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Formation of new 4-isocyanobut-2-enenitriles by thermal ring cleavage of 3-pyridyl azides

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2-(Thien-3-yl)-1*H*-pyrrole-3-carbonitrile

ABSTRACT

A new thermal ring cleavage of 3-pyridyl nitrenes for the formation of 4-isocyanobut-2-enenitrile products is reported. Thermolysis of 4-(thien-3-yl)-3-pyridyl azide **1** and 3-azido-4-(1-TIPS-1*H*-pyrrol-3-yl)pyridine **5** afforded two new isonitrile–nitrile products by ring cleavage; 4-isocyano-2-(thiophen-3-yl)but-2-enenitrile (**3**, 27%) and 4-isocyano-2-(1-TIPS-1*H*-pyrrol-3-yl)but-2-enenitrile (**7**, 20%), in addition to our previously reported pyrido[3,4-*b*]thienopyrrole (**2**, 29%) and pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole (**6**, 71%) products. Minor amounts of 2-(thien-3-yl)-1*H*-pyrrole-3-carbonitrile (**4**, 6%), formed by ring contraction, were also isolated after thermolysis of azide **1**. Isonitriles **3** and **7** underwent degradation into amine **3b** and formamide **7a** by acidic hydrolysis. The nature and chemistry of compounds **3**, **4** and **7** were investigated.

1. Introduction

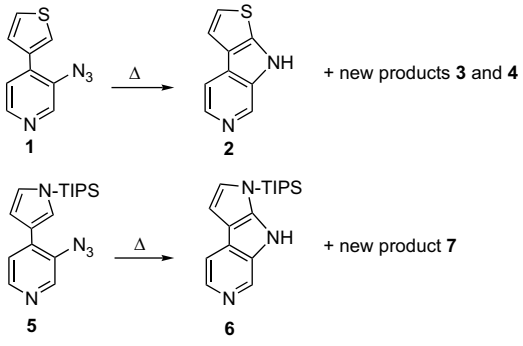
We have previously reported the preparation of new β-carboline thieno and pyrrole analogues (**2**, **6**) by thermal decomposition of 4-(thien-3-yl)-3-pyridyl azide (**1**) and 4-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)pyridyl azide (**5**), respectively (Scheme 1).[1–4]

The thermolysis of 3-pyridyl azides **1** and **5** also afforded additional products (**3**,**4** and **7**). In the present work we have identified these unknown products and studied the transformation reactions into the new compounds. Our results of the investigation of the properties of products **3**, **4** and **7**, in particular by NMR and IR spectroscopy, are discussed below.

2. Results and discussion

2.1. Synthesis

The preparation of the 3-pyridyl azides **1** and **5** was mainly based on pyridine nitration, directed metallation and a Suzuki cross-coupling strategy (Scheme 2).[1] 3-Pyridylpivaloyl amide (**9**) was obtained by nitration of pyridine,[5,6] followed by reduction of the nitro group (91%) and derivatisation with pivaloyl chloride (96%). 4-Bromo-3-amidopyridine (**10**) was prepared (55%) by regioselective electrophilic substitution of **9** by *ortho*-lithiation and reaction with ethylene dibromide. Hydrolysis of intermediate **10** (85%) and subsequent $NOBF_4$ diazotisation/azide substitution (60%) afforded 3-azido-4-bromopyridine **12**. Suzuki couplings of 4-bromopyridine **12** with 3-thienylboronic acid and *N*-TIPS-pinacolatopyrroloboronate ester, respectively, yielded the coupling products **1** (63%) and **5** (60%).



Scheme 1. Cyclisation to β-carboline analogues.

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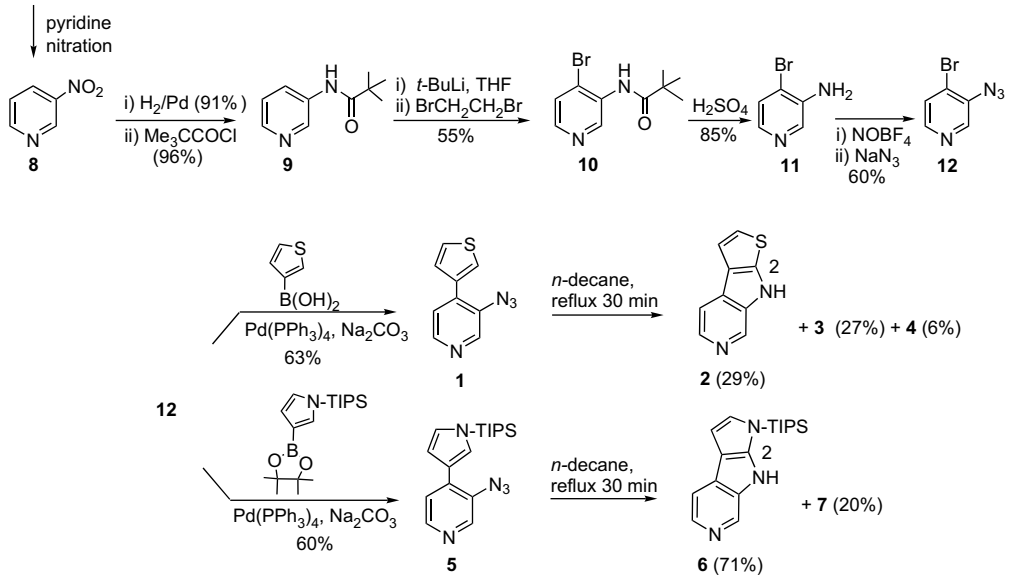
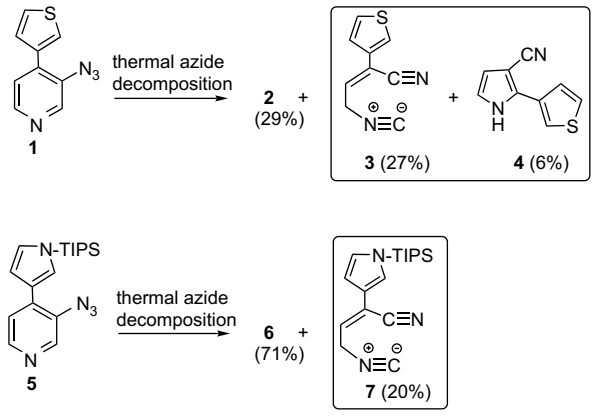


Scheme 2.

Cyclisation by thermal decomposition of azides **1** and **5** via the nitrenes, afforded the desired β-carboline analogues **2** (29%) and **6** (71%) by C–H insertion into the 2-thienyl/2-pyrrole positions (Scheme 1). The thermal decomposition of azides **1** and **5** also afforded two considerably less polar new compounds **3** (27%) and **7** (20%), isolated by chromatography after direct evaporation of the solvent (Scheme 3). Minor amounts of an additional product **4** (6%) were isolated from the cyclisation of the thienyl substrate **1**.



Scheme 3.

2.2. Compound 3

Product **3** was stable towards flash chromatography and handling. However, slow degradation was observed after storage in solution at room temperature for several weeks. The structure elucidation of product **3** was mainly based on the spectroscopic and chemical characteristics discussed below in (i)–(vi). In general, all NMR, IR and MS data, including results obtained by a thorough 2D NMR correlation experiments, ATP, NOESY, HSQC and HMBC (Table 1), supported the assumption that a ring cleavage to an isonitrile–nitrile structure, 4-isocyano-2-thiophenylbutenenitrile **3**, had taken place (Scheme 3).

(i) The IR spectrum of compound **3** points towards an isonitrile–nitrile structure. The characteristic absorptions caused by both nitrile and isonitrile stretching vibrations were observed at, respectively, 2231 cm^{-1} (w) and 2154 cm^{-1} (s). Characteristic nitrile MS-fragmentation of HCN (M−27) was observed for product **3**.

(ii) One remarkable structure element of product **3** was, based on ^{1}H NMR spectroscopy, an allylic methylene group, as shown by the characteristic =CH–C$\underline{H}_2$ doublet (δ 4.51, J 6.9 Hz) and the =C$\underline{H}$–CH$_2$ triplet (δ 6.64, J 6.9 Hz) signals. The large coupling constant shows that the allylic element is not part of a planar cyclic system. All the typical pyridyl proton signals from substrate **1** and product **2** were absent.

(iii) The most striking feature was, however, the triplet splitting of the C4 methylene (=CH–C$\underline{H}_2$) ^{13}C NMR signal (41.7 ppm, J 7.0 Hz). This phenomenon is characteristic for alkyl isonitriles. Similar spin ^{13}C–^{14}N coupling constants have been reported for analogous –C$\underline{H}_2$–N$\underline{C}$ systems.[7–10] Due to the electronic symmetry about the isonitrile nitrogen nucleus, coupling to the quadrupolar ^{14}N is observable. For this reason the ^{13}C NMR signal for a carbon next to an isonitrile appears as a triplet. As expected, a broad and partly split ^{13}C NMR signal was observed for the isonitrile carbon (–N$\underline{C}$ at 159.5 ppm) as well. In general, increasing temperature results in slower relaxation of the quadrupolar nucleus[11] and improves the coupling fine structure, observed as increased coupling constants. In contrast, reducing temperature would collapse the coupling. By increasing the temperature from 20 to 50 °C, we observed an increase of the ^{13}C–^{14}N NMR coupling constants for isonitrile **3**.

Table 1
J(C,H) and J(N,H) observed by HSQC and HMBC for compound **3**

	H_3	H_4	thi-H_2	thi-H_4	thi-H_5
C_1	^{3}J				
C_2	^{2}J	^{3}J	^{3}J	^{3}J	
C_3	^{1}J	^{2}J			
C_4	^{2}J	^{1}J			
C_5		^{3}J			
thi-C_2			^{1}J	^{3}J	^{3}J
thi-C_3	^{3}J		^{2}J	^{2}J	^{3}J
thi-C_4			^{3}J	^{1}J	^{2}J
thi-C_5			^{3}J	^{2}J	^{1}J
–CN					
–N$\underline{C}$	^{3}J	^{2}J			

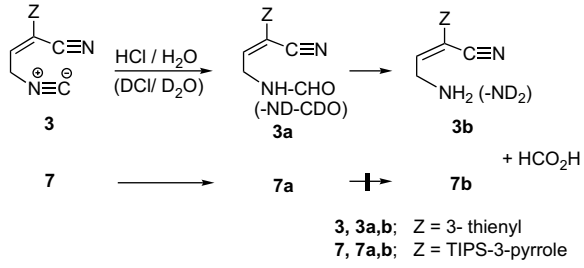
J_{C4-N} increased from 7.0 to 7.8 Hz and the broad singlet observed for –NC, turned into a triplet; J_{NC} 4.5 Hz, respectively.

(iv) HMBC $^{1}H–^{15}N$ NMR data confirmed the presence of an isonitrile function. Both H3 (CH=) and H4 (–CH_2) protons gave an ^{15}N correlation peak at 165 ppm (Table 1), characteristic for an isonitrile group (–NC, 150–200 ppm). As expected, H3 had no HMBC correlation with the nitrile (approx. 200–250 ppm), due to the longer distance between H3 and nitrile-CN.

(v) NOESY NMR spectroscopy of product **3** supported the 4-isocyano-2-thienylbut-2-enenitrile structure, since through-space proximity of the olefinic H3 and thienyl-H4 and -H2 was observed. In consequence, the data also indicate the less sterically hindered *Z*-configuration of the double bond in compound **3**.

(vi) Isonitriles undergo addition reactions by the addition of a nucleophile to the isonitrile carbon. Acid-catalysed hydrolysis of alkyl isonitriles has been examined and represents an addition reaction. Isonitriles are thus unstable in dilute aqueous acid. The initial hydrolysis product is the *N*-alkylformamide, which is further hydrolysed to the primary amine and formic acid at a slower rate.[12]

Compound **3** underwent such hydrolytic cleavage with treatment of isonitrile **3** with HCl/H_2O, monitored by ^{1}H NMR spectroscopy. The formamide intermediate **3a** was immediately formed and gradually, the amino degradation product **3b** was produced (Scheme 4). Depending on the amount of added HCl, quantitative conversion of **3** to amine **3b** was obtained in 2–30 h at room temperature. HRMS as well as ^{1}H and ^{13}C NMR data were in accordance with the amino structure **3b**. In particular, the increased shielding of H3 and H4 (=CH–CH_2, 0.3–0.4 ppm) and the disappearance of the isonitrile ^{13}C NMR signal (159.5 ppm) were typical for the reaction. When the reaction was carried out in DCl/D_2O, the amine ^{1}H NMR signals were not observed, due to deuteration (ND_2) in accordance with the mechanism. The hydrolytic degradation reactions were carried out in analytical scale. Product **3b** was unstable towards isomerisation by alkaline extraction and work-up.



Scheme 4.

2.3. Compound 4

HRMS data of the molecular ions of compound **3** and the other new product **4** confirmed their $C_9H_6N_2S$ composition. Strong nitrile IR absorption was observed for compound **4**. Product **4** was stable and isolated in 6% yield. ^{1}H NMR spectroscopy showed that the thien-3-yl group also was present in product **4**. However, the allylic methylene group from product **3** as well as typical pyridine protons from substrate **1** and product **2** was absent. The ^{1}H and ^{13}C NMR data fits entirely with the 2-(thien-3-yl)-pyrrole-3-carbonitrile structure **4** (Scheme 3). Assignments of all the NMR data were fully supported by 2D NMR experiments and confirmed that a ring contraction had taken place to give the stable aromatic 1*H*-pyrrole structure **4**. The pyrrole-NH of **4** is strongly hydrogen-bonded, as indicated by the high ^{1}H NMR N*H* frequency at 12.1 ppm. Due to the total aromaticity of the bis-aryl structure and the additional electron delocalisation, caused by the neighbouring conjugated cyano group, increased chemical shifts (approx. 0.3 ppm) of all thienyl protons of product **4** were observed relative to compound **3**.

NOESY experiments supported the structure of the 3-carbonitrile-3-thienylpyrrole **4**. The NOESY data left no doubt about the 2-thienyl-3-cyano-substitution pattern, since strong NOESY effects were observed between the pyrrole-NH and both thienyl-H2 and -H4.

2.4. Compound 7

Thermolysis of pyrrolopyridyl azide **5**[4] afforded the corresponding ring cleavage product as the former thienopyridyl azide **1**. 4-Isocyano-1-(2-TIPS-1*H*-pyrrol-3-yl)but-2-enenitrile (**7**, 20%) was isolated in addition to the main cyclisation product (**6**, 71%, Schemes 1 and 3). Triplet splitting was observed for both CH_2–NC ^{13}C NMR signals, due to the typical $^{13}C–^{14}N$ couplings of J_{CH2-N} 7.0 Hz and J_{NC} 4.5 Hz (20 °C). As seen for isonitrile **3**, the fine structure of these triplets was improved by increasing the temperature to 48 °C. Similar to product **3**, NOESY NMR data of product **7** supported the structure, showing the proximity of H3 and pyrrole-H4/-H2. Thus, compound **7** also seems to have *Z*-configuration.

Upon HCl treatment, isonitrile **7** did not undergo a complete degradation reaction to the amine **7b**, similar to the **3**–**3b** transformation. Instead, the formamide intermediate **7a** (Scheme 4) was isolated (95%). Due to the unpolar nature of the TIPS group, isonitrile **7** did not dissolve in HCl/H_2O and the reaction took place in a heterogeneous mixture. Thus, the effect of the acidic treatment was weaker than in the corresponding conversion of isonitrile **3**. Attempts to achieve full conversion of isonitrile **7** to the amine degradation product **7a** were made by carrying out the reaction in a homogeneous solution after addition of acetonitrile. However, all the pyrrole signals disappeared in the ^{1}H and ^{13}C NMR spectra, indicating decomposition of the pyrrole ring, due to the instability of pyrroles in acidic conditions.

NMR coupling patterns and shift values supported the formamide structure **7a**. The presence of the formamide CHO group was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The original ^{13}C NMR triplet observed for CH_2–NC of isonitrile **7**, as discussed above, was reduced to an ordinary singlet (CH_2–NH–CHO) in formamide **7a**. An HMBC ^{3}J-correlation between the indicated C–CH_2–NH–CH=O was observed.

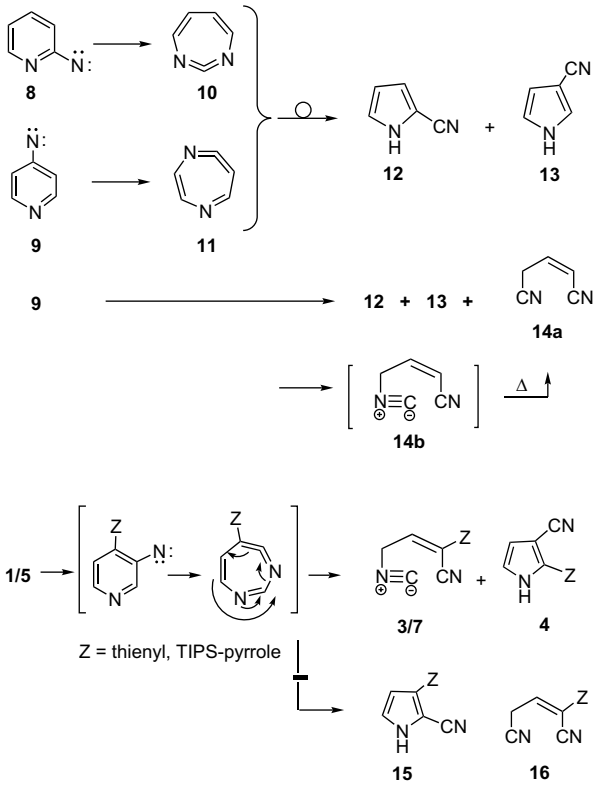
The IR spectra of **7** and **7a** were nearly identical, except for the lack of the strong isonitrile (2147 cm^{-1}) band and the respective appearance of a new amide-NH (3319 cm^{-1}) and a strong C=O (1668 cm^{-1}) stretch frequency in the **7a** spectrum. Both compounds **7** and **7a** showed the characteristic nitrile absorptions (2215 cm^{-1}).

When the reaction was carried out in DCl/D_2O, the aldehyde (CHO) and amide (NH–) ^{1}H NMR signals were not observed, due to deuteration (ND–CDO) in accordance with the mechanism. The CH–CH_2–ND signal appeared as a doublet, while the **7a** product formed by HCl hydrolysis showed a doublet of doublets for CH–CH_2–NH–.

2.5. Formation of products 3, 4 and 7

The chemistry of 2- and 4-pyridyl nitrenes (**8**, **9**) has previously been investigated. In particular, gas phase pyrolysis studies at above 450 °C were carried out..[13,14] The 2- and 4-pyridyl nitrenes both gave 2- and 3-cyanopyrroles (**12**, **13**), as shown in Scheme 5. The intermediate in the thermal interconversion was formulated as a seven-membered ring. The heteroarylnitrenes (**8**, **9**) underwent ring expansion and rearranged to diazacycloheptatetraenes; the carbodiimide **10** and the keteneimine **11**, in gas phase. Subsequent

ring contraction afforded the cyanopyrrole products **12** and **13**. By pyrolysis of **9** also minor amounts of the dicyano compound **14a** were formed.[13] In contrast, no studies were carried out on 3-pyridyl nitrenes.



Scheme 5.

If a corresponding mechanism takes place by the presently studied thermal decomposition of 3-pyridyl azides **1** and **5**, a diazaheptatetraene intermediate may be formed via the 3-pyridyl nitrene (Scheme 5). Subsequent ring contraction would explain the formation of minor amounts (6%) of the pyrrole product **4**, similar to **13**, from **1**. A ring opening mechanism, including a proton shift, would produce the nitrile isonitrile products **3** and **7**.

Neither tautomeric 2-cyano-3-thienylpyrrole **15** nor dicyano product **16**, similar to compounds **12** and **14a**, was observed. Isonitriles can however, rearrange thermally (>270 °C) into nitriles by pyrolysis.[19,20] Consequently, the previously reported dicyano product **14a** (Scheme 5)[13] may be formed by thermal rearrangement of an initially formed isonitrile–nitrile precursor **14b**, corresponding to the presently reported products **3** and **7**, due to the harsh pyrolysis conditions formerly used.

2.6. Isonitriles: occurrence, preparation and reactions

An increasing number of naturally occurring isonitrile compounds have been isolated. They have been reported to show a wide spectrum of biological, in particular antibiotic activity. Marine invertebrates and animals feeding on them contain isonitriles.[15–17]

Isonitriles are mostly prepared either by the reaction between alkyl halide and cyanide ion, by dehydration of *N*-alkylformamides or by reduction of isocyanides. The formation of cyclopentadienyl isonitriles by thermolysis of the appropriate azide precursors has once been reported. A nitrene mechanism including an intermediate aziridine ring opening is suggested.[18] However, no study of the ring cleavage of 3-pyridyl nitrenes for the formation of isonitriles has been carried out.

Isonitriles are used for synthetic transformations. In general, isonitriles readily undergo cyclisation reactions and these reactions provide useful methods for the preparation of five-membered heterocycles containing nitrogen, such as pyrroles, indoles, pyridazoles, oxazoles and thiazoles.[21] Isonitriles are simply oxidised to isocyanates with halogens and the polymers of isonitriles have a variety of applications. Isonitriles are used as ligands since they readily coordinate to metals. The organometallic syntheses of a series of metal isonitrile complexes and the reactions of these complexes have been studied.[22–25]

3. Conclusion

The present results demonstrate that 3-pyridyl azides may undergo thermal ring cleavage to form 4-isocyanobut-2-enenitrile products. Thermolysis of 4-(thien-3-yl)-3-pyridyl azide **1** and 3-azido-4-(1-TIPS-1*H*-pyrrol-3-yl)pyridine **5** afforded two new isonitrile–nitrile products by ring cleavage; 4-isocyano-2-(thiophen-3-yl)but-2-enenitrile (**3**, 27%) and 4-isocyano-2-(1-TIPS-1*H*-pyrrol-3-yl)but-2-enenitrile (**7**, 20%), in addition to our previously reported pyrido[3,4-*b*]thienopyrrole (**2**, 29%) and pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole (**6**, 71%) products. Minor amounts of 2-(thien-3-yl)-1*H*-pyrrole-3-carbonitrile (**4**, 6%), formed by ring contraction, were also isolated from thermolysis of azide **1**. Isonitriles **3** and **7** underwent degradation into, respectively, the amine **3b** and the formamide **7a** by acidic hydrolysis.

4. Experimental

4.1. General

Solvents: *pro analysi* quality. All reactions were performed under nitrogen atmosphere in pre-dried glassware. Flash column chromatography; SiO_2 (SDS, 60 Å, 40–63 μm). NMR: Bruker Avance DPX 300 and 400 MHz and Bruker DRX 600 MHz spectrometers. ^1H and ^{13}C chemical shifts are reported in parts per million downfield from TMS (or TSP-d_4 for compound **3b**). ^{15}N chemical shifts were referred indirectly to TMS, using absolute frequency ratios, and are reported in parts per million downfield from liquid ammonia.[26] *J* values are given in Hz. EIMS: Finnigan MAT 95 XL mass spectrometer (EI, 70 eV). ESI-MS accurate mass determination was 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 spectra were obtained with a Nicolet 20SXC FT-IR spectrophotometer. All melting points are uncorrected, measured on a Stuart apparatus. 3-Azido-4-(thien-3-yl)pyridine (**1**) and 3-azido-4-(1-TIPS-1*H*-pyrrol-3-yl)pyridine (**5**) were prepared according to literature.[1,4]

4.2. Preparation of 3 and 4

The title compounds were prepared from a solution of azide **1** (69 mg, 0.341 mmol) in *n*-decane (50 mL), by stirring at reflux (approx. 170 °C) for 30 min. The reaction mixture was allowed to cool to room temperature and decane was distilled off carefully. The crude product was purified by flash chromatography (CH_2Cl_2) to afford a mixture containing only **3** and **4** as an orange solid (21 mg, 35%). Use of internal standard (1,2,4,5-tetrachlorobenzene) confirmed the yield and gave the composition of **3** (17 mg, 29%) and **4** (4 mg, 6%). Increasing the polarity to 10% MeOH/CH_2Cl_2 afforded pyrido[3,4-*b*]thieno[2,3-*d*]pyrrole (**2a**).[1] Products **3** and **4** were individually isolated by flash chromatography (0.5% MeOH/CH_2Cl_2).

4.3. (*Z*)-4-Isocyano-2-(thiophen-3-yl)but-2-enenitrile (3)

The title compound was isolated as a yellow solid (16 mg, 27%), pure by NMR; R_f 0.37 (CH_2Cl_2); R_f 0.47 (0.5% MeOH/CH_2Cl_2); mp 61–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.60 (1H, dd, *J* 3.0, 1.2, thienyl-H2), 7.42 (1H, dd, *J* 5.1, 3.0, thienyl-H5), 7.26 (1H, dd, *J* 5.1, 1.2, thienyl-H4), 6.64 (1H, t, *J* 6.9, H3), 4.51 (2H, d, *J* 6.9, –CH_2, H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.5 (br s, CH_2–N*C*), 133.3 (thienyl-C3), 132.5 (C3), 128.2 (thienyl-C5), 125.8 (thienyl-*C*2), 123.8 (thienyl-C4), 114.9 (C2), 114.6 (*C*N, C1), 41.7 (t, *J* 7.0, *C*H_2–NC, C4); ^{1}H–^{15}N HMBC (600 MHz, $CDCl_3$) showed correlation between both H3/H4 and –*N*C (δ_N 165 ppm). NMR assignments are based on ATP, HSQC, NOESY and HMBC experiments; IR (KBr) ν_{max} 3080w, 2231w, 2154s, 1624w, 1437m, 1359w, 1276m, 1103w, 955m, 930m, 777s cm^{-1}; EIMS *m*/*z* (%) 174 (M^+, 100), 149 (38), 147 (48), 134 (12), 122 (52), 111 (29), 104 (14), 97 (21); ESI-HRMS calcd for $[M+Na]^+$ $C_9H_6N_2NaS$: 197.0143; obsd 197.0145; calcd for $[M+H]^+$ $C_9H_7N_2S$: 175.0324; obsd 175.0327.

4.4. (*Z*)-4-Amino-2-(thiophen-3-yl)but-2-enenitrile (3b)

Typical procedure for the formation of amine **3a**; isonitrile **3** (10 mg) was dissolved in 10% D_2O/H_2O (1 mL) in an NMR tube. HCl (concd, excess, approx. three drops) was added. Depending on the amount of added HCl, full conversion of **3** to amine **3a** was obtained in 2–30 h. The reaction was monitored by NMR; ^{1}H NMR (400 MHz, H_2O/D_2O/HCl) δ_H 8.31 (2H, br, NH_2), 7.75 (1H, dd, *J* 2.8, 1.2, thienyl-H2), 7.56 (1H, dd, *J* 5.2, 2.8, thienyl-H5), 7.42 (1H, dd, *J* 5.2, 1.2, thienyl-H4), 6.93 (1H, t, *J* 7.6, H3), 4.10 (2H, d, *J* 7.6, –CH_2; H4); ^{13}C NMR (100 MHz, H_2O/D_2O/HCl) δ_C 136.7 (C3), 136.3 (thienyl-C3), 131.3 (thienyl-C5), 128.8 (thienyl-C2), 127.3 (thienyl-C4), 118.4 (C2), 118.0 (-CN, C1), 42.7 (C4); NMR assignments are based on H,H-COSY, HSQC and HMBC experiments; ESI-HRMS calcd for $[M+H]^+$ $C_8H_9N_2S$: 165.0481; obsd 165.0480.

4.5. 2-(Thien-3-yl)-1*H*-pyrrole-3-carbonitrile (4)

The title compound was isolated as an orange oil (4 mg, 6%), pure by NMR; R_f 0.37 (CH_2Cl_2); R_f 0.40 (0.5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 12.1 (1H, br s, NH), 7.87 (1H, dd, *J* 2.8, 1.6, thienyl-H2), 7.72 (1H, dd, *J* 4.8, 2.8, thienyl-H5), 7.59 (1H, dd, *J* 4.8, 1.6, thienyl-H4), 6.97 (1H, dd, *J* 2.8, 2.8 pyrrole-H5), 6.53 (1H, dd, *J* 2.8, 2.4, pyrrole-H4); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 134.3 (pyrrole-C2), 131.0 (thienyl-C3), 127.7 (thienyl-C5), 125.0 (thienyl-C4), 121.5 (thienyl-C2), 119.9 (pyrrole-C5), 118.0 (CN), 112.1 (pyrrole-C4), 87.7 (pyrrole-C3); NMR assignments are based on H,H-COSY, HSQC, NOESY and HMBC experiments; IR (film) ν_{max} 3432br m, 2962w, 2215s, 1725s, 1653m, 1025s, 1006s, 790m cm^{-1}; ESI-HRMS calcd for $[M+H]^+$ $C_9H_7N_2S$: 175.0324; obsd 175.0324.

4.6. (*Z*)-4-Isocyano-2-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)but-2-enenitrile (7)

The title compound was prepared from **5** [4] as described for **3** above. Product **7** was separated from the main product **6** (71%) by flash chromatography (gradient: 0–10% MeOH/CH_2Cl_2) and obtained as a yellow solid (20%), pure by NMR; R_f 0.52 (CH_2Cl_2); mp 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.01 (1H, dd, *J* 2.0, 1.6, pyrrole-H2), 6.77 (1H, dd, *J* 2.8, 2.0, pyrrole-H5), 6.45 (1H, dd, *J* 2.8, 1.6, pyrrole-H4), 6.37 (1H, t, *J* 7.2, H3), 4.45 (2H, d, *J* 7.2, –CH_2, H4), 1.46 (3H, sept, *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 158.3 (t, $^1J_{CN}$ 4.5, CH_2–N*C*), 126.9 (C3), 126.8 (pyrrole-C5), 125.0 (pyrrole-C2), 119.6 (pyrrole-C3), 115.3 (C1, CN), 114.4 (C2), 107.2 (pyrrole-C4), 41.7 (t, *J* 7.0, *C*H_2–NC), 17.7 (TIPS-*C*H_3). 11.5 (TIPS–*C*H); NMR assignments are based on HSQC, HMBC and NOESY experiments; IR (film) ν_{max} 2948s, 2869s, 2215w, 2147s, 1624m, 1491m, 1463m, 1264m, 1227m, 1130s, 1097s, 884s, 795s cm^{-1}; ESI-HRMS calcd for $[M+Na]^+$ $C_{18}H_{27}N_3NaSi$: 336.1867; obsd 336.1882.

4.7. (*Z*)-*N*-(3-Cyano-3-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)allyl)-formamide (7a)

HCl (1.0 mL, concd) and H_2O (1.0 mL) were added to compound **7** (10.0 mg, 31.9 μmol) to form a heterogeneous mixture. The original solid turned into a brown oil after 1 h. Water (10.0 mL) was added and the oil was dissolved in CH_2Cl_2 (20 mL). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The product was obtained as a brown oil (10 mg, 95%). Full conversion of **7** into compound **7a** was obtained as shown by NMR; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.24 (1H, s, C*H*=O), 6.97 (1H, dd, *J* 2.8, 1.2, pyrrole-H2), 6.74 (1H, dd, *J* 2.8, 2.0, pyrrole-H5), 6.46 (1H, t, *J* 7.2, =C*H*–), 6.42 (1H, dd, *J* 2.8, 1.6, pyrrole-H4), 5.85 (1H, s, br, NH), 4.31 (2H, dd, *J* 7.2, 6.4, CH_2–NH), 1.45 (3H, sept, *J* 7.6, C*H*(CH_3)$_2$), 1.10 (18H, d, *J* 7.6, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.0 (*C*H=O), 132.8 (=*C*H–), 126.4 (pyrrole-C5), 124.0 (pyrrole-C2), 120.3 (pyrrole-C3), 116.4 (*C*N), 112.8 (CH=*C*–CN), 107.2 (pyrrole-C4), 38.2 (*C*H_2–NH), 17.7 (TIPS-*C*H_3), 11.5 (TIPS-*C*H); NMR assignments are based on HSQC and HMBC experiments; IR (film) ν_{max} 3319br, 2947s, 2868s, 2219w, 1668s, 1464m, 1385m, 1227m, 1132s, 1098s, 1017m, 884s cm^{-1}; ESI-HRMS calcd for $[M+H]^+$ $C_{18}H_{30}N_3OSi$: 332.2152; obsd 332.2161; calcd for $[M+Na]^+$ $C_{18}H_{29}N_3ONaSi$: 354.1972; obsd 354.1978.

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