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Preparation of novel pyridine-fused tris-heterocycles; pyrido[4,3-*e*]pyrrolo-/pyrido[4,3-*e*]furano[2,3-*c*]pyridazines and pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole

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Diazocoupling
Azide thermal decomposition
4-(3-Furanyl)pyridin-3-amine
4-(3-Pyrrolyl)pyridin-3-amine

ABSTRACT

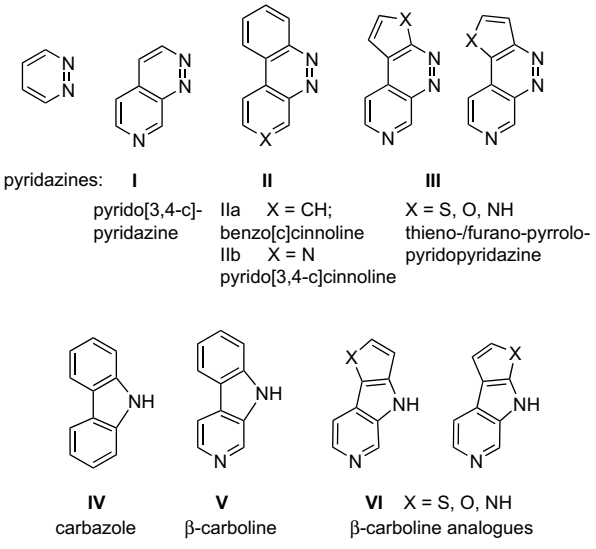
Three novel pyrido-fused tris-heterocycles have been prepared based on a Suzuki coupling and subsequent cyclisation approach. Pyrido[4,3-*e*]pyrrolo[2,3-*c*]pyridazine (**3b**, 77%) and pyrido[4,3-*e*]furano[2,3-*c*]pyridazine (**5b**, 76%) were obtained by intramolecular diazocoupling. Successful diazocoupling of furan (**5b**) is thus reported for the first time by $NOBF_4$ generation of the diazonium intermediate. *N*-TIPS-pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole (**TIPS-4b**) was synthesised by thermal cyclisation of pyridyl nitrene in considerably higher yield (71%) than previously experienced from similar cyclisations, due to TIPS-activation.

1. Introduction

We have previously[1] studied the preparation of two novel groups of thiophene-pyridine-fused tris-heterocycles, pyridazines **III** and β-carboline analogues **VI** (Scheme 1). (i) Pyridazines may, in general, exist as fused heterocycles, such as benzo[*c*]cinnolines (**IIa**), the *N*-analogues pyrido[3,4-*c*]cinnolines (**IIb**) and the pyridopyridazines (**I**). (ii) β-Carbolines (**V**), being *N*-analogues of carbazoles (**IV**), are naturally occurring alkaloids.

Both groups of compounds exhibit diverse biological activities and a number of studies of such effects have been carried out. Their ring structures are incorporated into a series of pharmaceuticals.[1] The phenyl-ring of benzo-fused compounds may be replaced by heterocyclic moieties in order to prepare a series of novel heterocyclic compounds. Such heterocycle-fused analogues may in general offer some advantages from a medicinal chemistry point of view, since the new heteroatom may provide better water solubility by offering an additional site for protonation or salt formation. The heteroatom might also enhance intermolecular interactions by formation of an additional hydrogen bond to target proteins.

Due to the biological activity, the therapeutic use and the generally interesting properties presented above, we are currently investigating the preparation of new closely related heterocyclic analogues of fused pyridazines (**III**) and β-carbolines (**VI**) (Scheme 1). There are, to the best of our knowledge, no reports on products such as **III**, **VI** or similar thieno/pyrrolo/furano compounds except



Scheme 1.

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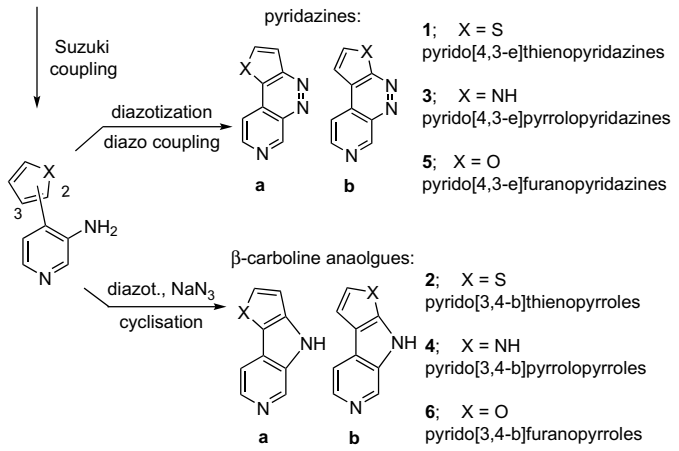
for our previous study on the thiophene-heterocycles shown in Scheme 2, the thienopyrido[3,4-*c*]pyridazines (**1a**,**b**) and the thienopyrrolo[2,3-*c*]pyridines (**2a**,**b**).[1] Thieno-compounds **1a**,**b** and **2a**,**b** (**III**, **VI**; X=S) were prepared by a Suzuki–diazotisation approach. Pyrroles and furans are also important heterocycles, being incorporated into many biologically active natural products, such as vitamin B_{12}/porphyrins/bile pigments and furocoumarins/furanterpenoids/ascorbic acid, respectively. Therefore, a subsequent study on the preparation of pyrrole and furan target compounds (**III**, **VI**; X=NH, O) has now been carried out. Our results based on the corresponding strategy, as shown in Scheme 2, are presented below.



Scheme 2.

2. Results and discussion

2.1. Target compounds

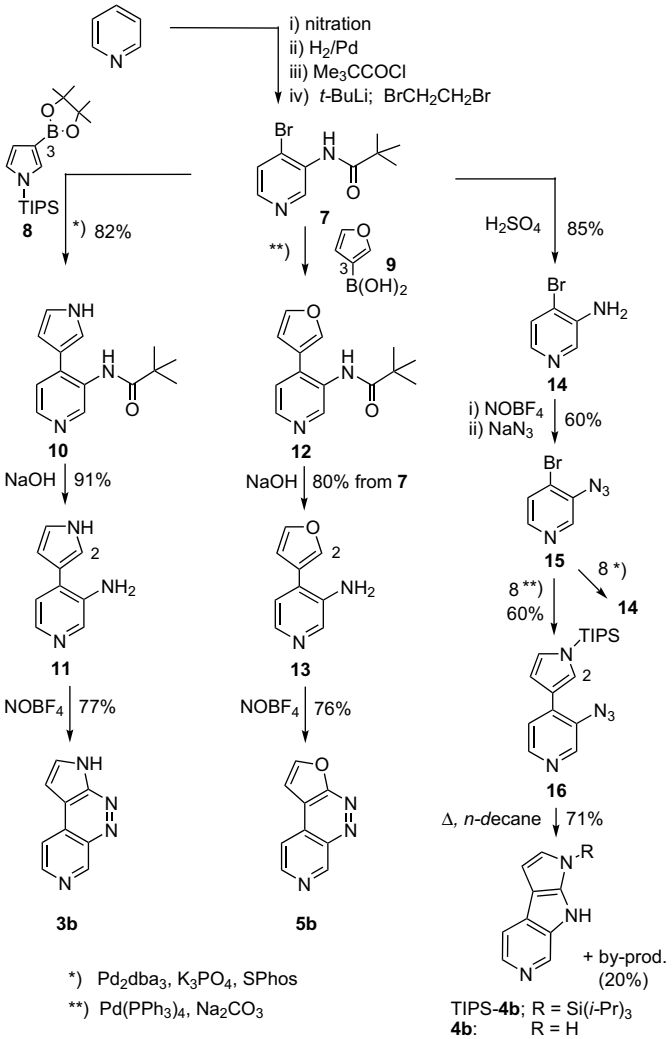
Based on our results with the former preparation[1] of the thieno-heterocycles **1a**,**b** and **2a**,**b**, some observations were made.

All the **b** products shown in Scheme 2, would be formed by ring closure involving the highly reactive 2-position of the thiophene/pyrrole/furan rings. We have previously demonstrated for the thiophene products that lower yields were obtained of **1a**/**2a** compared to **1b**/**2b**, due to the lower reactivity of the 3-position of the thiophene ring. The strongly acidic conditions required for the cyclisation to give thieno product **1a**,[1] would not be suitable for the preparation of **3a** and **5a**, since furans and pyrroles are unstable by such conditions. Consequently, the synthetic strategy presented in Scheme 2 is less appropriate for regioisomers **3a**–**6a**, as these products would be expected to be formed in lower yields than the corresponding **3b**–**6b**. Therefore, the present work was aimed at the pyrrole and furan **b** products (**3b**–**6b**).

The Suzuki–nitrene approach includes a thermal decomposition of an arylazide for the final pyrrole cyclisation by nitrene CH insertion. The method has been used with success for the preparation of carbazoles (**IV**, Scheme 1). However, only low yields (15–30%) of β-carboline **V**,[2] and thieno-analogues **VI** (X=S) have been obtained by thermal decomposition of the respective pyridyl azide precursors, as discussed elsewhere for **2a**,**b** (Scheme 2).[1] This may be caused by the electron-deficient character of the pyridine moiety. The method would, therefore, be expected to be less successful for pyrrolo and furano β-carboline analogues **4**,**6** as well. Thus, the present work mainly focussed on (i) the new pyridazine products **3**,**5**. However, the preparation of (ii) pyrrolo-β-carboline analogue **VI** (X=NH) has been studied in the present work (**4b**), and an activation strategy was investigated to examine whether an *N*-triisopropylsilyl (TIPS) group attached to the pyrrole would compensate for the electron-deficient character of the pyridine ring. Consequently, the target compounds for this study were **3b**, **4b** and **5b**.

2.2. Pyridazines

The synthetic pathways for all the target products were based on the Suzuki coupling for the preparation of the essential pyrrolo/furano-pyridine intermediates, as shown in Scheme 3. In Suzuki coupling reactions, (i) electron-deficient aryl halides and (ii) electron-rich boronic acids are the substrates of choice, since those compounds are more reactive than the contrary in, respectively, (i) the oxidative addition and (ii) the transmetallation steps. The diaryl-coupling products **10** and **12**, key intermediates in order to prepare the pyridazine products **3b** and **5b**, were therefore prepared from 4-bromopyridine **7**[1] and the pyrrolo/furano boronic reactants **8** and **9**.



Scheme 3.

The appropriate 3-pyrrolylboronate reagent **8** can be made by borylation. In general, C-substitution of pyrrole most readily takes place at the 2-position and direct borylation would exclusively produce 2-borylated products. However, selective borylation at the 3-position of pyrrole has been reported,[5,6] providing a valuable precursor for Suzuki cross-coupling reactions. Coupling at C–H bonds located *ortho* to bulky substituents is slow due to steric hindrance. This effect allows a regioselective synthesis of

3-borylpyrrole, since 3-substitution becomes favoured using *N*-substituted substrates. Sterically hindered *N*-triisopropylsilyl (TIPS) derivatives provide 3-boryl isomers selectively. The TIPS group can eventually be removed by treatment with TBAF or TFA to afford isomerically pure 3-borylpyrrole.[5,6]

N-TIPS-pyrrole was quantitatively obtained from pyrrole and TIPS-Cl without further purification. Regioselective C–H coupling of TIPS-pyrrole with bis(pinacolato)diboron (pin_2B_2) was carried out in octane at 80 °C in the presence of 1/2[IrCl(COD)]-dtbpy catalyst (3 mol %) and afforded the 3-borylated pyrrole reagent **8** (77%).

The pyrrole–pyridine coupling product **10** was prepared (82%) by Suzuki coupling of bromide **7** and the *N*-TIPS-pinacolatopyrroloboronate ester **8**, using $K_3PO_4 \cdot 3H_2O$ and the Pd_2dba_3–SPhos catalytic system (SPhos: 2-dicyclohexylphosphino-2′,6′-dimethoxyphenyl).[3] An additional desilylation step was not required, as the *N*-TIPS group was cleaved in the coupling reaction to give the deprotected pyrrole product **10**. The coupling reaction was, however, not successful using the PEPPSI-IPr precatalyst protocol based on the diisopropylphenylimidazoliumpyridine *N*-heterocyclic carbene system.[4] Several advantages have been reported using Pd_2dba_3–SPhos catalysis for pyridines and pyrroles. Additionally, pyrrolylboronate esters are preferred compared to boronic acid in such Suzuki coupling reactions.[3]

Suzuki coupling of 4-bromopyridine **7** and furylboronic acid **9** afforded nearly quantitative yield of the furylpyridine coupling product **12**.

Alkaline hydrolysis was chosen for the conversion of pivalamides **10** and **12** to the unprotected aminopyridines **11** (91%) and **13** (80% from **7**). As expected, acidic conditions (25% H_2SO_4), previously used[1] for the hydrolysis of corresponding thiophene compounds, were not successful. A number of unidentified products were obtained by acidic hydrolysis of **10**, and only 36% of product **13** was afforded from amide **12**. It is well known that protonation of pyrroles and furans takes place in acidic media and often leads to hydrolysis, cleavage or rapid polymerisation/oligomerisation of the cations.[7]

The intramolecular diazocoupling to generate **3b** and **5b** is highly favoured, as electrophilic substitution at the most reactive 2-position of pyrrole is involved. Due to the instability of furan and pyrrole in acidic media, traditional $NaNO_2/H_2SO_4$ also had to be avoided for the diazotisation of amines **11** and **13**. Exclusive formation of pyrrolopyridazine **3b** (77%) and furanopyridazine **5b** (76%) was obtained by intramolecular diazocoupling of the diazonium intermediate generated by $NOBF_4$ from aminopyridines **11** and **13**, respectively.

To the best of our knowledge, this is the first reported successful diazocoupling of furans. Furan is less electron-rich and hence less reactive than pyrroles towards electrophiles. Conventional electrophilic substitution may, in general, be difficult to achieve for furans. While pyrroles readily undergo diazocoupling, azo-coupling reactions have been reported to fail with furan, due to its lower reactivity compared with pyrrole. Furanophenyl azo compounds have, therefore, been made by oxidation of 2-furanone hydrazones,[8] or by *ipso* arene diazonium substitution of 2-substituted furans.[9] Only the activated benzo-fused 3-(acetylamino)-5-methoxybenzofuran has been reported to undergo azo-coupling.[10]

The dipole moment of pyrrole is directed from nitrogen to carbon, opposite to furan and thiophene. Due to the higher electron density of pyrrole compared with thiophene, expected lower pyrrole NMR shift values ($\Delta\delta_C$ 10–20 ppm and $\Delta\delta_H$ 0.5–0.7 ppm) were observed for all the pyrrole products (**10**,**11** and **3b**) compared to corresponding thiophene compounds previously prepared.[1]

2.3. β-Carboline analogue

In the synthesis of β-carboline analogue **TIPS-4b**, the azide functionality was introduced before the Suzuki cross-coupling. A possible direct preparation of azide **16** from amino precursor **11** by diazotisation and azide substitution[1] would only give the azo-coupling pyridazine product **3b**, due to the highly reactive pyrrole 2-position. However, the reaction of pinacolatopyrroloboronate ester **8** and 3-azido-4-bromopyridine **15**,[1] using $K_3PO_4 \cdot 3H_2O$ and the Pd_2dba_3–SPhos catalytic system described above, was unsuccessful for the preparation of coupling product **16**. Reduction of the azide group took place and only the 3-aminopyridine compound **14** was isolated. On the other hand, the coupling product **16** was readily formed (60%) by $Pd(PPh_3)_4$ catalysis, using Na_2CO_3 as a base. In contrast to the formation of **10** above, the *N*-TIPS group was not cleaved.

The cyclisation by thermal decomposition of azidopyridine **16** via the nitrene afforded **TIPS-4b** in 71% yield. The significantly higher yield obtained for **TIPS-4b** relative to the previously reported β-carboline[2] and thieno[1] products (15–30%), indicates that the *N*-TIPS group in substrate **16** offers an activating effect, which may compensate for the electron-deficient character of the pyridine ring. Small amounts of the TIPS group were cleaved in the cyclisation step in some of the experiments to afford approximately 10% of the unprotected product **4b**. Preparative desilylation of **TIPS-4b** was carried out by TBAF[5,6] cleavage. Full conversion into the deprotected product **4b** was directly obtained, as shown by NMR spectroscopy.

The thermal decomposition of azide **16** also afforded an additional by-product (20%). This new compound was similar to a by-product previously isolated from the formation of the corresponding thieno product **2b** (Scheme 2). The nature of these compounds is being investigated.[11]

3. Conclusion

Three novel pyrido-fused tris-heterocycles have been prepared by Suzuki coupling and subsequent cyclisations. Pyrido[4,3-*e*]pyrrolo[2,3-*c*]pyridazine (**4b**, 77%) and pyrido[4,3-*e*]furano[2,3-*c*]pyridazine (**5b**, 76%) were obtained by intramolecular diazocoupling. Successful diazocoupling of furans (**5b**) is thus reported for the first time by $NOBF_4$ generation of the diazonium intermediate. Due to activation by an *N*-TIPS group, thermal cyclisation of pyridyl nitrene afforded the β-carboline analogues *N*-TIPS-pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole (**TIPS-4b**) in considerably higher yield (71%) than previously experienced from similar cyclisations.[1,2]

4. Experimental

4.1. General

Chemicals: Pyrrole, TIPS-Cl, *n*-BuLi, pin_2B_2, 2-(4,4′-di-*tert*-butyl-2,2′-bipyridine) (dtbpy), [IrCl(COD)], Pd_2dba_3, SPhos, 3-furanboronic acid (Sigma–Aldrich); $NOBF_4$, $Pd(PPh_3)_4$ (Fluka); $K_3PO_4 \cdot 3H_2O$ (Merck). Solvents: pro analysi quality. $^1H/^{13}C$ NMR: Bruker Avance DPX 300 and 400 spectrometers, chemical shifts are reported in parts per million downfield from TMS. *J* values are given in hertz. EIMS: Finnigan MAT 95 XL (70 eV). ESI-MS accurate mass determinations were performed on an Agilent 6520 QTOF MS instrument equipped with a dual electrospray ion source for continuous injection of mass axis calibrants through the second nebuliser needle. Samples were injected into the MS using an Agilent 1200 series HPLC and analysis was performed as a flow injection analysis without any chromatographic step. IR: Nicolet 20SXC FT-IR spectrophotometer. All melting points are uncorrected, measured on a Stuart apparatus. Elemental analyses were done by the Laborator Beller/Matties, Göttingen, Germany. Flash chromatography: Silica (SDS, 60 Å, 40–63 μm). Organic solvent extracts were dried with anhydrous sodium sulfate. Compounds **7**, **14** and **15** were prepared according to the literature.[1] Compounds

3b, **TIPS-4b**, **5b** and **12** were synthesised by methods similar to previously described procedures for preparation of the corresponding thiophene compounds.[1] All reactions were conducted under nitrogen atmosphere unless otherwise noted.

4.2. Pyrido[4,3-*e*]pyrrolo[2,3-*c*]pyridazine (3b)

The title compound was prepared by diazocoupling[1] from amine **11** (58.0 mg, 0.64 mmol) in dry MeCN (7 mL) and $NOBF_4$ (110 mg, 0.942 mmol) in dry MeCN (5 mL). Product **3b** was obtained as an off-white solid (47.0 mg, 77%) after flash chromatography on a Al_2O_3 column (gradient; 0–5% MeOH in CH_2Cl_2), pure by NMR. R_f 0.38 (5% MeOH in CH_2Cl_2, Al_2O_3-TLC); mp >232 °C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ_H 13.36 (1H, br, NH), 9.81 (1H, s, py-H2), 8.77 (1H, d, *J* 6.0, py-H6), 8.32 (1H, d, *J* 6.0, py-H5), 8.09 (1H, t, *J* 2.8, pyrrole-H5), 7.32 (1H, dd, *J* 2.8, 1.6, pyrrole-H4); ^{13}C NMR (100 MHz, DMSO): δ_C 154.1 (py-C2), 148.9 (pyrrole-C2), 145.8 (py-C6), 139.9 (py-C3), 130.9 (pyrrole-C5), 124.8 (py-C4), 116.6 (py-C5), 112.5 (pyrrole-C3), 100.4 (pyrrole-C4); NMR assignments are based on HSQC and HMBC experiments; IR (KBr) ν_{max} 3265br, 3069m, 3010m, 1651s, 1434m, 1245m, 1113s, 813s, 767s cm^{-1}; MS *m*/*z* (%) 170 (M^+, 100), 115 (84), 88 (20); EI-HRMS calcd for $C_9H_6N_4$: 170.0593; obsd: 170.0587.

4.3. Pyrido[3,4-*b*]-(1-triisopropylsilyl-1*H*-pyrrolo)[3,2-*d*]pyrrole (TIPS-4b)

The title compound was prepared by thermal decomposition[1] of azide **16** (107 mg, 0.313 mmol) in dry *n*-decane (60 mL). The reaction mixture was heated to reflux and kept stirring for 40 min, cooled to room temperature and decane was distilled off. Flash chromatography (gradient; 1–10% MeOH/CH_2Cl_2) afforded **TIPS-4b** as an off-white solid (70 mg, 71%), pure by NMR. R_f 0.11 (10% MeOH in CH_2Cl_2); mp >95 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.71 (1H, s, py-H2), 8.26 (1H, d, *J* 5.6, py-H6), 7.57 (1H, d, *J* 5.6, py-H5), 6.76 (1H, d, *J* 3.2, pyrrole-H5), 6.64 (1H, d, *J* 3.2, pyrrole-H4), 1.63 (3H, sep, *J* 7.6, C*H*(CH_3)$_2$), 1.18 (18H, d, *J* 7.6, CH(C*H*$_3$)$_2$); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.91 (1H, br s, NH), 8.63 (1H, s, py-H2), 8.09 (1H, d, *J* 5.6, py-H6), 7.51 (1H, d, *J* 5.6, py-H5), 6.83 (1H, d, *J* 3.2, pyrrole-H5), 6.58 (1H, d, *J* 3.2, pyrrole-H4), 1.76 (3H, sep, *J* 7.6, C*H*(CH_3)$_2$), 1.10 (18H, d, *J* 7.6, CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 146.5 (pyrrole-C2), 137.7 (py-C6), 137.5 (py-C3), 132.4 (py-C2), 126.7 (py-C4), 125.1 (pyrrole-C5), 113.2 (py-C5), 109.9 (pyrrole-C3), 102.4 (pyrrole-C4), 18.0 (TIPS-*C*H$_3$), 12.2 (TIPS-*C*H); NMR assignments are based on HMBC experiments; IR (KBr) ν_{max} 3379w br, 3105m br, 3067m, 2947s, 2867s, 1609m, 1524m, 1095s, 883m, 707s cm^{-1}; ESI-HRMS: calcd for $[M+H]^+$ $C_{18}H_{28}N_3Si$: 314.2047; obsd: 314.2050.

4.4. Pyrido[3,4-*b*]-(pyrrolo)[3,2-*d*]pyrrole (4b)

To an NMR sample of **TIPS-4b** (approx. 4 mg in 1 mL $CDCl_3$) was added TBAF (excess). Quantitative conversion to **4b** took place within an hour, as shown by ^{1}H NMR spectroscopy. 1,2,4,5-Tetrachlorobenzene was used as internal standard. Compound **4b**: R_f 0.15 (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.75 (1H, s, py-H2), 8.12 (1H, d, *J* 5.6, py-H6), 7.44 (1H, d, *J* 5.6, py-H5), 6.81 (1H, d, *J* 3.2, pyrrole-H5), 6.35 (1H, d, *J* 3.2, pyrrole-H4); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.26 (2H, br s, 2×NH), 8.55 (1H, s, py-H2), 8.04 (1H, d, *J* 5.2, py-H6), 7.45 (1H, d, *J* 5.2, py-H5), 6.75 (1H, d, *J* 3.2, pyrrole-H5), 6.35 (1H, d, *J* 3.2, pyrrole-H4); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 142.7 (pyrrole-C2), 137.7 (py-C6), 137.1 (py-C3), 132.5 (py-C2), 127.1 (py-C4), 119.1 (pyrrole-C5), 113.2 (py-C5), 107.1 (pyrrole-C3), 99.7 (pyrrole-C4); NMR assignments are based on HSQC and HMBC experiments; ESI-HRMS calcd for $[M+H]^+$ $C_9H_8N_3$: 158.0713; obsd: 158.0712.

4.5. Pyrido[4,3-*e*]furano[2,3-*c*]pyridazine (5b)

The title compound was prepared by diazocoupling[1] from amine **13** (32.4 mg, 0.202 mmol) in dry MeCN (5 ml) and $NOBF_4$ (117 mg, 1.00 mmol) in dry MeCN (5 mL). Purification by flash chromatography (10% MeOH/CH_2Cl_2) afforded pyridazine **5b** (26.3 mg, 76%) as a white solid, pure by NMR. R_f 0.45 (10% MeOH/CH_2Cl_2); mp >200 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 10.09 (1H, d, *J* 0.9, py-H2), 8.87 (1H, d, *J* 6.0, py-H6), 8.17 (1H, d, *J* 2.4, furan-H5), 7.99 (1H, dd, *J* 6.0, 0.9, py-H5), 7.40 (1H, d, *J* 2.4, furan-H4); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 162.9 (furan-C2), 156.3 (py-C2), 148.8 (furan-C5), 147.2 (py-C6), 143.0 (py-C3), 126.1 (py-C4), 116.2 (py-C5), 115.3 (furan-C3), 105.4 (furan-C4); NMR assignments are based on HMBC experiments; IR (KBr) ν_{max} 3098w, 1619s, 1502s, 1401m, 1225m, 1113m, 1048m, 869m, 844m, 776s cm^{-1}; MS *m*/*z* (%)171 (M^+, 17%), 170 (100), 114 (40), 88 (47); EI-HRMS calcd for $C_9H_5N_3O$: 171.0433; obsd: 171.0436. Anal. Calcd for $C_9H_5N_3O$: C, 63.16; H, 2.94; N, 24.55. Found: C, 62.72; H, 2.54; N, 24.23.

4.6. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (8)[5,6]

The title compound was prepared according to the literature[5,6] from pyrrole via TIPS-pyrrole (1-(triisopropylsilyl)-1*H*-pyrrole);

(i) pyrrole (1.94 mL, 28 mmol), dry THF (45 mL), *n*-BuLi (18.1 mL, 30.8 mmol) and TIPS-Cl (5.7 mL, 26.9 mmol) afforded TIPS-pyrrole as a yellow oil (5.99 g, 99%) after extraction, pure by NMR;[12] R_f 0.95 (EtOAc/pentane 2:1), used without further purification;

(ii) pin_2B_2 (1.24 g, 4.88 mmol), $[IrCl(COD)]_2$ (69.5 mg, 0.103 mmol), dtbpy (58.8 mg, 0.219 mmol) and TIPS-pyrrole (6.41 g, 28.7 mmol) in octane (20 mL), gave a black crude product after stirring for 48 h at 80 °C and subsequent evaporation of the solvent. Excess TIPS-pyrrole was removed by distillation (4–6 mbar, approx. 80 °C) and flash chromatography of the residue (EtOAc/pentane 1:5) afforded product **8** as a white solid (2.61 g, 77% from pin_2B_2), pure by NMR. R_f 0.85 (EtOAc/pentane 1:5); mp 70–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.23 (1H, dd, *J* 1.4, 2.6), 6.81 (1H, dd, *J* 2.6, 2.1), 6.62 (1H, dd, *J* 2.6, 1.4), 1.46 (3H, sep, *J* 7.4), 1.32 (12H, s), 1.09 (18H, d, *J* 7.4).

4.7. *N*-[4-(1*H*-Pyrrol-3-yl)pyridin-3-yl]pivalamide (10)

A solution of **7** (1.04 g, 4.04 mmol), pyrrole **8** (1.70 g, 4.87 mmol), $K_3PO_4 \cdot 3H_2O$ (2.16 g, 8.11 mmol), Pd_2dba_3 (109 mg, 0.119 mmol), SPhos (97 mg, 0.236 mmol) in *n*-butanol (30 mL) and distilled water (12 mL) was heated to 100 °C, stirred overnight and cooled to room temperature.[3] The solution was concentrated and water (20 mL) was added. After extraction with ether (3×20 mL), evaporation of the solvent and flash chromatography (gradient; 1–5% MeOH/CH_2Cl_2) product **10** was obtained as a white solid (804 mg, 82%), pure by NMR spectroscopy. R_f 0.20 (5% MeOH/CH_2Cl_2); mp >135 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.54 (s, 1H, py-H2), 9.05 (br s, 1H, NH), 8.32 (d, 1H, *J* 5.2, py-H6), 7.92 (1H, br s, NH), 7.22 (d, 1H, *J* 5.2, py-H5), 6.99 (m, 2H, pyrrole-H2/H5), 6.39 (dd, 1H, *J* 4.2, 2.8, pyrrole-H4), 1.27 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 176.7 (C=O), 145.1 (py-C6), 143.2 (py-C2), 134.4 (py-C4), 132.3 (py-C3), 123.9 (py-C5), 120.1 (pyrrole-C2), 118.6 (pyrrole-C3), 117.6 (pyrrole-C5), 108.5 (pyrrole-C4), 40.0 (*C*Me$_3$), 27.8 (C(*C*H$_3$)$_3$); NMR assignments are based on HSQC and HMBC experiments; IR (KBr) ν_{max} 3318s br, 2966w, 1653s, 1419m, 1307s, 1034m, 789m cm^{-1}; MS *m*/*z* (%) 243 (M^+, 51), 159 (35), 131 (18), 104 (8); EI-HRMS calcd for $C_{14}H_{17}N_3O$: 243.1373; obsd: 243.1372.

4.8. 4-(1*H*-3-Pyrrolyl)pyridin-3-amine (11)

Pivalamide **10** (475 mg, 1.95 mmol) was dissolved in NaOH (8 M, 50 mL) and ethanol (50 mL) and heated at reflux for 26 h. The mixture was cooled to room temperature and the solvent was evaporated. Water (50 mL) was added and the product was extracted into CH_2Cl_2 (5×30 mL). Product **11** was obtained as a slightly yellow solid (283 mg, 91%), pure by NMR, after flash chromatography (5% MeOH in CH_2Cl_2). R_f 0.11 (5% MeOH in CH_2Cl_2); mp 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.08 (1H, br s, NH), 8.10 (1H, s, py-H2), 8.00 (1H, d, *J* 4.2, py-H6), 7.16 (2H, m, py-H5/pyrrole-H5), 6.92 (1H, dd, *J* 4.4, 2.7, pyrrole-H2), 6.52 (1H, dd, *J* 4.4, 2.7, pyrrole-H4), 3.93 (2H, br, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 140.3 (py-C6), 139.7 (py-C3), 138.0 (py-C2), 129.1 (py-C4), 123.0 (py-C5), 119.7 (pyrrole-C3), 119.2 (pyrrole-C2), 117.0 (pyrrole-C5), 108.1 (pyrrole-C4); NMR assignments are based on HSQC and HMBC experiments; IR (KBr) ν_{max} 3389m, 3322w, 3159w, 1586s, 1324s, 1085s, 1037s, 671s cm^{-1}; MS *m*/*z* 159 (M^+, 80%), 158 (44), 132 (21), 104, (18); EI-HRMS calcd for $C_9H_9N_3$: 159.0797; obsd: 159.0791.

4.9. *N*-(4-(Furan-3-yl)pyridin-3-yl)pivalamide (12)

The title compound was prepared by Suzuki coupling[1] from **7** (1.07, 4.16 mmol) and **9** (557 mg, 4.98 mmol) affording 1.10 g of a solid (containing small amounts of aromatic impurities, as shown by NMR spectroscopy) after flash chromatography (4% Et_3N in EtOAc/pentane (2:1)). This crude product was used directly in the next step for the preparation of **13** below. A pure sample prepared for analysis had R_f 0.30 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.36 (1H, s, py-H2), 8.36 (1H, d, *J* 5.1, py-H6), 7.67 (1H, dd, *J* 1.4, 0.9, furan-H2), 7.62 (1H, dd, *J* 1.8, 1.4, furan-H5), 7.49 (1H, br s, NH), 7.20 (1H, d, *J* 5.1, py-H5), 6.59 (1H, dd, *J* 1.8, 0.9, furan-H4), 1.24 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 176.7 (C=O), 145.7 (py-C6), 144.7 (furan-C5), 144.5 (py-C2), 141.1 (furan-C2), 132.1 (py-C3), 131.5 (py-C4), 123.7 (py-C5), 120.8 (furan-C3), 110.4 (furan-C4), 40.0 (CMe_3), 27.7 ($C(CH_3)_3$); NMR assignments are based on HSQC and HMBC experiments; IR (film) ν_{max} 3287s br, 2967s, 1660s, 1602m, 1503s, 1414m, 1301m, 1161s, 1059w, 1017m, 874s, 796m cm^{-1}; MS *m*/*z* (%) 244 (M^+, 44), 160 (10), 131 (21), 91 (100); EI-HRMS calcd for $C_{14}H_{16}N_2O_2$: 244.1209; obsd: 244.1212.

4.10. 4-(Furan-3-yl)pyridin-3-amine (13)

The crude product (1.10 g) obtained from the preparation of **12** above, was dissolved in NaOH (50 mL, 8 M) and EtOH (60 mL, 96%). The solution was heated to reflux and kept stirring for 70 h. The reaction was allowed to cool to room temperature and concentrated under reduced pressure. Water (100 mL) and CH_2Cl_2 (50 mL) were added, the aqueous phase was extracted with CH_2Cl_2 (3×30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated. The brown, oily crude product was purified by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) to give amine **13** (533 mg, 80% from **7**) as a white solid, pure by NMR spectroscopy. R_f 0.24 (4% Et_3N in EtOAc/pentane (2:1)); mp 70–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.16 (1H, s, py-H2), 8.04 (1H, d, *J* 5.0, py-H6), 7.79 (1H, dd, *J* 1.6, 1.0, furan-H2), 7.56 (1H, dd, *J* 2.0, 1.6, furan-H5), 7.10 (1H, d, *J* 5.0, py-H5), 6.69 (1H, dd, *J* 2.0, 1.0, furan-H4), 3.85 (2H, br s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 144.0 (furan-C5), 140.8 (furan-C2), 140.5 (py-C6), 140.1 (py-C3), 138.6 (py-C2), 125.3 (py-C4), 123.1 (py-C5), 121.8 (furan-C3), 110.1 (furan-C4); NMR assignments are based on HSQC and HMBC experiments; IR (KBr) ν_{max} 3321s br, 3182s br, 1625m, 1423s, 1322m, 1161s, 1055w, 1017m, 874s cm^{-1}; MS *m*/*z* (%) 160 (M^+, 100%), 131 (99), 103 (13), 76 (11); EI-HRMS calcd for $C_9H_8N_2O$: 160.0637; obsd: 160.0638. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.09; H, 5.06; N, 16.81.

4.11. 3-Azido-4-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)-pyridine (16)

The title compound was prepared by Suzuki coupling from azide **5** (290 mg, 1.46 mmol), $Pd(PPh_3)_4$ (84.0 mg, 5.0 mol %) in toluene (20 mL), Na_2CO_3 (10 mL, 2 M) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (**8**) (610 mg, 1.75 mol) in MeOH (5 mL). The crude product was purified by flash chromatography (gradient; 0–5% CH_2Cl_2 in MeOH), to give product **16** as a brown oil (299 mg, 60%), pure by NMR. R_f 0.31 (2% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.47 (1H, s, py-H2), 8.28 (1H, d, *J* 5.4, py-H6), 7.51 (1H, dd, *J* 2.0, 1.6, pyrrole-H2), 7.41 (1H, d, *J* 5.4, py-H5), 6.82 (1H, dd, *J* 3.2, 2.0, pyrrole-H5), 6.74 (1H, dd, *J* 3.2, 1.6, pyrrole-H4), 1.48 (3H, sep, *J* 7.4, TIPS-C*H*), 1.13 (18H, d, *J* 7.4, TIPS-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 146.0 (py-C6), 141.5 (py-C2), 134.7 (py-C4), 132.2 (py-C3), 126.3 (pyrrole-C2), 125.1 (pyrrole-C5), 121.8 (py-C5), 120.2 (pyrrole-C3), 110.2 (pyrrole-C4), 17.9 (TIPS-CH_3), 11.8 (TIPS-*C*H); NMR assignments are based on HSQC and HMBC experiments; IR (film) ν_{max} 2946m, 2868m, 2108s, 1589s, 1308s, 1119s, 884s, 803s, 703s, 662s cm^{-1}; MS *m*/*z* (%) 341 (M^+, 8), 313 (94), 271 (68), 270 (100), 242 (23), 228 (95), 200 (65), 186 (63), 185 (18), 157 (15), 129 (10), 115 (33), 107 (13); ESI-HRMS calcd for $[M+H]^+$ $C_{18}H_{28}N_5Si$: 342.2108; obsd: 342.2104.

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