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New access to the 1*H*-pyrazolo[4,3-*c*]pyridine core from bis-acetylenic-*N*-benzoylhydrazones

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Abstract—1*H*-pyrazolo[4,3-*c*]pyridines were obtained from bis-acetylenic-*N*-benzoylhydrazones using aqueous ammonia.

1. Introduction

Bicyclic hetero-aromatic compounds are well known for their wide range of biological activity. For example the 3-furylindazole YC-1 (**1**) (Fig. 1) is now considered as a lead compound in the design of novel indazole derivatives potentially useful for treatment of various diseases linked to smooth muscle relaxation including cardiovascular insufficiency and erectile dysfunction.[1] The related pyrazolopyridines, which comprise five isomers [3,4-*b*], [3,4-*c*], [4,3-*c*], [4,3-*b*] and [1,5-*a*], were shown to display high biological activity; pyrazolo[4,3-*c*]pyridine **2** derivatives have use as angiotensin II antagonists and Bay 41-2272 (**3**) has been introduced as a novel orally available agent which directly stimulates soluble guanylate cyclase (sGC) and sensitizes it to its physiological stimulator, nitric oxide.[2]

The usual synthetic routes towards the pyrazolo[4,3-*c*]pyridine core are ring closure of the pyridine ring of a functionised pyrazole or ring closure of the pyrazole ring of a functionalised pyridine.[3] Herein we report a new synthesis of the pyrazolo[4,3-*c*]pyridine core based on an unusual one step tandem ring closure and rearrangement of bis-acetylenic N-acylated hydrazones using aqueous ammonia.

2. Results and discussion

Our initial aim was the synthesis of the nine membered ring compound **4**, starting from the commercially available 1,4-bis(trimethylsilyl)-1,3-butadiyne **8** as outlined in Scheme 1. The planned synthesis of **4** called for ammonolysis of a bis-acetylenic N-acetylated hydrazone **5** followed by a 9-*endo-dig* cyclisation.[4]

Our synthesis (Scheme 2) began with the commercially

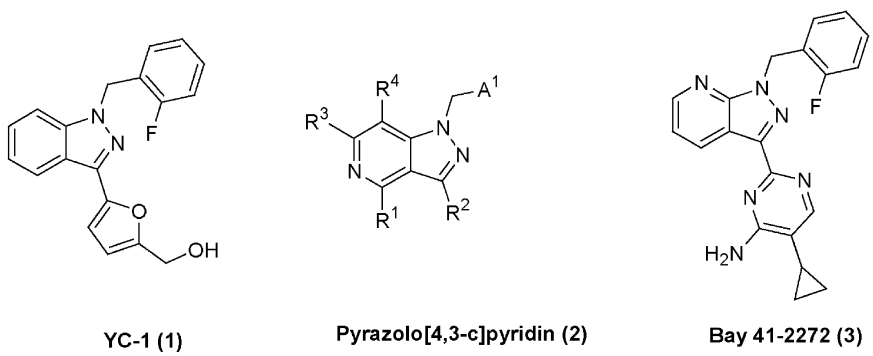

Figure 1.

Keywords: 3-Furylindazole; Angiotensin II antagonist; Pyrazole ring; 1*H*-Pyrazolo[4,3-*c*]pyridine.
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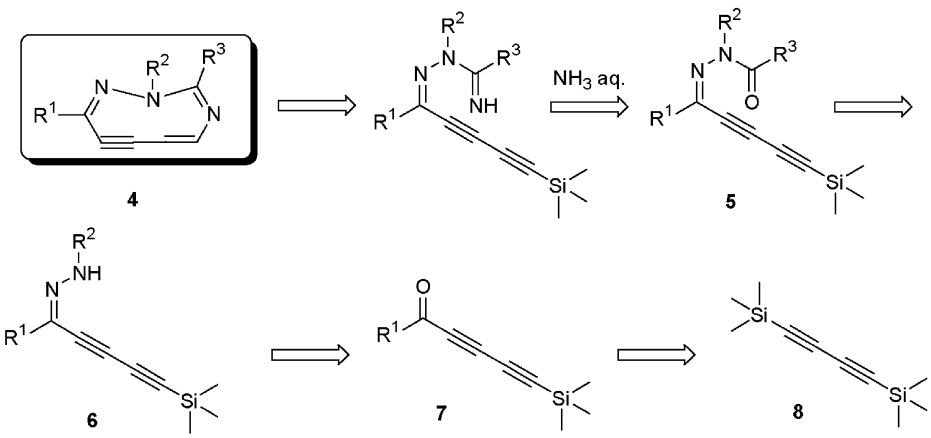
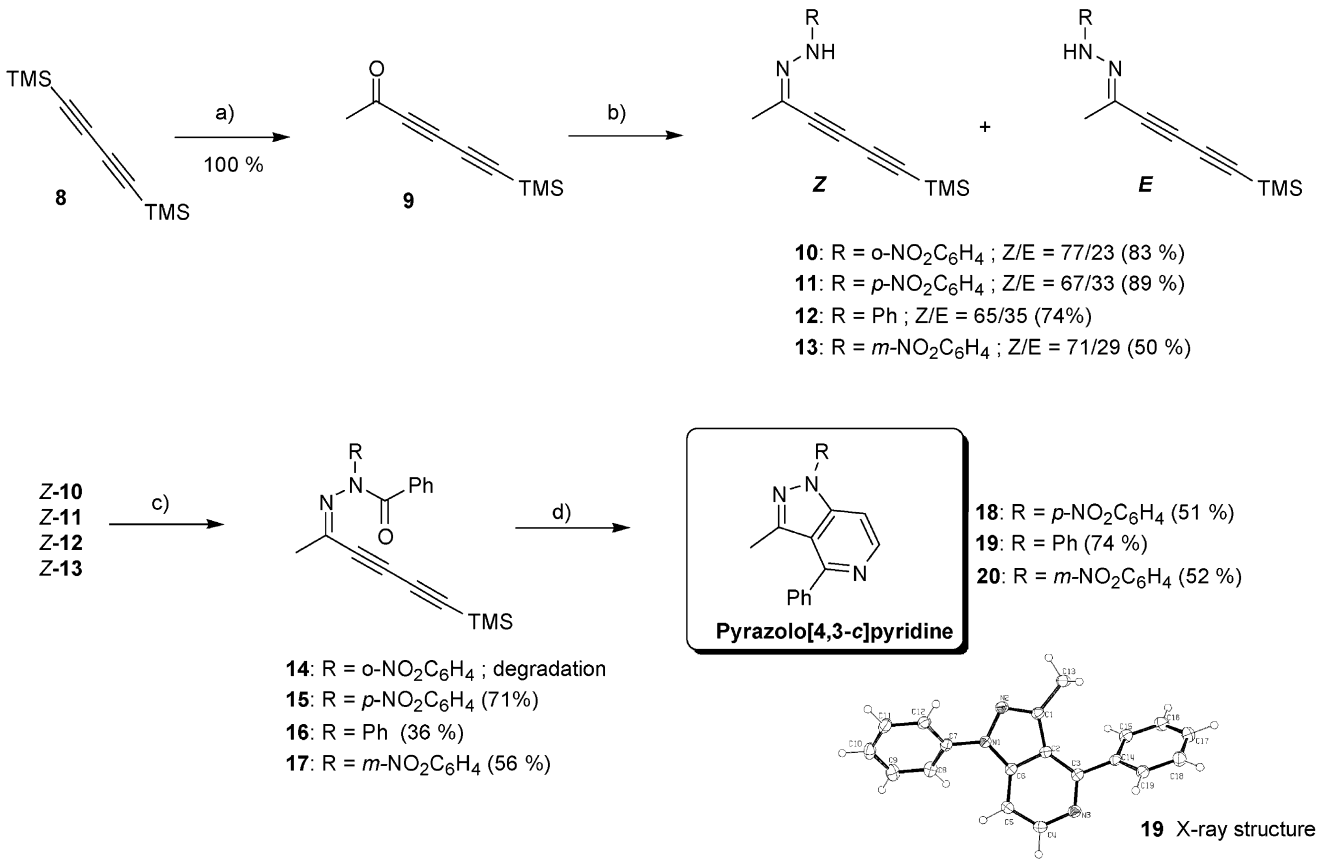


Scheme 1. Retrosynthetic analysis.

available 1,4-bis(trimethylsilyl)-1,3-butadiyne **8**, which upon treatment with acetyl chloride and anhydrous aluminium trichloride in CH_2Cl_2 furnished the corresponding ketone **9** in quantitative yield.[5] The acetylenic ketone **9**, upon reaction with phenylhydrazine or substituted analogues in MeOH was converted into the corresponding hydrazones **10**, **11**, **12** and **13** as separable mixtures of *Z* and *E* isomers. The structure of both of these isomers were confirmed by the intensity of the ^1H NMR NOE interactions between the methyl protons and the N–H proton. However, it was found that the hydrazones *E*-**11**, *E*-**12** and *E*-**13** was relatively unstable, and upon standing in $CDCl_3$ for a few hours, were cleanly converted to their corresponding *Z*-isomer (Fig. 2). *E*-**10** was found to be stable under these conditions and no isomerisation was observed. Thus, the next step of the synthesis was performed with the *Z*-compounds *Z*-**10**, *Z*-**11**, *Z*-**12** and *Z*-**13** which upon treatment with benzoyl chloride and anhydrous aluminium trichloride in refluxing of CH_2Cl_2 gave, in fair yields, the corresponding *N*-benzoyl compounds.[6] Unfortunately hydrazone *Z*-**10** was degraded and no *N*-benzoylated product was observed. However *Z*-**11**, *Z*-**12** and *Z*-**13** gave **15**, **16** and **17** in 71, 36 and 56% yields, respectively.

Next, the ring closure of the *N*-benzoylated hydrazones with aqueous ammonia was attempted.

However, after exposure of compounds **15**, **16** and **17** to



Scheme 2. (a) MeCOCl, $AlCl_3$, DCM, 0 °C; (b) NH_2NHR, MeOH; (c) PhCOCl, $AlCl_3$, DCM, reflux; (d) 33% aq. NH_3, EtOH, 85 °C.

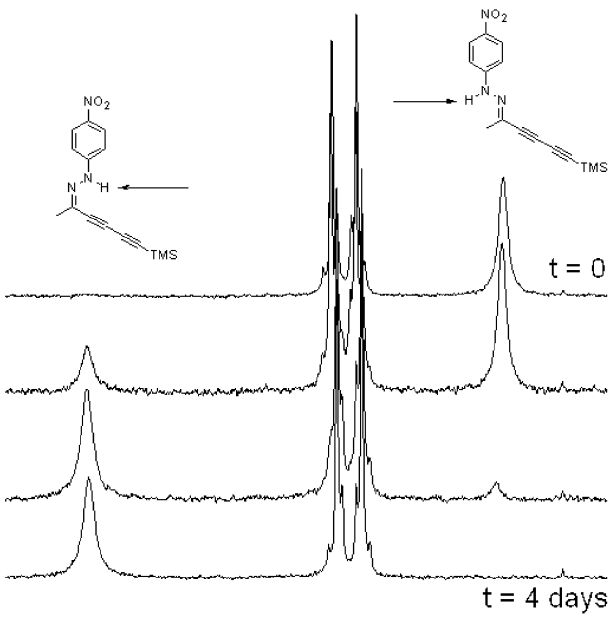


Figure 2.

ethanolic aqueous ammonia,[7] the corresponding pyrazolo[4,3-*c*]pyridines **18**, **19** and **20** were obtained, rather than the nine membered ring **4**. The structure of these compounds was confirmed by X-ray analysis of **19**[8] and by further spectral comparison of **18** and **20** to **19**.

To explain the formation of the pyrazolo[4,3-*c*]pyridines from the corresponding hydrazones, we propose the following mechanistic rationale (Schemes 3 and 4). In Scheme 3, the first step is the formation of the imino-hydrazone **21**[9] followed by 9-*endo-dig* cyclisation of the amidine moiety on the terminal alkyne.[4] However, under the reaction conditions, further reaction of **22** with another equivalent of ammonia presumably gives rise to **23** which undergoes consecutive 5-*endo-dig* pyrazole cyclisation followed by thermal 6πe disrotary ring closure and elimination of ammonia to form the isolated pyrazolo[4,3-*c*]pyridine compounds. An alternative mechanism, which does not require a nine membered ring, is also a possibility (Scheme 4).

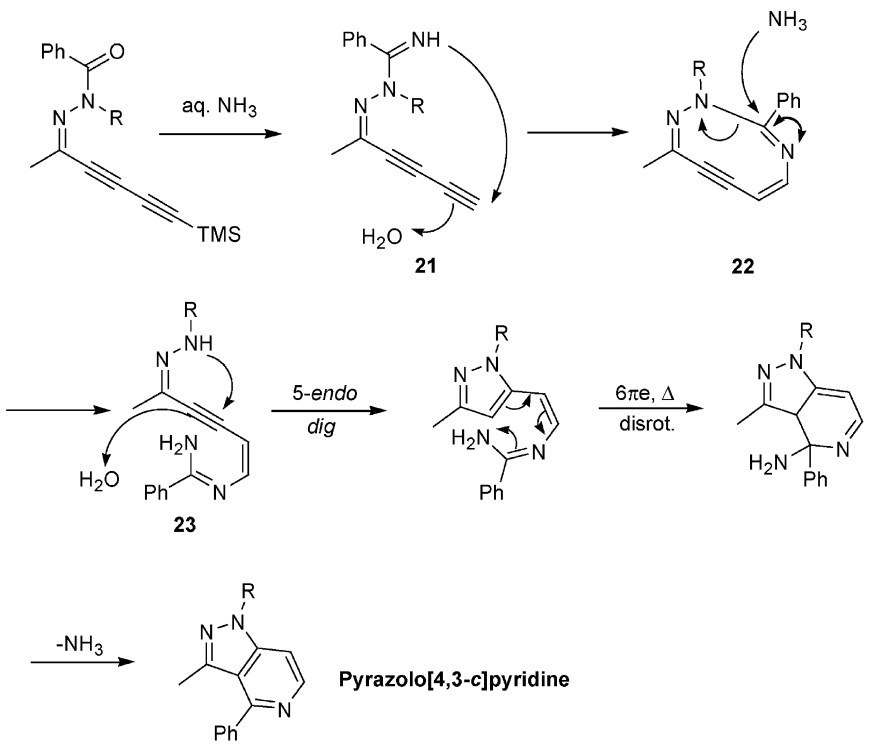
3. Conclusion

A concise novel route to the pyrazolo[4,3-*c*]pyridine core by an unusual mechanistic pathway has been developed.

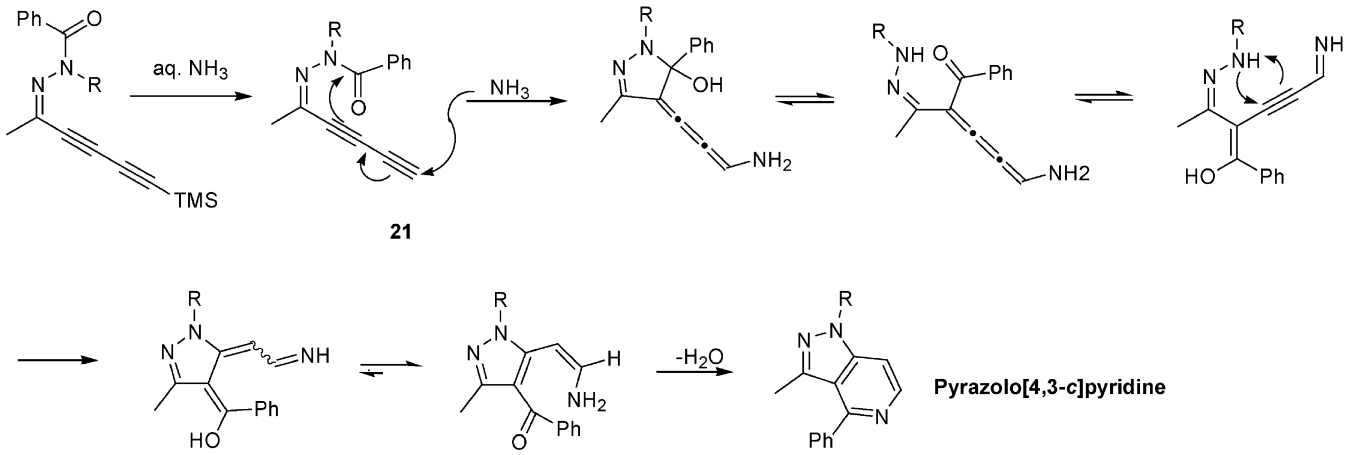
4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Amarego, W. L. F. Purification of laboratory chemicals, 3rd ed.; Pergamon: Oxford, 1988 or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 Rotavapor fitted with a water or dry ice condenser as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 2 mmHg. All experiments were carried out under inert atmosphere unless otherwise stated. ^{1}H NMR spectra were recorded at 400 MHz using Bruker DPX400. For ^{1}H spectra recorded in $CDCl_3$, chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The



Scheme 3.



Scheme 4.

following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate). Coupling constants (*J*) are reported in Hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 100 MHz using Bruker DPX400 instrument. Carbon spectra assignments are supported by DEPT-135 spectra, $^{13}C-^{1}H$ (HMQC and HMBC) correlations where necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak. Flash column chromatography was carried out using Sorbsil™ C60 (40–63 mm, 230–40 mesh) silica gel. Thin layer chromatography was carried out on glass plates precoated with Merck silica gel 60 F_{254} which were visualised by quenching of UV fluorescence or by staining with 10% w/v ammonium molybdate in 2 M sulphuric acid or 1% w/v potassium permanganate in aqueous alkaline solution followed by heat, as appropriate. Melting points were recorded using a Cambridge Instruments Gallen™ III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected. Infrared spectra were recorded either as a thin film between NaCl plates or as a KBr disc (as indicated) on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Absorption maxima are reported in wavenumbers (cm^{-1}). High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer.

4.1.1. 6-Trimethylsilanyl-hexa-3,5-diyn-2-one (9). To a solution of 1,4-bis(trimethylsily)-1,3-butadiyne (5.30 g, 27.26 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added acetyl chloride (2.14 mL, 29.98 mmol) then anhydrous aluminium trichloride (3.99 g, 29.98 mmol). The reaction was stirred further 30 min at 0 °C and quenched with a mixture of 10% aqueous hydrochloric acid and ice (50 mL, 1/1). The aqueous phase was extracted with CH_2Cl_2 (3×50 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ solution (50 mL), dried over $MgSO_4$, and concentrated under vacuum to afford the crude product. Purification by flash column chromatography (SiO_2, 1:9 to 4:6, CH_2Cl_2/light petroleum) furnished in quantitative yield (4.48 g) the desired ketone **9** as an oil. ν_{max} (film/cm^{-1}) 2963, 2206, 2097, 1678, 1252, 1236, 847; ^{1}H NMR (400 MHz, $CDCl_3$) 0.21 (9H, s), 2.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) −0.7, 32.7, 73.6, 74.8, 85.7, 97.5, 183.3; HRMS found 165.0732 (MH^+), $C_9H_{13}OSi$ requires 165.0736.

4.2. General procedure for the preparation of 10–13

4.2.1. *Z*-6-Trimethylsilanyl-hexa-3,5-diyn-2-one, 2-nitrophenylhydrazone (*Z*-10) and *E*-6-trimethylsilanyl-hexa-3,5-diyn-2-one, 2-nitrophenylhydrazone (*E*-10). To a solution of 6-trimethylsilanyl-hexa-3,5-diyn-2-one **9** (1.00 g, 6.09 mmol) in MeOH (16 mL) was added, at 0 °C, 2-nitrophenyl-hydrazine (1.03 g, 6.70 mmol). The solution was stirred at 0 °C and followed by TLC. After disappearance of starting material (approximately 4 h), the mixture was evaporated under vacuum. Water (20 mL) and CH_2Cl_2 (20 mL) were added, the aqueous layer extracted with CH_2Cl_2 (2×20 mL) and the combined organic extracts were washed with saturated aqueous NaCl solution (15 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2, 1:9 to 3:7, CH_2Cl_2/light petroleum) to give, in 83% yield (1.52 g), 77% of *Z*-**10** and 23% of *E*-**10**. *Z*-**10**: mp=104 °C; ν_{max} (KBr disc/cm^{-1}) 3300, 2090, 1615, 1503, 1344, 1141, 1075; ^{1}H NMR (400 MHz, $CDCl_3$) 0.26 (9H, s), 2.21 (3H, s), 6.86 (1H, bt, *J*=8.0 Hz), 7.51 (1H, bt, *J*=8.0 Hz), 7.81 (1H, d, *J*=8.5 Hz), 8.17 (1H, d, *J*=8.5 Hz), 11.59 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) −0.5, 22.2, 67.5, 85.9, 86.8, 98.3, 116.4, 118.9, 126.0, 129.1, 131.4, 136.1, 140.9; HRMS found 300.1178 (MH^+), $C_{15}H_{18}N_3O_2Si$ requires 300.1168. *E*-**10**: mp=85 °C; ν_{max} (KBr disc/cm^{-1}) 3304, 2198, 2098, 1613, 1499, 1313, 1275, 1147, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) 0.23 (9H, s), 2.16 (3H, s), 6.92 (1H, bt, *J*=8.0 Hz), 7.55 (1H, bt, *J*=8.0 Hz), 7.89 (1H, bd, *J*=8.5 Hz), 8.16 (1H, bd, *J*=8.5 Hz), 11.02 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) −0.4, 17.3, 74.8, 75.5, 87.4, 93.4, 116.6, 119.8, 125.9, 131.9, 132.1, 136.5, 140.6; HRMS found 300.1168 (MH^+), $C_{15}H_{18}N_3O_2Si$ requires 300.1168.

4.2.2. *Z*-6-Trimethylsilanyl-hexa-3,5-diyn-2-one, 4-nitrophenylhydrazone (*Z*-11) and *E*-6-trimethylsilanyl-hexa-3,5-diyn-2-one, 4-nitrophenylhydrazone (*E*-11). Prepared as above for *E*,*Z*-**10** using **9** (798 mg, 4.86 mmol) in MeOH (13 mL) and 4-nitrophenylhydrazine (818 mg, 5.34 mmol). The crude product was purified by flash chromatography

(SiO_2, 4:6 to 7:3, CH_2Cl_2/light petroleum) to give, in 89% yield (1.30 g), 67% of *Z*-**11** and 33% of *E*-**11**. *Z*-**11**: mp=95 °C; ν_{max} (KBr disc/cm^{-1}) 3288, 2094, 1594, 1498, 1319, 1268, 1140, 1109; ^1H NMR (400 MHz, $CDCl_3$) 0.26 (9H, s), 2.17 (3H, s), 7.09 (2H, d, *J*=9.0 Hz), 8.16 (2H, d, *J*=9.0 Hz), 8.66 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) −0.5, 22.0, 67.0, 85.9, 86.7, 98.4, 112.4, 126.2, 126.6, 141.0, 148.6; HRMS found 298.1005 ($M-H^+$), $C_{15}H_{16}N_3O_2Si$ requires 298.1012. *E*-**11**: mp=153 °C; ν_{max} (film/cm^{-1}) 3306, 2196, 2097, 1595, 1502, 1325, 1260, 1150, 1108; ^1H NMR (400 MHz, $CDCl_3$) 0.22 (9H, s), 2.08 (3H, s), 7.15 (2H, d, *J*=9.0 Hz), 8.04 (1H, bs), 8.15 (2H, d, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) −0.4, 16.4, 74.4, 75.5, 87.4, 93.2, 113.0, 126.1, 129.5, 141.5, 148.4; HRMS found 298.1012 ($M-H^+$), $C_{15}H_{16}N_3O_2Si$ requires 298.1012.

4.2.3. *Z*-6-Trimethylsilanyl-hexa-3,5-diyn-2-one, phenylhydrazone (*Z*-12) and *E*-6-trimethylsilanyl-hexa-3,5-diyn-2-one, phenylhydrazone (*E*-12). Prepared as above for *E*,*Z*-**10** using **9** (291 mg, 1.77 mmol) in MeOH (5 mL) and phenylhydrazine (0.191 mL, 1.95 mmol). The crude product was purified by flash chromatography (SiO_2, 1:9 to 3:7, CH_2Cl_2/light petroleum) to give, in 74% yield (335 mg), 65% of *Z*-**12** and 35% of *E*-**12**. *Z*-**12**: mp=33 °C; ν_{max} (KBr disc/cm^{-1}) 3301, 2199, 2095, 1600, 1504, 1247, 1150, 1088; ^1H NMR (400 MHz, $CDCl_3$) 0.30 (9H, s), 2.17 (3H, s), 6.92 (1H, bt, *J*=7.5 Hz), 7.09 (2H, bd, *J*=8.5 Hz), 7.29 (2H, bdd, *J*=8.5, 7.5 Hz), 8.40 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) −0.4, 21.7, 68.4, 85.7, 86.5, 96.9, 113.2, 120.8, 121.2, 129.4, 143.7; HRMS found 255.1312 (MH^+), $C_{15}H_{19}N_2Si$ requires 255.1318. *E*-**12**: mp=45 °C; ν_{max} (KBr disc/cm^{-1}) 3301, 2195, 2095, 1601, 1504, 1252, 1150, 1073; ^1H NMR (400 MHz, $CDCl_3$) 0.23 (9H, s), 2.03 (3H, s), 6.94 (1H, bt, *J*=7.5 Hz), 7.12 (2H, bd, *J*=8.0 Hz), 7.28 (2H, bt, *J*=8.0 Hz), 7.58 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) −0.3, 15.9, 73.0, 76.8, 88.0, 91.9, 113.7, 121.6, 124.8, 129.4, 143.5; HRMS found 255.1315 (MH^+), $C_{15}H_{19}N_2Si$ requires 255.1318.

4.2.4. *Z*-6-Trimethylsilanyl-hexa-3,5-diyn-2-one, 3-nitrophenylhydrazone (*Z*-13) and *E*-6-trimethylsilanyl-hexa-3,5-diyn-2-one, 3-nitrophenylhydrazone (*E*-13). Prepared as above for *E*,*Z*-**10** using **9** (1.00 g, 6.09 mmol) and 3-nitrophenylhydrazine hydrochloride (1.27 g, 6.70 mmol) at reflux in MeOH (16 mL) for 4 h. The crude product was purified by flash chromatography (SiO_2, 2:8 to 5:5, CH_2Cl_2/light petroleum) to give, in 50% yield (915 mg), 71% of *Z*-**13** and 29% of *E*-**13**. *Z*-**13**: mp=90 °C; ν_{max} (KBr disc/cm^{-1}) 3295, 2206, 2100, 1618, 1529, 1344, 1256, 1143, 1094; ^1H NMR (400 MHz, $CDCl_3$) 0.25 (9H, s), 2.14 (3H, s), 7.31 (1H, bdt, *J*=8.0, 2.0 Hz), 7.34 (1H, bd, *J*=8.0 Hz), 7.67 (1H, bdt, *J*=8.0, 2.0 Hz), 7.88 (1H, bt, *J*=2.0 Hz), 8.49 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) −0.6, 21.8, 67.4, 86.0, 86.3, 97.8, 107.8, 115.1, 118.7, 124.3, 130.0, 144.7, 149.3; HRMS found 300.1179 (MH^+), $C_{15}H_{18}N_3O_2Si$ requires 300.1168. *E*-**13**: mp=205 °C; ν_{max} (KBr disc/cm^{-1}) 3334, 2196, 1622, 1530, 1342, 1253, 1173, 1073; ^1H NMR (400 MHz, $CDCl_3$) 0.22 (9H, s), 2.07 (3H, s), 7.40 (1H, bd, *J*=8.0 Hz), 7.43 (1H, bdt, *J*=8.0, 2.0 Hz), 7.73 (1H, bdt, *J*=8.0, 2.0 Hz), 7.81 (1H, bs), 7.92 (1H, bt, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) −0.4, 16.2, 73.8, 75.9, 87.6, 92.7, 108.4, 115.9, 119.3, 127.7, 130.2, 144.6, 149.3; HRMS found 300.1167 (MH^+), $C_{15}H_{18}N_3O_2Si$ requires 300.1168.

4.3. General procedure for the preparation of 15–17

4.3.1. *Z*-6-Trimethylsilanyl-hexa-3,5-diyn-2-one, *N*-benzoyl-4-nitrophenylhydrazone (15). To a stirred solution of *Z*-**11** (200 mg, 0.67 mmol) in CH_2Cl_2 (4 mL) was added, at 0 °C, benzoyl chloride (0.077 mL, 0.67 mmol) then $AlCl_3$ (89 mg, 0.67 mmol). The solution was stirred at 0 °C for 15 min then heating to reflux and followed by TLC. After disappearance of starting material (approximately 2 h), the reaction was quenched with 10% aqueous HCl. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2, 3:7 Et_2O/light petroleum) to give **15** (191 mg) in 71% yield. Mp=76 °C; ν_{max} (KBr disc/cm^{-1}) 2189, 2090, 1676, 1520, 1344, 1255, 1227, 1171, 1065; ^1H NMR (400 MHz, $CDCl_3$) 0.17 (9H, s), 2.20 (3H, s), 7.35–7.48 (5H, m), 7.62 (2H, m), 8.21 (2H, bd, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) −0.7, 24.2, 68.3, 85.2, 86.7, 100.1, 124.4, 126.1, 128.1, 129.6, 131.5, 134.4, 145.7, 146.9, 149.9, 169.4; HRMS found 404.1409 (MH^+), $C_{22}H_{22}N_3O_3Si$ requires 404.1430.

4.3.2. *Z*-6-Trimethylsilanyl-hexa-3,5-diyn-2-one, *N*-benzoylphenylhydrazone (16). Prepared as above for **15** using *Z*-**12** (200 mg, 0.79 mmol) in CH_2Cl_2 (5 mL), benzoyl chloride (0.091 mL, 0.79 mmol) and $AlCl_3$ (104 mg, 0.79 mmol). The crude product was purified by flash chromatography (SiO_2, 2:8 Et_2O/light petroleum) to give **16** as an oil (103 mg) in 36% yield. ν_{max} (film/cm^{-1}) 2193, 2097, 1670, 1597, 1490, 1339, 1252, 1148, 1073; ^1H NMR (400 MHz, $CDCl_3$) 0.19 (9H, s), 2.23 (3H, s), 7.20–7.40 (8H, m), 7.61 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) −0.6, 24.4, 68.7, 85.2, 86.1, 98.3, 127.6, 127.8, 128.0, 129.0, 129.4, 130.6, 135.3, 141.4, 168.9; HRMS found 359.1590 (MH^+), $C_{22}H_{23}N_2OSi$ requires 359.1580.

4.3.3. *Z*-6-Trimethylsilanyl-hexa-3,5-diyn-2-one, *N*-benzoyl-3-nitrophenylhydrazone (17). Prepared as above for **15** using *Z*-**13** (210 mg, 0.70 mmol) in CH_2Cl_2 (5 mL), benzoyl chloride (0.081 mL, 0.70 mmol) and $AlCl_3$ (94 mg, 0.70 mmol). The crude product was purified by flash chromatography (SiO_2, 3:7 Et_2O/light petroleum) to give **17** as an oil (159 mg) in 56% yield. ν_{max} (film/cm^{-1}) 2097, 1673, 1531, 1350, 1252, 1078; ^1H NMR (400 MHz, $CDCl_3$) 0.17 (9H, s), 2.17 (3H, s), 7.29–7.47 (3H, m), 7.54 (1H, m, *J*=8.0 Hz), 7.57 (1H, bdt, *J*=8.0, 2.0 Hz), 7.63 (2H, m), 8.10 (1H, bdt, *J*=8.0, 2.0 Hz), 8.15 (1H, bt, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) −0.8, 24.2, 68.3, 85.2, 86.7, 99.9, 122.2, 122.3, 128.0, 129.5, 129.7, 131.3, 132.5, 134.3, 142.3, 147.3, 148.4, 169.6; HRMS found 404.1445 (MH^+), $C_{22}H_{22}N_3O_3Si$ requires 404.1430.

4.4. General procedure for the preparation of 18–20

4.4.1. 3-Methyl-1-(4-nitro-phenyl)-4-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine (18). A solution of **15** (87 mg, 0.22 mmol) in EtOH (9 mL) and 33% aq. NH_3 (9 mL) was heated at 85 °C in a sealed tube for 4 h. The solvent was then removed under vacuum. Water (5 mL) and CH_2Cl_2 (5 mL)

were added, the aqueous layer was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2, 5:5 to 10:0 Et_2O/light petroleum) to give **18** (36 mg) in 51% yield. Mp=144 °C; ν_{max} (KBr disc/cm^{-1}) 1523, 1344, 1058; ^1H NMR (400 MHz, $CDCl_3$) 2.33 (3H, s), 7.52–7.54 (3H, m), 7.59–7.63 (2H, m), 7.65 (1H, d, *J*=6.0 Hz), 7.95 (2H, d, *J*=9.0 Hz), 8.42 (2H, d, *J*=9.0 Hz), 8.59 (1H, d, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 15.2, 104.0, 120.5, 121.7, 125.5, 128.4, 129.4, 129.4, 138.8, 143.7, 144.6, 145.5, 145.7, 147.1, 157.4; HRMS found 331.1196 (MH^+), $C_{19}H_{15}N_4O_2$ requires 331.1195.

4.4.2. 3-Methyl-1-phenyl-4-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine (19). Prepared as above for **18** using **16** (100 mg, 0.28 mmol), EtOH (10 mL) and 33% aq. NH_3 (10 mL). The crude product was purified by flash chromatography (SiO_2, 5:5 to 10:0 Et_2O/light petroleum) to give **18** (59 mg) in 74% yield. Mp=68 °C; ν_{max} (KBr disc/cm^{-1}) 1561, 1508, 1443, 1241, 1053; ^1H NMR (400 MHz, $CDCl_3$) 2.34 (3H, s), 7.38 (1H, bt, *J*=7.5 Hz), 7.47–7.56 (5H, m), 7.53 (1H, d, *J*=6.0 Hz), 7.62–7.65 (2H, m), 7.68–7.70 (2H, m), 8.48 (1H, d, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 15.1, 103.9, 119.6, 122.8, 127.2, 128.2, 129.0, 129.4, 129.7, 139.2, 139.3, 143.5, 144.5, 144.8, 156.9; HRMS found 286.1344 (MH^+), $C_{19}H_{16}N_3$ requires 286.1344.

4.4.3. 3-Methyl-1-(3-nitro-phenyl)-4-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine (20). Prepared as above for **18** using **17** (90 mg, 0.22 mmol), EtOH (9 mL) and 33% aq. NH_3 (9 mL). The crude product was purified by flash chromatography (SiO_2, 5:5 to 10:0 Et_2O/light petroleum) to give **20** (38 mg) in 52% yield. Mp=129 °C; ν_{max} (KBr disc/cm^{-1}) 1566, 1534, 1346; ^1H NMR (400 MHz, $CDCl_3$) 2.34 (3H, s), 7.51–7.55 (3H, m), 7.60–7.63 (3H, m), 7.74 (1H, t, *J*=8.0 Hz), 8.10 (1H, bdd, *J*=8.0, 2.0 Hz), 8.21 (1H, bdd, *J*=8.0, 2.0 Hz), 8.58 (1H, d, *J*=6.0 Hz), 8.62 (1H, t, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 15.2, 103.6, 117.0, 120.1, 121.3, 127.6, 128.3, 129.3, 129.4, 130.7, 138.8, 140.5, 143.6, 145.5, 146.4, 149.1, 157.3; HRMS found 331.1187 (MH^+), $C_{19}H_{15}N_4O_2$ requires 331.1195.

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References and notes

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