Synthesis of Diisothiocyanato-Functionalized 2,2′-Bipyridines

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Abstract: Three new diisothiocyanato-functionalized 2,2′-bipyridines have been synthesized in four consecutive steps. Starting from 4-amino-2-chloro- and 2-amino-6-bromopyridine, respectively, we first prepared the corresponding diamino-2,2′-bipyridines via homo- or Negishi cross-coupling reactions which were subsequently reacted with thiophosgene.

Key words: bipyridine, isothiocyanates, amines, thiophosgene, cross-coupling reactions

Functionalized 2,2′-bipyridines represent a very important class of chelating ligands[1] that have found numerous applications in supra-, nano-, and macromolecular chemistry,[2–4] but also in analytical and photochemistry[5] as well as in catalysis.[6] They are even found as structural motifs in natural products.[7] Therefore, many efforts have been made to develop reliable protocols for the synthesis of 2,2′-bipyridines carrying a broad variety of functional groups that ensure the desired properties or establish interesting building blocks for the synthesis of more sophisticated ligand architectures.[8]

We became interested in this class of compounds and their synthesis during the course of our studies on self-assembled supramolecular aggregates[9] and allosteric receptors.[10] During the latter ones we employed ester and ethynyl groups to link recognition units such as resorcinarene cavitands to a central 2,2′-bipyridine core. In order to enlarge the number of suitable linker groups we were wondering if we could install other functional groups on the bipyridine skeleton. One very attractive group would be the thiourea group that can, itself, be used for very different purposes ranging from anion recognition[11] to organocatalysis[12] and it even has application as an antifungal agent.[13]

The synthesis of thioureas, however, can best be achieved through nucleophilic addition of an amine to an isothiocyanate. Isothiocyanates are very important compounds that are widely applied as chemoselective electrophiles that even tolerate aqueous reaction conditions.[14] So far only 5,5′-diisothiocyanato-2,2′-bipyridine[15] has been synthesized which, however, is the only substitution pattern of a 2,2′-bipyridine that is not suitable to let the bipyridine unit act as an allosteric center for our purposes. Thus, we would like to report the synthesis of 4,4′-, 6,6′- and 4,6′-diisothiocyanate-functionalized 2,2′-bipyridines.

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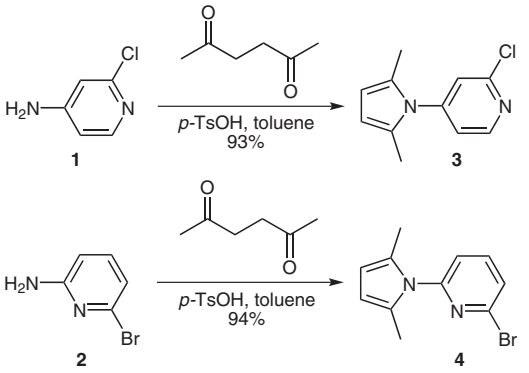
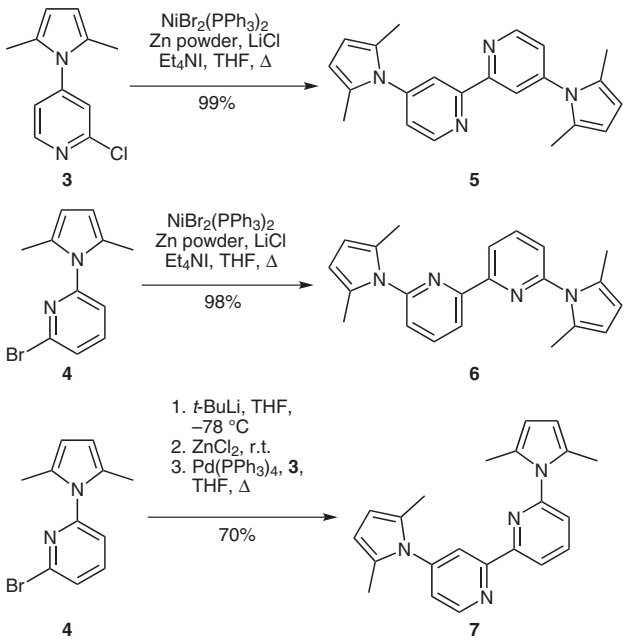
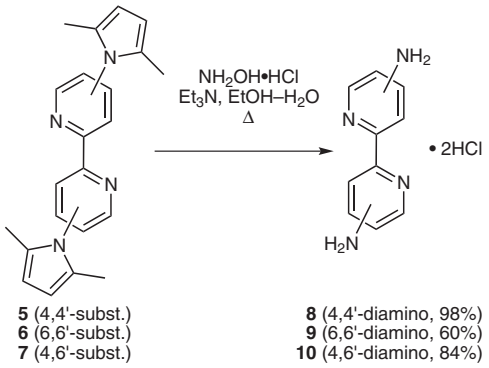


Scheme 1 Synthesis of pyrrole-protected aminopyridines **3** and **4**



Scheme 2 Synthesis of pyrrole-protected diamino-2,2′-bipyridines **5–7**

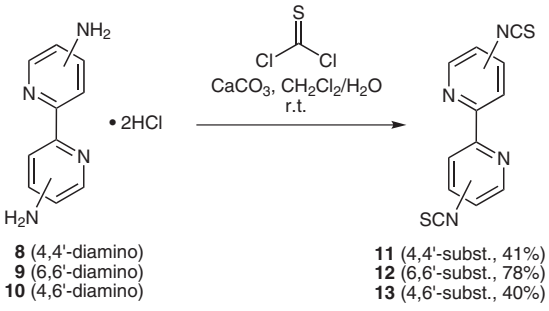
The syntheses started from commercially available 4-amino-2-chloro- (**1**) and 2-amino-6-bromopyridine (**2**), respectively, which were transformed into the corresponding 4,4′-, 6,6′- and 4,6′-diamino-2,2′-bipyridine dihydrochlorides (**8**–**10**) as reported earlier.[16] This was achieved in three consecutive steps involving the introduction of pyrrole protecting groups via reaction of the amines with hexane-2,5-dione, nickel-catalyzed homo- or palladium-catalyzed Negishi cross-coupling, and subsequent deprotection of the amines as depicted in Schemes 1–3.



Scheme 3 Synthesis of diamino-2,2′-bipyridine dihydrochlorides

With the diamine hydrochlorides **8**–**10** in hand, we then explored the transformation into the corresponding diisothiocyanates. The first protocol we tested has recently been developed by Boas and co-workers using a mixture of carbon disulfide, di-*tert*-butyl dicarbonate (Boc_2O), triethylamine, and 4-(dimethylamino)pyridine (DMAP) which was reported to convert alkyl- and arylamines smoothly into the corresponding isothiocyanates.[17] Unfortunately, this reaction did not work at all in our case, presumably because the electron-poor aminopyridines are simply not nucleophilic enough to attack the carbon disulfide.

Therefore, we changed to a protocol developed by Janiak and co-workers using thiophosgene and calcium carbonate in a two-phase system of dichloromethane and water.[15] Employing this procedure we were able to prepare 4,4′-, 6,6′-, and 4,6′-diisothiocyanato-2,2′-biypridines (**11**–**13**) in acceptable to good yields as shown in Scheme 4.



Scheme 4 Synthesis of diisothiocyanato-2,2′-bipyridines

These diisothiocyanates are versatile building blocks for the synthesis of more sophisticated ligand structures and we are currently exploring their potential in the synthesis of new allosteric receptors. Furthermore, however, these compounds can also be envisioned to act as starting points for the synthesis of thioureas or heterocyclic systems for other purposes.

Solvents were dried, distilled and stored under argon according to standard procedures. Reactions with air- and moisture-sensitive transition-metal compounds were performed under an argon atmosphere in oven-dried glassware using standard Schlenk techniques. TLC was performed on aluminum plates (silica gel 60 F254) from Merck and the products were visualized under UV light (254 or 366 nm). Products were purified by column chromatography on silica gel 60 (0.04–0.063 mm).

^1H and ^{13}C NMR spectra were recorded at 298 K at 300.1 and 75.5 MHz, respectively; ^1H NMR relative to residual non-deuterated solvent as the internal standard and ^{13}C NMR relative to the deuterated solvent as the internal standard. Signals were assigned on the basis of ^1H, ^{13}C, HMQC, and HMBC-NMR experiments. ESI-MS were recorded on an ESI-QToF mass spectrometer. Elemental analyses were carried out with a Heraeus Vario EL.

Chemicals and reagents (except for the solvents) obtained from commercial sources were used as received. 2-Chloro-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine (**3**),[18] 2-bromo-6-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine (**4**),[19] 4,4′-bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (**5**),[16] 6,6′-bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (**6**),[16] 4,6′-bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (**7**),[16] 4,4′-diamino-2,2′-bipyridine dihydrochloride (**8**),[16] and 6,6′-diamino-2,2′-bipyridine dihydrochloride (**9**)[16] were prepared according to published procedures.

4,6′-Diamino-2,2′-bipyridine Dihydrochloride (10)

4,6′-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (**7**, 0.83 g, 2.4 mmol) was mixed with $NH_2OH{\cdot}HCl$ (3.36 g, 48 mmol, 20 equiv), Et_3N (1.2 mL), EtOH (23 mL), and H_2O (6 mL). The resulting mixture was refluxed for 4 d. After cooling to r.t. the mixture was quenched by pouring into ice-cold 1 M HCl (20 mL). The resulting soln was washed with *i*-Pr_2O (20 mL) and the pH was adjusted to 9–10 by careful addition of 6 M NaOH. The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined extracts were dried (Na_2SO_4). After removal of the solvent the brownish residue was dissolved in EtOH. Et_2O (30 mL) was added and the mixture was filtered. 2 M HCl in Et_2O (2.2 mL, 4.4 mmol) was added to the filtrate and pure **10** precipitated, which was collected and dried in vacuo to give a slightly off-white solid; yield: 520 mg (84%).

^1H NMR (300.1 MHz, D_2O, 298 K): δ = 6.94 (dd, ^3J = 7.1 Hz, ^4J = 2.4 Hz, 1 H, H5), 7.15 (dd, ^3J = 9.0 Hz, ^4J = 0.8 Hz, 1 H, H5′), 7.19 (d, ^4J = 2.4 Hz, 1 H, H3), 7.26 (dd, ^3J = 7.4 Hz, ^4J = 0.8 Hz, 1 H, H3′), 7.97 (dd, ^3J = 9.0 Hz, ^3J = 7.4 Hz, 1 H, H4′), 8.09 (d, ^3J = 7.1 Hz, 1 H, H6).

^{13}C NMR (75.8 MHz, D_2O, 298 K): δ = 110.3 (C3), 111.2 (C5), 115.1 (C3′), 117.7 (C5′), 140.5 (C2′), 142.2 (C6), 144.7 (C2), 145.1 (C4′), 157.5(C6′), 162.1 (C4).

This compound has been described as the non-protonated diamine before.[16]

4,4′-Diisothiocyanato-2,2′-bipyridine (11); Typical Procedure

Compound **8** (0.2 g, 0.77 mmol) and $CaCO_3$ (0.39 g, 3.9 mmol, 5 equiv) were suspended in a mixture of CH_2Cl_2 (7 mL) and H_2O (4 mL). After the addition of thiophosgene (0.2 mL, 2.5 mmol), the mixture was stirred at r.t. for 24 h. Excess $CaCO_3$ was filtered off and washed with CH_2Cl_2 (3 × 10 mL); the filtrates were collected. The combined organic phases were dried ($MgSO_4$). After evaporation of the solvent the crude product was washed with H_2O (15 mL) and subjected to column chromatography (silica gel, cyclohexane–EtOAc, 9:1) to give the desired product as a light-yellow solid; yield: 85 mg (41%); mp 143 °C; R_f = 0.39 (cyclohexane–EtOAc, 9:1).

^1H NMR (300.1 MHz, $CDCl_3$, 298 K): δ = 7.13 (dd, ^3J = 5.1 Hz, ^4J = 1.9 Hz, 2 H, H5, H5′), 8.26 (d, ^4J = 1.9 Hz, 2 H, H3/H3′), 8.64 (d, ^3J = 5.1 Hz, 2 H, H6/H6′).

^{13}C NMR (75.8 MHz, $CDCl_3$, 298 K): δ = 118.1 (C3/C3′), 120.2 (C5/C5′), 140.6 (NCS), 141.1 (C4/C4′), 150.6 (C6/C6′), 156.7 (C2/C2′).

MS (ESI+, MeOH): *m/z* (%) = 271.0 $[M + H]^+$.

Anal. Calcd for $C_{12}H_6N_4S_2 \cdot 0.5H_2O \cdot 0.125EtOAc$: C, 51.71; H, 2.78; N, 19.30; S, 22.09. Found: C, 51.62; H, 3.07; N, 19.02; S, 22.39.

6,6′-Diisothiocyanato-2,2′-bipyridine (12)

Following the typical procedure using **9** (0.2 g, 0.77 mmol), $CaCO_3$ (0.39 g, 3.9 mmol, 5 equiv), and thiophosgene (0.2 mL, 2.5 mmol) with column chromatography (silica gel, cyclohexane–EtOAc, 9:1) as a light-yellow solid; yield: 160 mg (78%); mp 154 °C; R_f = 0.42 (cyclohexane–EtOAc, 9:1).

^{1}H NMR (300.1 MHz, $CDCl_3$, 298 K): δ = 7.15 (dd, ^3J = 7.8 Hz, ^4J = 0.8 Hz, 2 H, H5, H5′), 7.85 (dd, ^3J = 7.8 Hz, ^3J = 7.8 Hz, 2 H, H4/H4′), 8.32 (dd, ^3J = 7.8 Hz, ^4J = 0.8 Hz, 2 H, H3/H3′).

^{13}C NMR (75.8 MHz, $CDCl_3$, 298 K): δ = 119.8 (C3/C3′), 120.3 (C5/C5′), 139.7 (C4/C4′), 141.5 (NCS), 145.7 (C6/C6′), 155.0 (C2/C2′).

MS (ESI+, MeOH): *m/z* (%) = 271.0 $[M + H]^+$, 303.1 [M + MeOH + H]$^+$.

Anal. Calcd for $C_{12}H_6N_4S_2 \cdot 0.125EtOAc$: C, 53.36; H, 2.51; N, 19.91; S, 22.79. Found: C, 53.63; H, 2.66; N, 19.83; S, 23.00.

4,6′-Diisothiocyanato-2,2′-bipyridine (13)

Following the typical procedure using **10** (0.2 g, 0.77 mmol), $CaCO_3$ (0.39 g, 3.9 mmol, 5 equiv), and thiophosgene (0.2 mL, 2.5 mmol) with column chromatography (silica gel, cyclohexane–EtOAc, 2:1) as a light-yellow solid; yield: 82 mg (40%); mp 98 C; R_f = 0.37 (cyclohexane–EtOAc, 2:1).

^{1}H NMR (300.1 MHz, $CDCl_3$, 298 K): δ = 7.12 (dd, ^3J = 5.2 Hz, ^4J = 2.0 Hz, 1 H, H5), 7.17 (dd, ^3J = 7.8 Hz, ^4J = 0.7 Hz, 1 H, H5′), 7.85 (dd, ^3J = 7.8 Hz, ^3J = 7.8 Hz, 1 H, H4′), 8.20 (d, ^4J = 2.0 Hz, 1 H, H3), 8.33 (dd, ^3J = 7.8 Hz, ^4J = 0.7 Hz, 1 H, H3′), 8.63 (d, ^3J = 5.2 Hz, 1 H, H6).

^{13}C NMR (75.8 MHz, $CDCl_3$, 298 K): δ = 117.9 (C3), 119.8 (C3′), 120.2 (C5), 120.6 (C5′), 139.7 (C4′), 140.2 (NCS at C6′), 141.0 (C4), 141.4 (NCS at C4), 145.8 (C6′), 150.6 (C6), 155.2 (C2′), 156.7 (C2).

MS (ESI+, MeOH): *m/z* (%) = 271.0 $[M + H]^+$, 303.1 [M + MeOH + H]$^+$.

Anal. Calcd for $C_{12}H_6N_4S_2 \cdot 0.1H_2O \cdot 0.1EtOAc$: C, 53.01; H, 2.51; N, 19.94; S, 22.83. Found: C, 52.98; H, 2.58; N, 20.03; S, 23.07.

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