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Practical Synthesis of Iodo Phenothiazines. A Facile Access to Electrophore Building Blocks

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Abstract: Bromine−lithium exchange of the mono- and dibromophenothiazines **1** and **3a** regiospecifically furnishes upon electrophilic trapping with iodine the iodo- and diiodophenothiazines **2**, **3b**, and **3d** in excellent yield. The 3-bromo-7-iodophenothiazine **3d** can be submitted to regioselective and sequential Suzuki coupling reactions with phenothiazine mono- and bisboronates **4** and **5** and/or (hetero)aryl boronic acids to give the bromodiphenothiazine **6a**, the dibromo terphenothiazine **7**, and the (hetero)aryl-substituted phenothiazine dyads **6b**−**d** in moderate to good yields.

Iodo (hetereo)arenes are the most reactive halogen components in all types of cross-coupling reactions.[1] In addition, carbon−iodine bonds can be selectively and often sequentially addressed if other bromo or chloro substituents are present within a halide substrate. This opens new perspectives for directed and unsymmetrical functionalizations of all kinds of (hetero)aromatic compounds. Just recently, as part of our program[2] directed to synthesize and investigate phenothiazinyl-based molecular wires, we have focused on the syntheses of suitable phenothiazine derivatives that can be applied as building blocks in palladium-catalyzed cross-coupling reactions.[2,3] Although, 3-bromo- and 3,7-dibromophenothiazines represent excellent substrates in Suzuki coupling reactions and they can be either synthesized by bromination of phenothiazines[4] or de novo construction of the phenothiazine framework,[5] there is also need for iodophenothiazines, in particular, to exploit their higher reactivity in oxidative additions for the selective synthesis of oligo(phenothiazines) by cross-coupling strategies. Surprisingly, for phenothiazines, an important class of heterocycles with a broad pharmacological application[6,7] and with low reversible oxidation potentials[6,8] that makes them suitable as electrophores in organic materials[9] and probes for photoinduced electron-transfer studies,[10] the conventional protocols to 3-iodophenothiazine derivatives are rather tedious. They comprise the electrophilic mercuration of phenothiazine (with all associated difficulties and ecological short comings) followed by a mild iodolysis[11] or the de novo construction of the tricyclic phenothiazine core by a sequence of nucleophilic addition and a Smiles rearrangement.[12] In contrary to related electron-rich aromatic systems, in particular, anilines[13] and carbazoles,[14] the electrophilic iodination of phenothiazines under similar conditions was met with failure and resulted only in the generation of phenothiazine radical cation salts.

Inspired and encouraged by the ease of bromo−lithium exchange in bromophenothiazines[15] and the subsequent electrophilic trapping reactions of the resulting lithio phenothiazines that we could extend to the synthesis of borylated phenothiazines,[3] we considered the trapping

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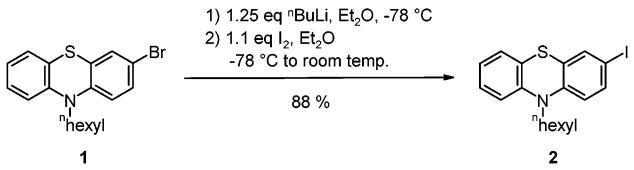
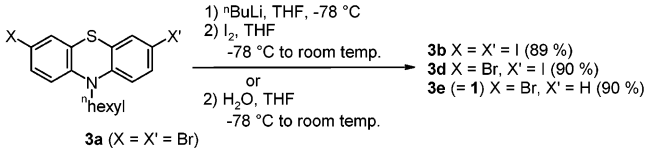
SCHEME 1. Synthesis of 10-*n*-Hexyl-3-iodo-10*H*-phenothiazine (2)



SCHEME 2. Iodo and Diiodo Phenothiazines 3b, 3d, and 3e by Lithiation of Dibromophenothiazine 3a



of the corresponding lithio- and dilithiophenothiazines with iodine. Thus, upon treating the 3-bromophenothiazine **1** with *n*-butyllithium at −78 °C and adding iodine to the resulting 3-lithiophenothiazine, the 3-iodophenothiazine **2** is regiospecifically formed in excellent yield as a pale yellow oil (Scheme 1).

The structure of **2** is unambiguously supported by spectroscopic data (^{1}H, ^{13}C NMR, IR, UV/vis, MS) and a correct combustion analysis. Most characteristically, in the ^{13}C NMR spectrum of **2**, the diagnostic quaternary carbon resonance of the center bearing the iodo substituent appears at δ 85.2. This signal is shifted to rather high field as a consequence of the heavy atom effect.[16]

Likewise, the 3,7-dibromophenothiazine **3a** is transformed into the dilithio derivative which, in turn, is trapped with iodine to give the 3,7-diiodophenothiazine **3b** in good yield as a pale yellow crystalline solid (Scheme 2). The symmetric C_S-structure of **3b** is supported by the characteristic appearance of only a single set of aromatic proton and carbon resonances in the NMR spectra. Expectedly, the diagnostic iodine bearing quaternary carbon nuclei are shifted to higher field and can be detected at δ 84.8.

However, upon addition of only 1 equiv of *n*-butyllithium to the dibromide **3a** and subsequent addition of 1 equiv of iodine the unsymmetrical 3-bromo-7-iodophenothiazine **3d** is formed in excellent yield as pale yellow needles. The intermediacy of the presumed 3-bromo-7-lithio derivative **3c** (X = Br, X′ = Li) is additionally supported by the addition of water which, in turn, furnishes the 3-bromo phenothiazine **3e** in excellent yield as a yellow oil. This selective mono debromination represents an alternative access to 3-bromophenothiazines such as compound **1**.

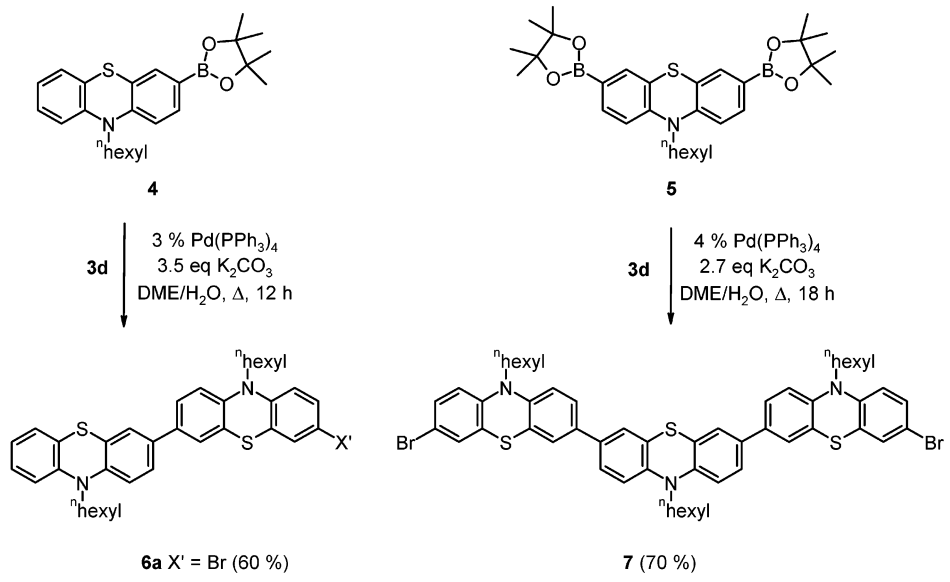
In the ^{13}C NMR spectrum of the bromo iodo derivative **3d** the diagnostic quaternary nuclei bearing the bromo and the iodo substituent can be found at δ 115.0 and δ 84.8, respectively. The molecular composition is strongly supported by the characteristic isotope pattern in the FAB mass spectrum.

With this bromo iodo derivative in hand, we wanted to probe the utility of the compound **3d** for selective Suzuki coupling reactions, addressing only the carbon−iodine bond in the oxidative addition. Indeed, upon subjecting the bromo iodo derivative **3d** with phenothiazine mono- and bisboronic esters **4** and **5**,[3] respectively, to the conditions of the Suzuki coupling, the bromodiphenothiazine **6a** and the dibromoterphenothiazine **7** can be selectively obtained in good yields as yellow glassy resins (Scheme 3).

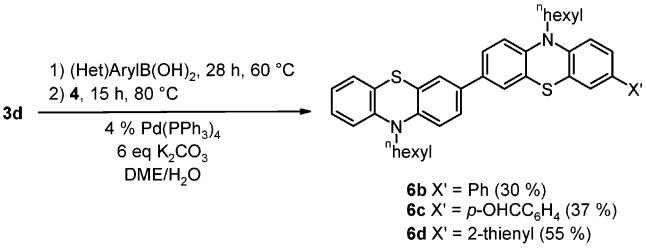
The unsymmetrical structure of **6a** and the symmetrical structure of **7** is reflected and can be assigned by the expected sets of resonances in the ^{1}H and ^{13}C NMR spectra. The selective cross-coupling of only the carbon−iodine center is confirmed by the appearance of the bromine bearing quaternary carbon resonance at δ 114.7 for both compounds. In the FAB mass spectra the molecular peaks show the predicted isotope patterns for a mono- (**6a**) and a dibromo compound (**7**).

Finally, we wanted to exploit the gradual reactivity difference of carbon−iodine and carbon−bromine bonds of the bromo iodo phenothiazine **3d** in cross-coupling reactions for two sequential Suzuki couplings in a one-

SCHEME 3. Selective Suzuki Coupling with the Bromoiodophenothiazine 3d



SCHEME 4. Sequential Suzuki Coupling of 3d to the (Hetero)aryl-Substituted Phenothiazine Dyads 6



pot reaction. Thus, upon reacting the bromo iodo derivative **3d** under the conditions of the Suzuki coupling first with (hetero)aryl boronic acids for 28 h at 60 °C, and then, after addition of the phenothiazine monoboronic ester **4**,[3] for 15 h at 80 °C, the (hetero)aryl-substituted diphenothiazines **6b**−**d** are obtained in moderate to good yields as yellow to orange glassy resins (Scheme 4).

The structures of the (hetero)arylated dyads **6** are unambiguously supported by the appearance of the expected sets of resonances in the ^{1}H and ^{13}C NMR spectra, the vibrational, electronic, and mass spectra, and by correct combustion analyses. In the FAB mass spectra the molecular peaks are the base peaks and show the predicted isotope patterns for the compounds **6**.

In conclusion we have developed a straightforward access to iodophenothiazines by a sequence of bromine−lithium exchange and subsequent iodolysis of the intermediate lithiophenothiazine. This synthetic route to iodophenothiazines circumvents the tedious preparation of mercuriophenothiazines and overcomes the problem of lacking electrophilic iodinations of phenothiazines. In addition, we are able to synthesize bromo iodo phenothiazines that are versatile unsymmetrical phenothiazines for sequential cross-coupling reactions and suitable starting materials for the selective synthesis of longer arrays of conjugated oligo(phenothiazines). Besides, this easy access to iodo phenothiazines will stimulate the development of novel core-substituted phenothiazines with a high potential as effective pharmaceuticals. Studies addressing the synthetic exploitation of iodo phenothiazines and the electronic properties of oligo(phenothiazines) are currently under investigation.

Experimental Section

10-*n*-Hexyl-3,7-diiodo-10*H*-phenothiazine (3b). To a cooled solution of 2.00 g (4.53 mmol) of 3,7-dibromo-10*H*-hexylphenothiazine (**3a**) in 50 mL of dry THF was added dropwise over 10 min at −78 °C (dry ice/2-propanol) 5.7 mL (9.1 mmol) of a solution of 1.6 M *n*-butyllithium in hexanes. After the reaction mixture was stirred for 30 min at −78 °C, a solution of 2.3 g (9.1 mmol) of iodine in 30 mL of diethyl ether was slowly added over 15 min. After being stirred for another 30 min, the mixture was allowed to come to room temperature, 200 mL of water was added, and the aqueous phase was extracted several times with small portions of diethyl ether. The combined organic phases were dried with magnesium sulfate, and the solvents were removed in vacuo. The residue was chromatographed on silica gel (acetone/hexane 1:10) and crystallized from hexane to give 2.15 g (89%) of **3b** as colorless crystals, mp 81 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 0.81−0.86 (m, 3 H), 1.26−1.28 (m, 4 H), 1.39−1.45 (m, 2 H), 1.74 (m, J = 7.7 Hz, 2 H), 3.89 (t, J = 7.0 Hz, 2 H), 6.83 (d, J = 8.5 Hz, 2 H), 7.43 (d, J = 1.9 Hz, 2 H), 7,51 (dd, J = 8.5 Hz, J = 1.9 Hz, 2 H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 14.1 (CH_3), 23.1 (CH_2), 26.9 (CH_2), 27.1 (CH_2), 32.0 (CH_2), 47.7 (CH_2), 84.8 ($C_{quat.}$), 118.7 (CH), 127.3 ($C_{quat.}$), 135.7 (CH), 137.1 (CH), 145.8 ($C_{quat.}$). MS (FAB+) *m*/*z* (%): 535 (M^+). IR (KBr), $\tilde{\nu}$ 2952 cm^{-1}, 2924, 2853, 1627, 1455, 1394, 1250, 801. UV/vis (CH_2Cl_2), λ_{max} (ϵ) 268 nm (44700), 322 nm (6700). Anal. Calcd for $C_{18}H_{19}I_2NS$ (535.2): C 40.39, H 3.58, N 2.62, S 5.99, I 47.42; found: C 40.61, H 3.44, N 2.69, S 5.96, I 47.69.

7-Bromo-10,10′-bis(*n*-hexyl)-3,3′-bi(10*H*-phenothiazine) (6a). A solution of 4.43 g (9.1 mmol) of **3d**, 3.37 g (8.30 mmol) of **4**, 0.38 g (0.30 mmol) of $Pd(PPh_3)_4$, and 4.65 g (33 mmol) of potassium carbonate in a degassed mixture of 50 mL of DME and 20 mL of water was heated to reflux temperature for 30 h under nitrogen. After the reaction mixture was cooled to room temperature, a solution of 0.5 g of Na_2SO_3 in 100 mL of water was added. The aqueous phase was extracted with diethyl ether (2 × 50 mL), the combined organic layers were dried with magnesium sulfate, and the solvents were removed in vacuo. The residue was chromatographed on silica gel (acetone/hexane 1:10) to give 3.18 g (60%) of **6a** as a yellow glassy resin. ^{1}H NMR (acetone-d_6, 250 MHz): δ 0.82−0.87 (m, 6 H), 1.27−1.29 (m, 8 H), 1.43−1.45 (m, 4 H), 1.71−1.83 (m, 4 H), 3.89 (t, J = 6.8 Hz, 2 H), 3.92 (t, J = 7.0 Hz, 2 H), 6.90−7.03 (m, 5 H), 7.13−7.22 (m, 2 H), 7.26−7.32 (m, 2 H), 7.35 (d, J = 2.2 Hz, 2 H), 7.39−7.44 (m, 2 H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 14.2 (CH_3), 23.2 (CH_2), 27.1 (CH_2), 27.1 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 32.1 (CH_2), 32.2 (CH_2), 47.8 (CH_2), 47.9 (CH_2), 114.7 ($C_{quat.}$), 116.5 (CH), 116.6 (CH), 116.7 (CH), 117.0 (CH), 118.0 (CH), 123.2 (CH), 125.0 ($C_{quat.}$), 125.5 (CH), 125.6 (CH), 126.0 ($C_{quat.}$), 126.1 (CH), 126.3 (CH), 127.6 ($C_{quat.}$) 128.0 (CH), 128.3 (CH), 130.0 (CH), 130.9 (CH), 134.7 ($C_{quat.}$), 135.3 ($C_{quat.}$), 144.7 ($C_{quat.}$), 145.3 ($C_{quat.}$), 145.4 ($C_{quat.}$), 146.0 ($C_{quat.}$). MS (FAB+) *m*/*z* (%): 644 (M^+, 100), 599 (M^+, 27), 474 ($M^+ - 2\ C_6H_{13}$, 20). IR (KBr), $\tilde{\nu}$ 2952 cm^{-1}, 2925, 2853, 1600, 1575, 1457, 1250, 871, 806, 746. UV/vis (CH_2Cl_2), λ_{max} (ϵ) 268 nm (44000). Anal. Calcd for $C_{36}H_{39}BrN_2S_2$ (643.8): C 67.17, H 6.11, N 4.35, S 9.96, Br 12.41; found: C 67.13, H 6.20, N 4.35, S 9.89, Br 12.23.

10,10′-Bis(*n*-hexyl)-7-(2-thienyl)-3,3′-bi(10*H*-phenothiazine) (6d). A solution of 0.49 g (1.00 mmol) of **3d**, 0.13 g (1.00 mmol) of 2-thienyl boronic acid, 46 mg (40 μmol) of $Pd(PPh_3)_4$, and 0.83 g (6.00 mmol) of potassium carbonate in a degassed mixture of 25 mL of DME and 10 mL of water was heated to 60 °C for 28 h under nitrogen. After the reaction mixture was cooled to room temperature, 0.41 g (1.00 mmol) of **8** was added 10 mL of degassed DME, and the reaction mixture was heated at 80 °C for 12 h. After the reaction mixture was cooled to room temperature, a solution of 0.5 g of Na_2SO_3 in 100 mL of water was added. The aqueous phase was extracted with twice (2 × 50 mL) with diethyl ether, the combined organic layers were dried with magnesium sulfate, and the solvents were removed in vacuo. The residue was chromatographed on silica gel (acetone/hexane 1:20) to give 0.36 g (55%) of **6d** as a yellow glassy resin. ^{1}H NMR (acetone-d_6, 300 MHz): δ 0.85−0.87 (m, 6 H), 1.29−1.36 (m, 8 H), 1.43−1.52 (m, 4 H), 1.76−1.88 (m, 4 H), 3.96 (t, J = 6.7 Hz, 2 H), 3.98 (t, J = 6.7 Hz, 2 H), 6.91−6.96 (m, 1 H), 7.01−7.10 (m, 5 H), 7.14−7.23 (m, 2 H), 7.37−7.40 (m, 4 H), 7.43−7.44 (m, 2H), 7.45−7.49 (m, 2 H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 14.2 (CH_3), 23.3 (CH_2), 27.1 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 32.2 (CH_2), 47.9 (CH_2), 48.0 (CH_2), 116.6 (CH), 116.8 (CH), 116.6 (CH), 123.3 (CH), 123.4 (CH), 124.9 (CH), 125.2 (CH), 125.3 ($C_{quat.}$), 125.5 (CH), 125.6 (CH), 125.8 (CH), 126.0 ($C_{quat.}$), 126.1 (CH), 126.2 (CH), 128.0 (CH), 128.3 (CH), 129.0 (CH), 129.9 ($C_{quat.}$), 134.9 ($C_{quat.}$), 135.1 ($C_{quat.}$), 143.9 ($C_{quat.}$), 144.8 ($C_{quat.}$), 145.3 ($C_{quat.}$), 146.1 ($C_{quat.}$). MS (FAB+) *m*/*z* (%): 646 (M^+, 100), 561 ($M^+ - C_6H_{16}$, 15), 476 ($M^+ - 2\ C_6H_{13}$, 13). IR (KBr): $\tilde{\nu}$ 2953 cm^{-1}, 2926, 2854, 1630, 1529, 1384, 1333, 1249, 874, 808, 748, 689. UV/vis (CH_2Cl_2): λ_{max} (ϵ) 288 nm (50000). Anal. Calcd for $C_{40}H_{42}N_2S_3$ (647.0): C 74.26, H 6.54, N 4.33, S 14.87; found: C 74.03, H 6.64, N 4.40, S 15.10.

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Supporting Information Available: Experimental details of compounds **2**, **3d**, **3e**, **7**, and **6a**−**c**; proton and carbon NMR spectra of compounds **2**, **3b**, 3**d**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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