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

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Received: 18.06.2014  
Accepted after revision: 18.08.2014  
Published online: 02.10.2014  

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 (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 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, 6e, and 6fα 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-aminopyrazolopyridinones. 11

FVP of 3a and 3b at 600 °C (0.03 Torr) gave 1-methylpyrazolopyridinone (Figure 3) in 83–97% yields whilst 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 6fα 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-aminopyrazolopyridinones. 11

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-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 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 complete the precipitation of the product.

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

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 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 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.,9 mp 64–66 °C). 1H NMR (CDCl3): δ = 5.48 (s, 1 H), 3.46 (s, 2 H), 1.27 (s, 18 H). 13C NMR (CDCl3): δ = 157.8 (Cq), 144.1 (Cq), 90.2 (CH), 58.2 (Cq), 44.7 (Cq), 30.4 (3 CH3), 29.5 (3 CH3). Spectra differ significantly from those reported, but were recorded in a different solvent.

MS: m/z (%) = 195 (M+, 29), 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-amino-1H-pyrazole 5 (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.

MS: m/z (%) = 251 (M+, 16), 193 (100), 149 (14), 122 (40). Anal. Calcd for C13H17N2O3: 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), 88.5 (Cq), 27.1 (2 CH3), 14.0 (CH3).

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


5-(1-tert-Butyl-1H-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.

1H NMR (CDCl3): δ = 11.53 (d, J = 13.4 Hz, 1 H), 8.33 (d, J = 13.4 Hz, 1 H), 7.41 (d, J = 1.9 Hz, 1 H), 6.23 (d, J = 1.9 Hz, 1 H), 1.77 (s, 6 H), 1.70 (s, 9 H).

13C NMR (CDCl3): δ = 165.6 (Cq), 162.9 (Cq), 154.7 (CH), 137.5 (Cq), 137.3 (Cq), 105.6 (Cq), 97.8 (CH), 88.4 (Cq), 60.3 (Cq), 29.8 (3 CH3), 27.3 (2 CH3).

MS: m/z (%) = 293 (M+ 21), 235 (47), 197 (59), 161 (100).

HRMS: m/z calcd for C18H19N3O4 (M+): 293.1381; found: 293.1384.

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 (Tin), 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, Tin acetone/dry ice bath, Tf 600–850 °C, P = 0.03 Torr, t min).

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

FVP of 3a (recrystallized from MeOH, 203 mg, 0.81 mmol, Tin 199 °C, Tf 600 °C, P = 0.03 Torr, t 30 min) gave 7a; yield: 111 mg (92%); off-white solid; mp 164 °C (Lit.1, 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 calcd for C7H7N3O2 (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, Tin 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 = 7.8 Hz, 1 H), 6.66 (br s, 1 H), 2.68 (s, 3 H).

13C NMR (DMSO-d6): δ = 160.6 (Cq), 153.1 (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), 143.3 (CH3).

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

HRMS: m/z calcd for C15H11N3O (M+): 225.0897; found: 225.0896.

1-tert-Butyl-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (1c)

FVP of 3c (recrystallized from cyclohexane, 300 mg, 1.02 mmol, Tin 210 °C, Tf 500 °C, P = 0.03 Torr, t 0.5 h) gave 1c; yield: 185 mg (95%); yellow solid; mp 189–191 °C.
1.7-Dihydro[3,4-b]pyridin-4-one (1eb)

VFP of 3c (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 afford 1eb: yield: 275 mg (96% mix); off-white solid; mp 298 °C.

1H NMR (DMSO-d₆); 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).

13C NMR (DMSO-d₆); δ = 159.3 (Cq), 149.6 (CH), 140.7 (Cq), 131.3 (Cq), 130.5 (2 CH), 128.2 (CH), 117.2 (2 CH), 113.5 (Cq), 60.7 (Cq), 29.2 (3 CH₃).

MS: m/z (%) = 211 (M⁺, 100).

HRMS: m/z calc for C₁₁H₁₄N₃O (M⁺): 211.0751; found: 211.0751.

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

VFP 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 the insoluble product filtered under vacuum to afford 1fa: yield: 345 mg (97%); yellow solid; mp 264–266 °C.

1H NMR (CDCl₃); 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).

13C NMR (CDCl₃); δ = 159.3 (Cq), 154.4 (Cq), 148.9 (CH), 139.4 (Cq), 105.7 (Cq), 101.9 (CH), 59.0 (Cq), 33.7 (Cq), 29.1 (3 CH₃), 26.1 (3 CH₃).

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

HRMS: m/z calc for C₁₄H₂₁N₃O (M⁺): 247.1685; found: 247.1690.

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

VFP of 3d (100 mg, 0.33 mmol, T: 160 °C, T: 750 °C, P: 0.03 Torr, t: 0.5 h) gave 1da; yield: 0.40 g (82%); off-white solid; mp 254 °C.

1H NMR (CDCl₃); δ = 11.31 (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).

13C NMR (CDCl₃); δ = 160.7 (Cq), 152.2 (br Cq), 147.5 (CH), 137.4 (br Cq), 107.2 (br Cq), 101.5 (CH), 58.5 (Cq), 28.8 (3 CH₃), 143 (CH₃).

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

HRMS: m/z calc for C₁₅H₁₄N₄O (M⁺): 205.1210; found: 205.1210.
HRMS: m/z calcd for C18H14N4 (M+): 286.1224; found: 286.1218.

Acknowledgment

We thank Cancer Research UK (studentships to AN and MM; Grant Ref C21383/A6950) for financial support and Lorna Murray for assistance with NMR data.

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.