Found: C, 52.65; H, 5.2; N, 16.75.

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

A solution of 3-oxo-3-phenylpropanenitrile (1.5 g, 10.3 mmol) in ETOH (10 mL) was added to a slurry of tert-butyldihyrazine 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 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 in vacuo to give 6f as a pale yellow solid; yield: 1.8 g (66%); mp 67–69 °C (Lit.9a mp 64–66 °C).

MS: m/z calcd for C11H21N3 (M+): 195.1730; found: 175.1728.

5-(Methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (9b)

A solution of 5-aminopyrazole (3a) (2.6 g, 20.7 mmol) in ETOAc (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 9b as a pale orange solid; yield: 1.8 g (66%); mp 67–69 °C (Lit.9a mp 64–66 °C).

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

HRMS: m/z calcd for C11H20N2O2 (M+·HCl): 195.1728; 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-aminoaryl-pyrazole 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 calcd for C11H13N3O4: C, 52.6; yellow solid; mp 144 °C (MeOH).

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

Anal. Calcd for C11H13N3O4: 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), 151.3 (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 (%) = 307 (M+, 24), 291 (100), 217 (27), 202 (45), 176 (56).

HRMS: m/z calc for C18H16N2O4 (M+): 307.1196; found: 307.1196.

FV P 1H NMR (DMSO-d6); δ = 11.47 (d, J = 13.1 Hz, 1 H), 8.35 (d, J = 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).

13C NMR (DMSO-d6); δ = 166.6 (Cq), 163.1 (Cq), 158.9 (Cq), 154.6 (CH), 137.0 (Cq), 105.5 (Cq), 94.0 (CH), 87.8 (Cq), 59.8 (Cq), 32.3 (Cq), 30.3 (3 CH3), 29.9 (3 CH3), 27.1 (2 CH3).

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

HRMS: m/z calc for C18H16N2O4 (M+): 293.1384; found: 293.1384.

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

FVP of 3a (recrystallized from MeOH, 203 mg, 0.81 mmol, T = 199 °C, T = 600 °C, P = 0.03 Torr, t = 30 min) gave 1aa; yield: 111 mg (92%); off-white solid; mp 164 °C (Lit.12 mp 165–168 °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 for C7H7N3O (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 = 170 °C, T = 600 °C, P = 0.03 Torr, t = 45 min) gave 1ba; 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), 78 (39).

HRMS: m/z calc for C18H16N2O (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 = 210 °C, T = 500 °C, P = 0.03 Torr, t = 1 h) gave 1ca; yield: 185 mg (95%); yellow solid; mp 189–191 °C.

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1.7-Dihydropyrazolo[3,4-b]pyridin-4-one (1eb)

FVP of 3e (500 mg, 1.36 mmol, T: 220 °C, T: 750 °C, P: 0.03 Torr, t: 0.5 h) was followed by distillation of CHCl₃ into the U-tube trap. The solution was removed and the insoluble product filtered under vacuum to give 1eb; yield: 275 mg (96% mix); off-white solid; mp 298 °C.

1H NMR (DMSO-d₆): δ = 11.85 (s, 1 H), 7.36 (d, J = 4.7 Hz, 1 H), 6.77 (br s, 1 H), 6.50 (d, J = 5.4 Hz, 1 H), 1.80 (s, 9 H).

13C NMR (DMSO-d₆): δ = 151.9 (C₂), 147.3 (C₁), 141.6 (C₆), 137.7 (C₃), 133.1 (C₅), 130.5 (2 CH), 128.2 (CH), 127.9 (2 CH), 117.2 (CH), 113.5 (C₄), 60.7 (C₇), 29.2 (3 CH₃).

MS: m/z (%) = 253 [M⁺], 228 [M⁺-15], 140 (100), 88 (37).

HRMS: m/z calcd for C₁₁H₁₀N₃O (M⁺): 252.0878; found: 252.0877.

1.3-Di-tert-buty1-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (1fa)

FVP of 3f (500 mg, 1.43 mmol, T: 200 °C, T: 750 °C, P: 0.03 Torr, t: 0.5 h) was followed by distillation of CHCl₃ into the U-tube trap. The solution was removed and soluble product in vacuo to afford 1fa; yield: 345 mg (97%); yellow solid; mp 264–266 °C.

1H NMR (CDCl₃): δ = 11.93 (s, 1 H), 7.83 (d, J = 4.7 Hz, 1 H), 6.50 (d, J = 5.4 Hz, 1 H), 1.81 (s, 9 H), 1.43 (s, 9 H).

13C NMR (CDCl₃): δ = 159.3 (C₁), 154.4 (C₂), 148.9 (CH), 139.4 (C₃), 105.7 (C₄), 101.9 (CH), 59.0 (C₅), 33.7 (3 CH₃), 29.1 (3 CH₃).

MS: m/z (%) = 247 [M⁺], 232 (54), 232 (100).

HRMS: m/z calcd for C₁₃H₁₄N₄O (M⁺): 247.0744; found: 247.0690.

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

FVP of 3d (100 mg, 0.33 mmol, T: 160 °C, T: 750 °C, P: 0.03 Torr, t: 45 min) gave 1db; yield: 0.40 g (82%); off-white solid; mp 254 °C.

1H NMR (DMSO-d₆): δ = 13.11 (s, 1 H), 11.51 (s, 1 H), 7.50 (t, J = 6.3 Hz, 1 H), 5.55 (d, J = 6.3 Hz, 1 H), 2.53 (s, 3 H).

13C NMR (DMSO-d₆): δ = 160.7 (C₂), 152.2 (br C₂), 147.5 (CH), 137.4 (br C₂), 107.2 (br C₂), 101.5 (CH), 58.5 (C₅), 28.8 (3 CH₃), 143.8 (CH₃).

MS: m/z (%) = 211 [M⁺], 191 (100), 149 (28).

HRMS: m/z calcd for C₁₀H₁₀N₂O (M⁺): 205.0859; found: 205.0857.

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

FVP of 3e (500 mg, 1.36 mmol, T: 220 °C, T: 750 °C, P: 0.03 Torr, t: 0.5 h) was followed by distillation of CHCl₃ into the U-tube trap. The solution was removed and insoluble product filtered under vacuum to give 1eb; yield: 275 mg (96% mix); off-white solid; mp 298 °C.

1H NMR (DMSO-d₆): δ = 11.85 (s, 1 H), 7.36 (d, J = 4.7 Hz, 1 H), 6.50 (d, J = 5.4 Hz, 1 H), 1.80 (s, 9 H).

13C NMR (DMSO-d₆): δ = 151.9 (C₂), 147.3 (C₁), 141.6 (C₆), 137.7 (C₃), 133.1 (C₅), 130.5 (2 CH), 128.2 (CH), 127.9 (2 CH), 117.2 (CH), 113.5 (C₄), 60.7 (C₇), 29.2 (3 CH₃).

MS: m/z (%) = 253 [M⁺], 228 [M⁺-15], 140 (100), 88 (37).

HRMS: m/z calcd for C₁₁H₁₀N₃O (M⁺): 252.0878; found: 252.0877.
1H NMR (CDCl3): δ (major tautomer) = 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 tautomer) = 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 C18H14N4 (M+): 286.1242; found: 286.1245.

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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.