Tetrahedron 64 (2008) 7626–7632

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Preparation of new pyrido[3,4-*b*]thienopyrroles and pyrido[4,3-*e*]-thienopyridazines

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ARTICLE INFO

Article history:
Received 22 February 2008
Received in revised form 29 April 2008
Accepted 15 May 2008
Available online 18 May 2008

Keywords:
Pyrido[3,4-*b*]thieno[2,3-*d*]pyrrole
Pyrido[3,4-*b*]thieno[3,2-*d*]pyrrole
Pyrido[4,3-*e*]thieno[2,3-*c*]pyridazine
Pyrido[4,3-*e*]thieno[3,2-*c*]pyridazine
Suzuki cross coupling
Diazotization
Diazocoupling
Azide
Nitrene
Thermal decomposition

ABSTRACT

Two new types of pyrido-fused tris-heterocycles (**1a**,**b** and **2a**,**b**) have been prepared from 3-aminopyridine in five/six steps. A synthetic strategy for the preparation of the novel pyrido[3,4-*b*]thieno[2,3- and 3,2-*d*]pyrroles (**1a**,**b**) and pyrido[4,3-*e*]thieno[2,3- and 3,2-*c*]pyridazines (**2a**,**b**) has been studied. The Suzuki cross coupling of the appropriate 2- and 3-thienoboronic acids (**3**,**4**) and 4-bromo-3-pyridylpivaloylamide (**9**) afforded the biaryl coupling products (**10**,**11**) in high yields (85%). Diazotization of the hydrolysed (2-thienyl)-coupling product (**12**) and azide substitution gave the 3-azido-4-(2-thienyl)pyridine intermediate (72%, **14**). 3-Azido-4-(3-thienyl)pyridine (**15**) was prepared by exchanging the previous order of reactions. The desired β-carboline thiophene analogues (**1a**,**b**) were obtained via the nitrene by thermal decomposition of the azido precursors (**14**,**15**). By optimising conditions for intramolecular diazocoupling, the corresponding pyridazine products (72–83%, **2a**,**b**) were afforded.

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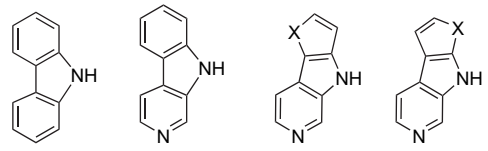
1. Introduction

1.1. Background

β-Carbolines (**II**, Scheme 1) are naturally occurring alkaloids that exhibit diverse biological and pharmacological activities. The β-carboline ring structure is thus incorporated into many natural products and pharmaceuticals. Numerous studies of natural occurrence, identification and isolation of β-carboline derivatives have been reported and studies of properties, biological and pharmacological effects of β-carboline alkaloids and derivatives have been carried out for several decades. Some of the most recent reports include studies of the antitumor/cytotoxic,[1] anticancer,[2] antimalaria,[3] antioxidant,[4] free radical scavenging and antithrombotic activities.[5] β-Carbolines have also been studied because of the neuroprotection[6] and photosensitiser abilities[7] as well as for treatment of ophthalmic/eye disorders.[8] β-Carbolines are *N*-analogues of carbazoles (**I**, Scheme 1), which are incorporated into a number of pharmaceutical agents as well. Both the Carvedilol[9] and the Carazolol[10] β-blockers are based on the carbazole tricyclic skeleton. By replacing the phenyl-ring of **II** by five-ring heterocycles, the novel thieno-, furano- or pyrrolo-β-carboline analogues (**III**, Scheme 1) would be constructed.



I carbazole **II** β-carboline **III** X = S, O, NH β-carboline analogues

Scheme 1.

Pyridazine (Scheme 2) compounds have also been shown to be biologically active and the pyridazine moiety is incorporated in a series of pharmaceuticals. Cinnolines (**IV**, Scheme 2)[11] are important intermediates in the preparation of the antidepressant Binodaline[12] and the antibiotic Cinoxacin.[13] A series of substituted benzo[*c*]cinnolines (**IVa**) have herbicidal activity,[14] while others are found to be mutagenic substances,[15] being identified as organic aza-heterocyclic pollutants.[16] The corresponding *N*-analogues pyrido[3,4-*c*]cinnoline (**IVb**) ring structure has also been reported.[17] Pyridopyridazines (**V**) have been studied for preventing and

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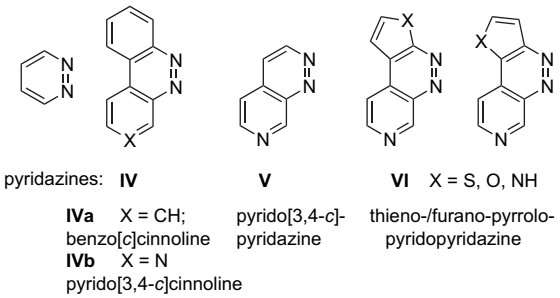
doi:10.1016/j.tet.2008.05.062

treating atherosclerosis[18] and have been used for the preparation of antiviral agents.[19] Structure **VI** represents potential five-ring-fused heterocyclic analogues.

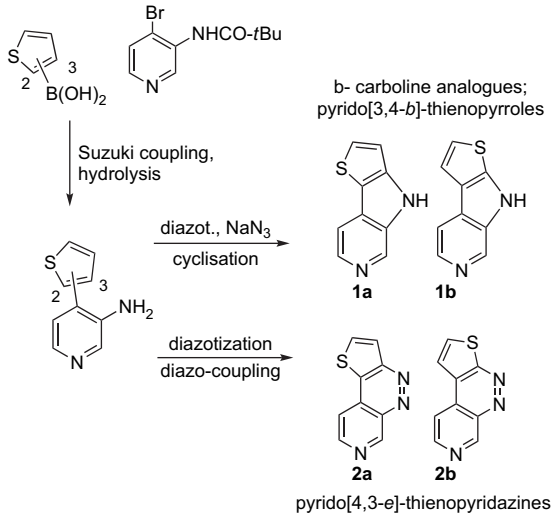


Scheme 2.

1.2. Objective

Referring to the biological activity, the therapeutic use and the generally interesting properties discussed above, it would be of interest to prepare new closely related heterocyclic analogues of both *β-carbolines* (**III**, Scheme 1) and fused *pyridazines* (**VI**, Scheme 2). Heterocycle-fused analogues of benzo-fused heterocycles 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 or it might enhance intermolecular interactions by formation of an additional hydrogen bond to target proteins. Many drugs are derived from thiophene. Bioisosteric effects have been observed, since the pharmacological effect of the thienyl moiety often is similar to phenyl or benzyl.[25,26]

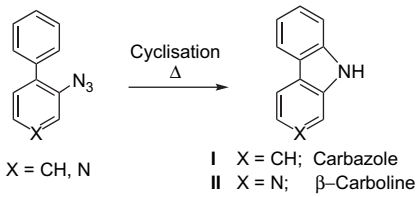
The thienyl-fused heterocycles shown in Scheme 3, the pyrido[3,4-*b*]thienopyrroles (**1a**,**b**) and the pyrido[4,3-*e*]thienopyridazines (**2a**,**b**), would therefore be promising target compounds, due to their potential biological properties. We wanted to study the preparation of these heterocyclic compounds.



Scheme 3.

1.3. Synthetic strategy

The synthetic preparation of β-carbolines has previously been based on different strategies. The most frequently used methods are, respectively, the reductive cyclisation of 3-nitro-4-phenylpyridines with $P(EtO)_3$[20] and the direct cyclisation of 3-azido-4-phenylpyridine by photolysis[21] or thermal decomposition[22] via the nitrene (Scheme 4). The nature of the aryl groups affects the cyclisation reactivity. The decomposition of biphenyl azides (X=CH) is known to afford the carbazoles (**I**) in high yields,[23,24] while the introduction of pyridine azide in these reactions reduces the reactivity towards cyclisation and the corresponding heterocyclic phenylpyridine azide produces β-carboline (**II**, X=N) in significantly lower yield.[25] Attempts to improve the yields of β-carboline by Lewis acid thermal cyclisation have met with no success.



Scheme 4.

The lower yield obtained for β-carboline (**II**, Scheme 4) compared to carbazole (**I**), may be caused by the electron-deficient character of the pyridine moiety. To improve the reactivity and compensate for the effect of the pyridine-ring, we wanted to replace the phenyl group in the biaryl system of the precursor by more electron-rich heterocyclic groups, such as five-ring heterocycles (thiophene/furan/pyrrole) to study whether more reactive biaryl azido-intermediates could be obtained in order to give five-ring β-carboline analogues (**III**).

In the present work, we examined the preparation of the new thieno-β-carboline analogue compounds (**1a**,**b**) shown in Scheme 3. These pyrido[3,4-*b*]thienopyrroles products can be prepared from 3-amino-4-bromopyridine by palladium catalysed Suzuki cross-coupling with suitable 2-/3-thiphene boronic acids followed by diazotization, azide substitution and thermal decomposition to afford the new thieno-β-carboline analogue products (**1a**,**b**).

This strategy would also give access to the novel pyrido[3,4-*c*]thienopyridazines **2a**,**b** by intramolecular diazocoupling of the diazonium intermediate.

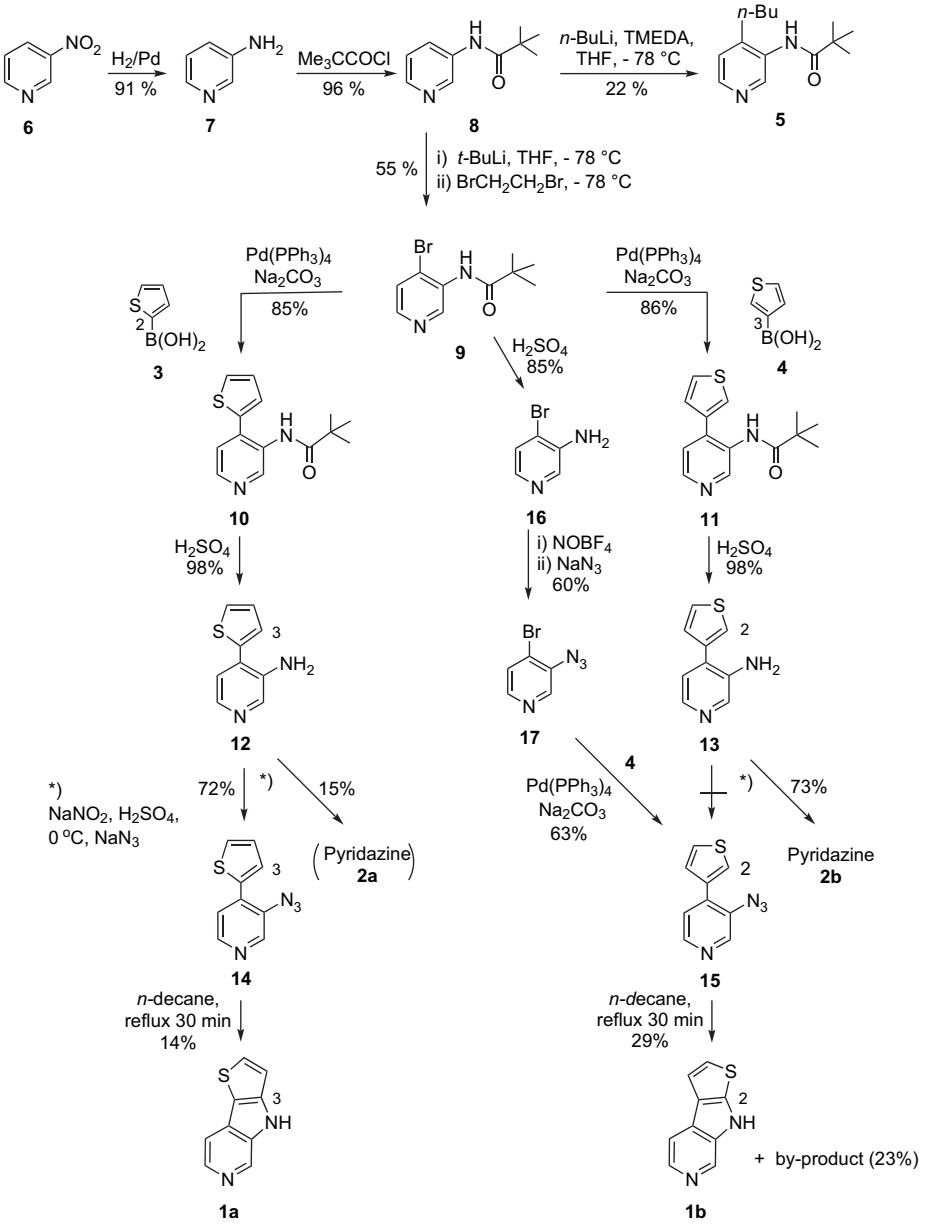
Our results for the preparation of the new potential biologically active pyridothienopyrroles (**1a**,**b**) and pyridothienopyridazines (**2a**,**b**) are discussed below.

2. Results and discussion

2.1. Intermediates

The synthetic sequences for the preparation of pyrido[3,4-*b*]-thieno[2,3-/3,2-*d*]pyrroles **1a**,**b** and pyrido[4,3-*e*]thieno[2,3-/3,2-*c*]-pyridazines **2a**,**b** are presented in Scheme 5. These two new groups of tricyclic heterocycles were prepared from 3-nitropyridine (**6**) through seven- and six-step pathways. Nitropyridines are now readily available through an improved nitration method[26,27] and an investigation of the chemistry of nitropyridines is in progress in our laboratories.

3-Aminopyridine (**7**) and the pivaloyl amide intermediate (**8**)[28] were obtained in high yields by nitro-reduction (91%) followed by derivatisation with pivaloyl chloride (96%). Pivaloylaminopyridines are known to undergo regioselective electrophilic substitution by *ortho*-lithiation[29] and the 4-bromo-3-amido compound **9** was prepared from **8**.[30] However, by using the *n*-BuLi/TMEDA method for lithiation, substantial quantities (22%) of the Ziegler alkylation product (**5**) was formed,[31] caused by nucleophilic attack at C-4 by *n*-BuLi. This problem has been reported by others as well.[32] The problem was avoided by using *t*-BuLi and the 4-bromo-3-



Scheme 5.

aminopyridine derivative **9** was isolated (55%) after lithiation of **8** and subsequent reaction with the electrophilic ethylene dibromide.

In Suzuki couplings 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 Suzuki coupling of 4-bromopyridine (**9**) with commercially available 2- and 3-thienylboronic acids (**3**,**4**) afforded the corresponding thien-2-/3-ylpyridine coupling products **10** and **11** in high yields (85–86%). The yields were not altered by reducing the amount of $Pd(PPh_3)_4$ from 5 to 2.5 mol % or the reaction time (12–6 h). Acidic hydrolysis afforded the aminopyridine intermediates **12** and **13** in quantitative yields.

2.2. Pyrido[3,4-*b*]thienopyrroles (1a,b)

Diazotisation of aminopyridine **12** and subsequent nucleophilic substitution of the diazonium group with azide afforded the azide product **14** in 72% yield. By the corresponding reaction of thien-3-yl intermediate **13**, the azide product **15** was not observed at all, due to the competing exclusive formation of the intramolecular diazo-coupling compound (73%, **2b**) (see Section 2.3 below). By exchanging the order of the Suzuki coupling, the hydrolysis and diazotisation steps described above, an alternative method was used for the preparation of the azide product **15** (Scheme 5). Hydrolysis of intermediate **9** (85%) followed by $NOBF_4$ diazotisation/azide substitution (60%) and subsequent Suzuki coupling (63%) yielded the azide **15** via intermediates **16** and **17**.

Cyclisation by thermal decomposition of azides **14** and **15** via the nitrenes, afforded the desired β-carboline analogues **1a**,**b** by C–H insertion into the 3- and 2-positions of thethiophene, respectively. As expected from the higher reactivity of the 2-position of the thiophene compared to the 3-position, an increased yield was obtained by cyclisation of azide **15** to give **1b** (29%) compared to **14** for the formation of **1a** (14%). However, the yields were reproducibly low and was not changed or improved by altering the reaction time (10 min—5 days), the solvent (*n*-nonane, *n*-decane, and undecane), the reflux temperature (150–195 °C) or by

introducing a Lewis acid (Ti(O–*i*-Pr)$_4$). Attempts at performing the cyclisation by microwave irradiation offered no advantages compared to conventional heating.

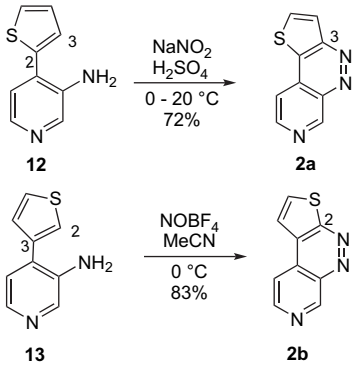
The thermal decomposition of azide **15** also afforded an additional by-product. This new compound was isolated in equivalent amounts (23%) as the desired cyclisation product **1b** but was considerably less polar. The nature of this compound is being investigated.[43] In all reactions, small amounts of the corresponding primary amine (<5% for azide **14** and <1% for azide **15**) and tarry inseparable products were formed. It is known that such competing reactions may take place when ring closure is too difficult under the conditions employed, since the nitrene may abstract hydrogens from the solvent or similar molecules. Such azide reductions are also reported to occur together with tar formation.[33–36]

X-ray analysis of the tricyclic product **1b** reveal that there are 16 molecules in an unusual cell packing structure.[37]

The present results show that replacing the phenyl group in the biaryl azide precursor of β-carboline (Scheme 4) by the more electron-rich thiophene moiety did not improve or compensate for the lower reactivity of the electron-deficient pyridine substrates.[25] Thus, similar reactivity of the phenylpyridyl and thienopyridyl azides (**14**,**15**) to give β-carboline and the thiophene analogues has been demonstrated.

2.3. Pyrido[4,3-*e*]thienopyridazines (2a,b)

Due to the electron-rich and electron-deficient character of the thienyl and pyridine moieties, respectively, compounds **12** and **13** represent appropriate intermediates for the formation of intramolecular diazocoupling pyridazine products. Even if electrophilic substitution at the 3-position of thiophene is known to be negligible, minor amounts (15%) of thienopyrido[3,4-*c*]pyridazine **2a** was isolated from the diazotisation and azide substitution reaction of aminopyridine **12** (Scheme 5), aiming at the azide product **14** (72%, Section 2.2). However, pyridazine product **2b** was exclusively formed (73%) from **13**. Pyridazine **2b** is a regioisomer of **2a**, formed by electrophilic substitution at the highly reactive 2-position of the thiophene **13**. As expected, no product due to reaction in the thienyl-4-position of **13** was observed. In the absence of azide nucleophile, in order to optimise diazocoupling, the pyridazine products **2a** and **2b** were afforded in 72% and 83% yields, respectively (Scheme 6). Their structures were confirmed by X-ray analysis.[38,39]



Scheme 6.

The higher reactivity of the 2-position compared to the 3-position of the thiophene was also demonstrated by the fact that strongly acidic conditions ($NaNO_2/H_2SO_4$, see Scheme 6) were definitely required for the conversion of thien-2-yl **12** to **2a** to take place. The strong acid would activate the diazonium group by protonation of the pyridine moiety. As shown in Scheme 6, no such activation was needed for diazocoupling of the thien-3-yl **13** to give **2b**, since this reaction also took place using $NOBF_4$/MeCN. Due to the electron-deficient and hence more reactive thienopyridine diazonium ion, the obtained yields of the present pyridazines **2a**,**b** are considerably higher than reported for the corresponding thienophenyl diazonium analogues for the formation of thieno[3,2- and 2,3-*c*]cinnolines (13–69%).[40]

3. Conclusion

Two new types of pyrido-fused tris-heterocycles have been prepared from 3-aminopyridine in five/six steps. The novel β-carboline analogues pyrido[3,4-*b*]thieno[2,3/3,2-*d*]pyrroles (**1a**,**b**) have been prepared by the Suzuki—nitrene approach. Additionally, this diazonium intermediate pathway allowed the synthesis of the new pyrido[4,3-*e*]thieno[2,3/3,2-*c*]pyridazines (**2a**,**b**) products by diazocoupling. The preparation of analogous furan and pyrrole products is now in progress in our laboratories.

4. Experimental

4.1. General

Chemicals: 2- and 3-Thiophene boronic acid, *n*-BuLi, *t*-BuLi (Sigma–Aldrich), $NaNO_2$ (Merck), BF_4NO, $C_2H_4Br_2$, $Pd(PPh_3)_4$ (Fluka). *Solvents*: Pro analysi quality. THF and ether were distilled from sodium metal and benzophenone and used directly. All moisture or air sensitive reactions were performed under nitrogen atmosphere in pre-dried glassware. Flash column chromatography; SiO_2 (SDS, 60 Å, 40–63 μm). ^{1}H and ^{13}C NMR: Bruker Avance DPX 300 and 400 MHz spectrometers, chemical shifts are reported in parts per million downfield from TMS. *J* values are given in hertz. MS: Finnigan MAT 95 XL mass spectrometer (EI, 70 eV). IR spectra were obtained with a Nicolet 20SXC FT-IR spectrophotometer, recorded using a Smart Endurance reflexion cell, unless film or KBr are specified. All melting points are uncorrected, measured on a Stuart apparatus. Elemental analyses were done by the Laborator Beller/Matties, Göttingen, Germany. 3-Nitropyridine (**6**) was prepared by nitration of pyridine.[26,27] 3-Aminopyridine (**7**)[41] was prepared by hydrogenation of **6**, according to the literature[42] or purchased from Aldrich and used directly.

4.2. Pyrido[3,4-*b*]thieno[2,3-*d*]pyrrole (1a)

Thermal cyclisation of azide **14** was carried out by heating a stirred solution of **14** (141 mg, 0.697 mmol) in *n*-decane (50 mL) to above 170 °C. The mixture was kept stirring at reflux until full conversion of azide **14** (approx. 30 min, monitored by TLC). The reaction was allowed to cool to room temperature and the decane was distilled off. Flash chromatography (gradient; 0–10% MeOH/CH_2Cl_2) afforded **1a** as a white solid (17 mg, 14%), pure by NMR; R_f 0.20 (10% MeOH/CH_2Cl_2); mp 217–218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 11.81 (1H, br s, NH), 8.83 (1H, s, *J* 0.9, pyr-H2), 8.20 (1H, d, *J* 5.4, pyr-H6), 7.84 (1H, d, *J* 5.4, thieno-H5), 7.74 (1H, dd, *J* 5.4, 0.9, pyr-H5), 7.29 (1H, d, *J* 5.4, thieno-H4); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.98 (1H, s), 8.31 (1H, d, *J* 5.6), 7.67 (1H, d, *J* 5.6), 7.60 (1H, d, *J* 5.2), 7.17 (1H, d, *J* 5.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 148.0 (thieno-C3), 137.8 (pyr-C2), 135.0 (pyr-C6), 133.0 (thieno-C4), 132.3 (pyr-C3), 127.8 (pyr-C4), 116.6 (thieno-C2), 113.4 (pyr-C5), 111.9 (thieno-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 2919, 2851, 1609, 1459, 1344, 1280, 1091, 1053, 986, 817, 806, 797, 762, 707, 667 cm^{-1}; MS *m*/*z* (%): 174 (M^+, 100), 149 (12), 129 (4), 87 (5), 57 (7), 43 (4), 28 (25); HRMS calcd for $C_9H_6N_2S$: 174.0252; obsd 174.0249.

4.3. Pyrido[3,4-*b*]thieno[3,2-*d*]pyrrole (1b)

The title compound was prepared from azide **15** (150 mg, 0.742 mmol) in *n*-decane (50 mL) as described above for the formation of **1a** from **14**. Product **1b** was obtained as a light grey solid (38 mg, 0.218 mmol, 29%), pure by NMR. This procedure also afforded a less polar by-product (23%) after flash chromatography.[43] Compound **1b**: R_f 0.19 (10% MeOH/CH_2Cl_2); mp 225–226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 12.02 (1H, br s, NH), 8.80 (1H, s, *J* 5.4, pyr-H2), 8.21 (1H, d, *J* 5.4, pyr-H6), 7.76 (1H, d, *J* 5.4, pyr-H5), 7.47 (1H, d, *J* 5.4, thieno-H5), 7.17 (1H, d, *J* 5.4, thieno-H4); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 145.2, 138.8, 138.2, 133.8, 125.4, 122.9, 119.2, 117.9, 113.4; IR (KBr) ν_{max}: 3102, 2586, 1608, 1575, 1491, 1477, 1276, 1110, 1035, 805, 715, 709, 667, 640, 594 cm^{-1}; MS *m*/*z* (%): 174 (M^+, 18), 149 (9), 109 (19), 95 (31), 69 (42), 57 (48), 44 (100); HRMS calcd for $C_9H_6N_2S$: 174.0252; obsd 174.0250. Anal. Calcd for $C_9H_6N_2S$: C, 62.05; H, 3.47; N, 16.08; S, 18.40. Found: C, 61.95; H, 3.40; N, 15.98; S, 18.26. X-ray analysis.[37]

4.4. Pyrido[4,3-*e*]thieno[3,2-*c*]pyridazine (2a)

To a stirred solution of amine **12** (106 mg, 0.602 mmol) in H_2SO_4 (10 mL) at 0 °C was added $NaNO_2$ (62 mg, 0.899 mmol) in H_2O (6 mL) dropwise during 30 min. The reaction was kept stirring for 30 min at 0 °C and then allowed to warm to room temperature and stirred overnight. The reaction was added to NaOH (90 mL, 5 M) and ice. The aqueous solution was extracted with CH_2Cl_2 (3×30 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) affording **2a** as a white solid (81 mg, 72%), pure by NMR; **2a** (15% yield) was also isolated from a 15:72% mixture with **14**, (see preparation of **14** below). Compound **2a**: R_f 0.30 (4% Et_3N in EtOAc/pentane (2:1)); mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.12 (1H, d, *J* 0.8, pyr-H2), 8.89 (1H, d, *J* 6.0, pyr-H6), 8.23 (1H, d, *J* 5.6, thieno-H5), 7.99 (1H, d, *J* 5.6, thieno-H4), 7.93 (1H, dd, *J* 6.0, 0.8, pyr-H5); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 156.4 (thieno-C3), 156.1 (pyr-C2), 147.8 (pyr-C6), 139.9 (pyr-C3), 131.2 (thieno-C4), 130.2 (thieno-C2), 126.1 (thieno-C5), 125.7 (pyr-C4), 115.3 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3085, 1603, 1414, 1354, 1331, 1279, 1243, 1234, 1130, 1098, 991, 867, 829, 811, 804, 743, 690 cm^{-1}; MS *m*/*z* (%): 187 (M^+, 100), 176 (59), 149 (33), 132 (91), 57 (78), 41 (52); HRMS calcd for $C_9H_5N_3S$: 187.0204; obsd 187.0201. X-ray analysis.[38]

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

To a stirred solution of $NOBF_4$ in MeCN (5 mL) at 0 °C, amine **13** (116 mg, 0.658 mmol) in MeCN (5 mL) was added over 15 min. The reaction was kept stirring for 30 min at 0 °C before NaOH (15 mL, 5 M) was added. The crude product obtained after extraction with CH_2Cl_2 (3×20 mL), drying over Na_2SO_4 and concentration under reduced pressure was purified by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) to give the product **2b** as a yellow solid (102 mg, 83%), pure by NMR; R_f 0.25 (4% Et_3N in EtOAc/pentane (2:1)); (alternatively, **2b** was exclusively formed in 73% yield from **13** by the reaction conditions described for the formation of **14** and minor amounts of **2a** below); mp 203–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.09 (1H, s, pyr-H2), 8.91 (1H, d, *J* 5.6, pyr-H6), 8.13 (1H, d, *J* 5.6, thieno-H5), 8.08 (1H, dd, *J* 5.6, 0.8, pyr-H5), 7.95 (1H, d, *J* 6.0, thieno-H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 161.8 (thieno-C2), 155.6 (pyr-C2), 147.7 (pyr-C6), 141.0 (pyr-C3), 134.2 (thieno-C5), 126.4 (thieno-C3), 125.2 (pyr-C4), 119.3 (thieno-C4), 115.3 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3039, 1604, 1429, 1389, 1337, 1277, 1260, 1198, 1141, 1079, 1025, 945, 839, 823, 809, 756, 678 cm^{-1}; MS *m*/*z* (%): 187 (M^+, 100), 159 (7), 132 (45), 44 (22), 28 (8); HRMS calcd for $C_9H_5N_3S$: 187.0204; obsd 187.0203. X-ray analysis.[39]

4.6. 4-Butyl-3-pivaloylaminopyridine (5)[44]

The title compound was formed[31,32] in a reaction of **8**, TMEDA (tetramethyl-1,2-diaminoethane) and *n*-BuLi in THF, and was isolated as a yellow solid (22%) by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)), pure by NMR; R_f 0.26 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.89 (1H, s, H1), 8.34 (1H, d, *J* 4.8, H6), 7.21 (1H, br s, NH), 7.12 (1H, d, *J* 4.8, H5), 2.55 (2H, t, *J* 8.0, 1′-CH_2), 1.59 (2H, m, 2′-CH_2), 1.40 (2H, m, 3′-CH_2), 1.37 (9H, s, *t*-Bu), 0.96 (3H, t, *J* 7.6, 4′-CH_3); MS *m*/*z* (%): 234 (M^+, 66), 192 (33), 150 (17), 121 (23), 108 (42), 107 (19), 85 (12), 57 (100).

4.7. *N*-(Pyridin-3-yl)pivalamide (8)[28]

The title compound was prepared from amine **7** (1.37 g, 14.6 mmol) as described elsewhere.[29] Product **8** was isolated as a slightly yellow solid (2.50 g, 96%), pure by NMR; R_f 0.25 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.58 (1H, d, *J* 2.8, H2), 8.32 (1H, dd, *J* 4.8, 1.2, H6), 8.15 (1H, ddd, *J* 8.4, 2.8, 1.2, H4), 7.80 (1H, br s, NH), 7.25 (1H, dd, *J* 8.4, 4.8, H5), 1.32 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 177.3 (C=O), 145.0 (C6), 141.5 (C2), 135.0 (C3), 127.6 (C4), 123.5 (C5), 39.6 (quart-C), 27.4 (CH_3); NMR assignments are based on HSQC experiments; IR ν_{max}: 3172w, 2968w, 1677s, 1584s, 1537s, 1475s, 1420s, 1397s, 1325s, 1282s, 1264s, 1162s, 801s, 747m, 704s cm^{-1}; MS *m*/*z* (%): 178 (M^+, 6), 94 (20), 85 (10), 78 (4), 67 (5), 57 (100), 41 (25), 39 (16); HRMS calcd for $C_{10}H_{14}N_2O$: 178.1106; obsd 178.1108.

4.8. *N*-(4-Bromo-3-pyridinyl)-2,2-dimethylpropanamide (9)[30]

t-BuLi (61 mL, 103.8 mmol, 1.7 M in pentane) was added dropwise in 30 min to a stirred solution of **8** (7.40 g, 41.51 mmol) in THF (60 mL) and ether (110 mL) at −78 °C. The reaction was stirred for 30 min at −78 °C, 30 min at −20 °C and 1.5 h at room temperature. The reaction was cooled to −78 °C and ethylene dibromide (10.73 mL, 124.5 mmol) was added dropwise during 30 min. The mixture was allowed to heat to room temperature and stirred overnight before water (100 mL) was added. Extraction and flash chromatography (1:1 EtOAc/pentane) afforded **9** as a light yellow solid (5.85 g, 55%), pure by NMR; R_f 0.28 (EtOAc/pentane (1:1)); mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.53 (1H, s, H2), 8.17 (1H, d, *J* 5.2, H6), 7.83 (1H, br s, NH), 7.50 (1H, d, *J* 5.2, H5), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 176.5 (C=O), 145.2 (C6), 143.5 (C2), 133.3 (C3), 127.0 (C5), 123.3 (C4), 40.1 (quart-C), 27.6 (CH_3); NMR assignments are based on HSQC experiments; IR ν_{max}: 3282m, 2965w, 1654s, 1568s, 1555s, 1495s, 1466s, 1398s, 1289m, 1174s, 1074m, 1064m, 862m, 805s, 669s cm^{-1}; MS *m*/*z* (%): 256 (M^+, 6), 172 (14), 85 (22), 57 (100), 41 (25), 39 (9); HRMS calcd for $C_{10}H_{13}BrN_2O$: 256.0211; obsd 256.0209.

4.9. *N*-(4-(Thien-2-yl)pyridin-3-yl)pivalamide (10)

A solution of **9** (2.00 g, 7.78 mmol) and $Pd(PPh_3)_4$ (419 mg, 0.363 mmol) in toluene (15 mL) was stirred and added Na_2CO_3 (7.5 mL, 2 M) and 2-thienylboronic acid (1.19 g, 9.30 mmol) in MeOH (5 mL).[45] The reaction was heated to 80–90 °C overnight. The reaction was allowed to cool to room temperature before CH_2Cl_2 (60 mL) and NH_3 (4 mL, concd) in Na_2CO_2 (40 mL, 2 M) was added. The white/yellow crude product, obtained by extraction, was purified by flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) to give **10** as a white solid (1.72 g, 6.61 mmol, 85%), pure by NMR; R_f 0.31 (4% Et_3N in EtOAc/pentane (2:1)); mp/decomp. 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.43 (1H, s, pyr-H2), 8.39 (1H, d, *J* 4.8,

pyr-H6), 7.72 (1H, br s, NH), 7.53 (1H, dd, *J* 4.8, 1.2, thieno-H5), 7.31 (1H, dd, *J* 4.8, pyr-H5), 7.26 (1H, dd, *J* 3.6, 1.2, thieno-H3), 7.20 (1H, dd, *J* 4.8, 3.6, thieno-H4), 1.25 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 176.5 (C=O), 145.3 (pyr-C6), 144.6 (pyr-C2), 136.3 (thieno-C2), 132.6 (pyr-C4), 131.6 (pyr-C3), 128.1 (thieno-C5), 128.0 (thieno-C4), 127.8 (thieno-C3), 123.9 (pyr-C5), 39.8 (CMe_3), 27.4 (C(CH_3)$_3$); IR ν_{max}: 3094, 2966, 1670, 1603, 1555, 1512, 1475, 1429, 1410, 1305, 1164, 823, 806, 746, 729, 704, 689 cm^{-1}; MS *m*/*z* (%): 260 (M$^+$, 90), 175 (42), 149 (14), 131 (16), 85 (16), 57 (100), 43 (26), 41 (17), 29 (10); HRMS calcd for $C_{14}H_{16}N_2OS$: 260.0983; obsd 260.0987. Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19; N, 10.76; S, 12.32. Found: C, 64.62; H, 6.20; N, 10.71; S, 12.20.

4.10. *N*-(4-(Thien-3-yl)pyridin-3-yl)pivalamide (11)

The title compound was prepared from **9** (5.02 g, 19.5 mmol) and Pd(PPh_3)$_4$ (1.13 g, 0.977 mmol) in toluene (40 mL), Na_2CO_3 (20 mL, 2 M) and 3-thienylboronic acid (3.00 g, 23.4 mmol) in MeOH (12 mL) as described above for the preparation of **10**.[45] The crude product was purified by flash chromatography (EtOAc/pentane (1:1)) to give **11** as a white solid (4.35 g, 16.7 mmol, 86%), pure by NMR; R_f 0.18 (EtOAc/pentane (1:1)); mp/decomp. 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.50 (1H, s, pyr-H2), 8.39 (1H, d, *J* 4.8, pyr-H6), 7.56 (1H, dd, *J* 4.8, 3.2, thieno-H5), 7.51 (1H, br s, NH), 7.43 (1H, d, *J* 2.4, thieno-H2), 7.22 (1H, d, *J* 5.2, thieno-H4), 7.18 (1H, d, *J* 4.8, pyr-H5), 1.24 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 176.4 (C=O), 145.2 (pyr-C6), 143.8 (pyr-C2), 135.8 (thieno-C3), 134.7 (pyr-C4), 131.9 (pyr-C3), 127.8 (thieno-C4), 127.4 (thieno-C5), 124.7 (thieno-C2), 123.7 (pyr-C5), 39.7 (CMe_3), 27.4 (C(CH_3)$_3$); NMR assignments are based on HMBC experiments; IR ν_{max}: 3105, 2965, 1668, 1558, 1513, 1475, 1417, 1398, 1303, 1171, 1160, 858, 830, 788, 747, 734, 671, 652 cm^{-1}; MS *m*/*z* (%): 260 (M$^+$, 21), 176 (16), 131 (7), 85 (6), 57 (100), 41 (16); HRMS calcd for $C_{14}H_{16}N_2OS$: 260.0983; obsd 260.0986. Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19; N, 10.76; S, 12.32. Found: C, 64.77; H, 6.30; N, 10.58; S, 12.23.

4.11. 4-(Thien-2-yl)pyridin-3-amine (12)

A solution of amide **10** (1.87 g, 7.19 mmol) in H_2SO_4 (100 mL, 25%, aq) was heated to reflux and kept stirring for 3 h. The reaction was allowed to cool to room temperature before a mixture of NH_3 (150 mL, concd) and ice was added (pH=11). Extraction afforded the yellow/brown crude oily product. Flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) afforded amine **12** as a pale yellow oil (1.24 g, 98%), which soon turned brown: R_f 0.19 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.17 (1H, s, pyr-H2), 8.03 (1H, d, *J* 4.8, pyr-H6), 7.43 (1H, dd, *J* 5.2, 1.2, thieno-H5), 7.35 (1H, dd, *J* 3.6, 1.2, thieno-H3), 7.16 (2H, m, *J* 5.2, 4.8, 3.6, pyr-H5), 4.08 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 140.1 (pyr-C6), 139.5 (pyr-C3), 138.7 (pyr-C2), 138.3 (thieno-C2), 127.9 (thieno-C5), 126.6 (thieno-C4), 126.5 (thieno-C3), 126.2 (pyr-C4), 123.7 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3307, 3169, 1615, 1588, 1550, 1488, 1432, 1418, 1323, 1289, 1237, 1193, 1063, 853, 816, 699 cm^{-1}; MS *m*/*z* (%): 176 (M$^+$, 100), 131 (57), 77 (16), 51 (9), 39 (6); HRMS calcd for $C_9H_8N_2S$: 176.0408; obsd 176.0407. Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90. Found: C, 61.31; H, 4.51; N, 15.85.

4.12. 4-(Thien-3-yl)pyridin-3-amine (13)

The title compound was prepared from **11** (4.11 g, 15.8 mmol) in H_2SO_4 (200 mL, 25%, aq) as described above for the preparation of **12**. Extraction afforded a yellow-brown crude oil and flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) gave amine **13** as a transparent oil, which soon turned brown (2.72 g, 98%), pure by NMR; R_f 0.19 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.15 (1H, s, pyr-H2), 8.03 (1H, d, *J* 4.8, pyr-H6), 7.51 (1H, dd, *J* 3.2, 1.2, thieno-H2), 7.46 (1H, dd, *J* 5.2, 3.2, thieno-H5), 7.29 (1H, dd, *J* 5.2, 1.2, thieno-H4), 7.09 (1H, d, *J* 4.8, pyr-H5), 3.94 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 140.1 (pyr-C6), 139.9 (pyr-C3), 138.3 (pyr-C2), 137.2 (thieno-C3), 128.5 (pyr-C4), 127.4 (thieno-C4), 126.8 (thieno-C5), 123.7 (thieno-C2), 123.6 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3311, 3175, 1614, 1591, 1555, 1490, 1423, 1321, 1285, 1233, 1185, 1062, 1039, 842, 825, 788, 750 cm^{-1}; MS *m*/*z* (%): 176 (M$^+$, 100), 131 (75), 77 (45), 51 (33), 45 (31), 41 (16); HRMS calcd for $C_9H_8N_2S$: 176.0408; obsd 176.0407. Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90; S, 18.19. Found: C, 61.45; H, 4.58; N, 15.67; S, 18.09.

4.13. 3-Azido-4-(thien-2-yl)pyridine (14)

To a stirred solution of **12** (256 mg, 1.45 mmol) in H_2SO_4 (13 mL) at 0 °C was added $NaNO_2$ (150 mg, 2.18 mmol) in H_2O (10 mL) dropwise during 30 min. The reaction mixture was kept stirring for 20 min at 0 °C before NaN_3 (140 mg, 2.15 mmol) was added dropwise during 40 min at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then kept stirring overnight at room temperature. NaOH (100 mL, 5 M) was added slowly (pH=14). After extraction with CH_2Cl_2, the crude product was purified by flash column chromatography (4% Et_3N in EtOAc/pentane (2:1)). Azide **14** was isolated as a brown oil, crystallising from pentane (212 mg, 72%), pure by NMR. Pyridazine **2a** (40.5 mg, 15%) was also isolated as crystals. Compound **14**: R_f 0.53 (4% Et_3N in EtOAc/pentane (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.58 (1H, s, pyr-H2), 8.37 (1H, d, *J* 5.2, pyr-H6), 7.70 (1H, dd, *J* 4.0, 1.2, thieno-H5), 7.50 (2H, d, *J* 5.2, pyr-H5+thieno-H3), 7.16 (1H, dd, *J* 5.2, 4.0, thieno-H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 145.7 (pyr-C2), 141.7 (pyr-C6), 136.1 (thieno-C2), 132.4 (pyr-C4), 132.1 (pyr-C3), 128.6 (2×C, thieno-C4/-C5), 127.6 (thieno-C3), 122.0 (pyr-C5); NMR assignments are based on HMBC experiments; IR ν_{max}: 3053, 2127, 2103, 1580, 1544, 1236, 1478, 1413, 1309, 1298, 1259, 1056, 855, 836, 825, 727, 712, 662 cm^{-1}; MS *m*/*z* (%): 202 (M$^+$, 6), 174 (100), 146 (39), 120 (18), 103 (24), 96 (14), 69 (15), 45 (31), 39 (17), 28 (48); HRMS calcd for $C_9H_6N_4S$: 202.0313; obsd 202.0311.

4.14. 3-Azido-4-(thiophen-3-yl)pyridine (15)

To a stirred solution of azide **17** (434 mg, 2.18 mmol) and Pd(PPh_3)$_4$ (127 mg, 0.110 mmol) in toluene (20 mL) was added Na_2CO_3 (10 mL, 2 M) and 3-thienylboronic acid (337 mg, 2.630 mmol) in MeOH (5 mL).[45] The reaction was heated to 80 °C and kept stirring for 4 h. The reaction mixture was cooled to room temperature, CH_2Cl_2 (40 mL) and NH_3 (2 mL, concd) in Na_2CO_2 (20 mL, 2 M) added and extracted with CH_2Cl_2 (2×20 mL). The brown, oily crude product was purified by flash chromatography (1:2 EtOAc/pentane) to give **15** as a brown oil crystallising from pentane (277 mg, 63%); R_f 0.38 (EtOAc/pentane (1:2)), pure by NMR; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.57 (1H, s, pyr-H2), 8.39 (1H, d, *J* 5.1, pyr-H6), 7.80 (1H, dd, *J* 2.7, 1.5, pyr-H5), 7.45–7.40 (2H, m, thieno-H2/H5), 7.38 (1H, d, *J* 5.1, thieno-H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 146.1, 141.6, 135.3 134.3, 133.3, 127.6, 126.2, 125.9, 123.4; IR (film) ν_{max}: 2124, 2102, 1587, 1420, 1307, 791, 744, 695 cm^{-1}; MS *m*/*z* (%): 202 (M$^+$, 5), 174 (100), 146 (47), 120 (14), 103 (17), 45 (16); HRMS calcd for $C_9H_6N_4S$: 202.0313; obsd 202.0312. Anal. Calcd for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70. Found: C, 53.39; H, 3.05; N, 27.78.

4.15. 3-Amino-4-bromopyridine (16)[46]

The title compound was prepared from **9** (7.00 g, 27.2 mmol) in H_2SO_4 (120 mL, 20%, aq) as described above for the preparation of **12**. Extraction afforded a yellow crude oil and flash chromatography (4% Et_3N in EtOAc/pentane (2:1)) gave **16** as a colourless oil, which

soon turned brown (3.98 g, 23.0 mmol, 85%), pure by NMR; R_f 0.24 (4% Et_3N in EtOAc/pentane (2:1)); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.09 (1H, s, H2), 7.76 (1H, d, *J* 5.2, H6), 7.31 (1H, d, *J* 5.2, H5); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 141.5 (C3), 139.6/137.4 (C2/C6), 127.4 (C5), 117.9 (C4); IR (film) ν_{max}: 3449, 3315, 3180, 1623, 1574, 1556, 1484, 1417, 1328, 1235, 1058, 811, 669 cm^{-1}; MS *m*/*z* (%): 174 ($C_5H_5^{81}BrN_2$, M^+, 44), 172 ($C_5H_5^{79}BrN_2$, M^+, 47), 147 (12), 145 (12), 93 (47), 66 (100), 39 (38); HRMS calcd for $C_5H_5^{79}BrN_2$: 171.9636; obsd 171.9639.

4.16. 3-Azido-4-bromopyridine (17)

To a stirred solution of $NOBF_4$ in MeCN (15 mL) at −10 °C, amine **16** (2.42 g, 13.99 mmol) in MeCN (5 mL) was added over 15 min. The reaction was allowed to heat to 0 °C and then kept stirring for 30 min. The reaction was cooled to −10 °C and NaN_3 in H_2O (5 mL)/MeCN (2 mL) was added over 30 min. The reaction was kept stirring for 30 min at 0 °C before H_2O (10 mL) was added. Extraction with CH_2Cl_2 afforded an oily crude product. Purification by flash chromatography (1:5 EtOAc/pentane) gave **17** as a light brown oil (1.657, 8.33 mmol, 60%), pure by NMR; R_f 0.25 (1:5 EtOAc/pentane); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.46 (1H, s, C2), 8.19 (1H, d, *J* 5.2, C6), 7.50 (1H, d, *J* 5.2, C5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.1, 141.2, 136.3, 128.3, 123.6; IR (film) ν_{max}: 2113, 1551, 1477, 1405, 1325, 1312, 1066, 824, 703 cm^{-1}; MS *m*/*z* (%): 200 ($C_5H_5^{81}BrN_4$, M^+, 4), 198 ($C_5H_5^{79}BrN_4$, M^+, 4), 172 (28), 170 (25), 91 (32), 64 (100) 37 (27); HRMS calcd for $C_5H_3^{79}BrN_4$: 197.9541; obsd 197.9548.

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