Practical Synthesis of Iodo phenothiazines – A Facile Access to Electrophore Building Blocks

Markus Sailer, Radu-Adrian Gropeanu, and Thomas J. J. Müller*

Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer

Feld 270, D-69120 Heidelberg

SUPPORTING INFORMATION

Table of Contents:

I. Experimental procedures	S2
1. General procedure (GP) for the bromine lithium exchange and the subsequent iodolysis of the lithio phenothiazines.	S2
1.1. 10-<i>n</i>-Hexyl-3-iodo-10<i>H</i>-phenothiazine (2)	S3
1.2. 3-Bromo-10-<i>n</i>-hexyl-7-iodo-10<i>H</i>-phenothiazine (3d)	S3
1.3. 3-Bromo-10-<i>n</i>-hexyl-10<i>H</i>-phenothiazine (3e)	S4
2. 3',7''-Dibromo-10',10''-bis(<i>n</i>-hexyl)-3,7':7,3''-ter(10<i>H</i>-phenothiazine) (7)	S4
3. 10,10'-Bis(<i>n</i>-hexyl)-7-phenyl-3,3'-bi(10<i>H</i>-phenothiazine) (6b)	S5
4. 7-(4-Formylphenyl)-10,10'-bis(<i>n</i>-hexyl)-3,3'-bi(10<i>H</i>-phenothiazine) (6c)	S6
I. ¹H NMR spectra	S9
II. ¹³C NMR spectra	S13

I. Experimental procedures

General Experimental

Reagents, catalysts, ligands and solvents were purchased reagent grade and used without further purification. Diethylether, dimethoxyethane, and THF were dried and distilled according to standard procedures.¹ The bromo phenothiazine **1**,² the dibromo phenothiazine **3a**,³ and the borylated phenothiazines **4** and **5**⁴ were prepared according to literature procedures. - Column chromatography: silica gel 60, mesh 70-230. TLC: silica gel plates. Melting points: uncorrected values. - ¹H and ¹³C NMR spectra: [D₆] acetone (locked to Me₄Si).⁵ The assignments of quaternary C, CH, CH₂ and CH₃ has been made by using DEPT spectra.

1. General procedure (GP) for the bromine lithium exchange and the subsequent iodolysis of the lithio phenothiazines.

To a cooled solution of 1 equivalent of 3-bromo-10*H*-hexylphenothiazine (**1**) or 3,7-dibromo-10*H*-hexylphenothiazine (**3a**) in 50 mL of dry diethylether or dry THF was added dropwise over 5 to 10 min at -78 °C (dry ice/iso-propanol) 1 or 2 equivalents of 1.6 *M* *n*-butyllithium in hexane. After stirring for 30 min at -78 °C a solution of 1 or 2 equivalents of iodine (or water) in 30 mL of diethylether was slowly added over 15 min to the reaction mixture. After stirring for another 30 min the mixture was allowed to come to room temp. and 200 mL of water were added and the aqueous phase was extracted several times with small portions of diethylether. 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) to give the pure iodo phenothiazine derivatives.

1.1. 10-*n*-Hexyl-3-iodo-10*H*-phenothiazine (**2**).

According to the GP the reaction of 0.70 g (1.93 mmol) of 3-bromo-10-*n*-hexyl-10*H*-phenothiazine (**1**) in 50 mL of dry diethylether, 1.5 mL (2.4 mmol) of butyllithium and 0.52 g (2.05 mmol) of iodine furnished after chromatography on silica gel (acetone/hexane 1:10) and after crystallization from hexane 0.63 g (88 %) of **2** as a pale yellow oil.

¹H NMR ([D₆] acetone, 300 MHz): δ 0.80-0.85 (m, 3 H), 1.24-1.28 (m, 4 H), 1.39-1.44 (m, 2 H), 1.69-1.79 (m, $J = 7.2$ Hz, 2 H), 3.87 (t, $J = 7.0$ Hz, 2 H), 6.78 (d, $J = 8.67$ Hz, 1 H), 6.93 (dt, $J = 7.5$ Hz, $J = 1.3$ Hz, 1 H), 6.98 (d, $J = 7.8$ Hz, 1 H), 7.11 (dd, $J = 7.5$ Hz, $J = 1.5$ Hz, 1 H), 7.15-7.21 (m, 1 H), 7.40 (d, $J = 2.1$ Hz, 1 H), 7.46 (dd, $J = 8.7$ Hz, $J = 2.1$ Hz, 1 H). ¹³C NMR ([D₆] acetone, 75 MHz): δ 14.9 (CH₃), 23.9 (CH₂), 27.7 (CH₂), 28.0 (CH₂), 32.8 (CH₂), 48.4 (CH₂), 85.2 (C_{quat.}), 117.5 (CH), 119.2 (CH), 124.2 (CH), 125.4 (C_{quat.}), 128.8 (CH), 128.8 (C_{quat.}), 129.2 (CH), 136.4 (CH), 137.6 (CH), 146.5 (C_{quat.}), 147.0 (C_{quat.}). MS (FAB+) m/z (%): 409 (M⁺). IR (neat), $\tilde{\nu}$ 2953 cm⁻¹, 2926, 2854, 1589, 1559, 1482, 1455, 1389, 1295, 1250, 805. UV/VIS (CH₂Cl₂), λ_{max} (ε) 264 nm (38800). Anal. calcd. for C₁₈H₂₀INS (409.3): C 52.82, H 4.92, N 3.42, S 7.83, I 31.00; found: C 53.14, H 4.97, N 3.48, S 7.91, I 31.08.

1.2. 3-Bromo-10-*n*-hexyl-7-iodo-10*H*-phenothiazine (**3d**)

According to the GP the reaction of 4.00 g (9.07 mmol) of 3,7-dibromo-10*H*-hexylphenothiazine (**3a**) in 50 mL of dry THF, 5.7 mL (9.1 mmol) of butyllithium and 2.3 g (9.1 mmol) of iodine in 20 mL of THF furnished after chromatography on silica gel (acetone/hexane 1:10) and after crystallization from hexane 3.98 g (90 %) of **3d** as pale yellow needles, Mp. 62-63 °C.

¹H NMR ([D₆] acetone, 300 MHz): δ 0.81-0.86 (m, 3 H), 1.26-1.28 (m, 4 H), 1.36-1.44 (m, 2 H), 1.74 (m, $J = 7.0$ Hz, 2 H), 3.87 (t, $J = 7.0$ Hz, 2 H), 6.82 (d, $J = 8.4$ Hz, 1 H), 6.93 (d, $J = 8.8$ Hz, 1 H), 7.26 (d, $J = 2.2$ Hz, 1 H), 7.32 (dd, $J = 8.9$ Hz, $J = 2.2$ Hz, 1 H), 7.42 (d, $J = 2.2$ Hz, 1 H), 7.50 (dd, $J = 8.4$ Hz, $J = 2.2$ Hz, 1 H). ¹³C NMR ([D₆] acetone, 75 MHz): δ 14.1

(CH₃), 23.1 (CH₂), 26.9 (CH₂), 27.2 (CH₂), 32.0 (CH₂), 47.8 (CH₂), 84.8 (C_{quat.}), 115.0 (C_{quat.}), 118.2 (CH), 118.6 (CH), 127.2 (C_{quat.}), 127.2 (C_{quat.}), 130.0 (CH), 131.0 (CH), 135.7 (CH), 137.2 (CH), 145.1 (C_{quat.}), 145.8 (C_{quat.}). MS (FAB+) *m/z* (%): 489 (⁸¹BrM⁺), 487 (⁷⁹BrM⁺). IR (KBr), $\tilde{\nu}$ 2953 cm⁻¹, 2926, 2854, 1638, 1456, 1269, 1250, 801. UV/VIS (CH₂Cl₂), λ_{max} (ε) 266 nm (43200). Anal. calcd. for C₁₈H₁₉BrINS (488.2): C 44.28, H 3.92, N 2.87, S 6.57; found: C 44.62, H 4.07, N 2.97, S 7.09.

1.3. 3-Bromo-10-*n*-hexyl-10*H*-phenothiazine (**3e**).

According to the GP the reaction of 2.10 g (4.76 mmol) of 3,7-dibromo-10*H*-hexylphenothiazine (**3a**) in 50 mL of dry THF, 3.0 mL (4.8 mmol) of butyllithium and 1 mL of water furnished after chromatography on silica gel (acetone/hexane 1:10) 1.38 g (90 %) of **3e** as a yellow oil.

¹H NMR ([D₆] acetone, 500 MHz): δ 0.82-0.86 (m, 3 H), 1.27-1.29 (m, 4 H), 1.41-1.44 (m, 2 H), 1.72-1.76 (m, *J* = 7.1 Hz, 2 H), 3.90 (t, *J* = 7.0 Hz, 2 H), 6.92 (d, *J* = 7.0 Hz, 1 H), 6.94 (dt, *J* = 7.4 Hz, *J* = 0.8 Hz, 1 H), 7.01 (dd, *J* = 8.2 Hz, *J* = 0.8 Hz, 1 H), 7.12 (dd, *J* = 6.0 Hz, *J* = 1.3 Hz, 1 H), 7.19 (ddd, *J* = 8.3 Hz, *J* = 7.3 Hz, *J* = 1.2 Hz, 1 H), 7.25 (d, *J* = 1.8 Hz, 1 H), 7.30 (dd, *J* = 7.0 Hz, *J* = 1.8 Hz, 1 H). ¹³C-NMR ([D₆] acetone, 125 MHz): δ 14.2 (CH₃), 23.2 (CH₂), 27.0 (CH₂), 27.4 (CH₂), 32.1 (CH₂), 47.8 (CH₂), 114.7 (C_{quat.}), 116.8 (CH), 118.1 (CH), 118.3 (CH), 123.6 (CH), 124.6 (C_{quat.}), 128.1 (CH), 128.5 (C_{quat.}), 129.9 (CH), 130.9 (CH), 145.7 (C_{quat.}), 145.8 (C_{quat.}). MS (EI) *m/z* (%): 363 (⁸¹BrM⁺, 96), 361 (⁷⁹BrM⁺, 96), 292 (⁸¹BrM⁺ - C₃H₁₁, 70), 290 (⁷⁹BrM⁺ - C₃H₁₁, 70), 277 (⁸¹BrM⁺ - C₆H₁₄, 100), 275 (⁷⁹BrM⁺ - C₆H₁₄, 100).

2. 3',7''-Dibromo-10',10''-bis(*n*-hexyl)-3,7':7,3''-ter(10*H*-phenothiazine) (**7**)

A solution of 3.01 g (6.17 mmol) of **3d**, 1.50 g (2.80 mmol) of **5**, 0.13 g (0.12 mmol) of Pd(PPh₃)₄, and 2.32 g (16.8 mmol) of potassium carbonate in a degassed mixture of 85 mL of DME and 25 mL of water was heated to reflux temp. for 18 h under nitrogen. After cooling to

room temp. 100 mL of water were added to the reaction mixture. The aqueous phase was extracted with several times with dichloromethane and 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 1:15) to give 1.82 g (70 %) of **7** as a yellow glassy resin.

^1H NMR ($[\text{D}_6]$ acetone, 300 MHz): δ 0.84-0.88 (m, 9 H, CH_3), 1.27-1.31 (m, 12 H), 1.43-1.48 (m, 6 H), 1.76-1.84 (m, 6 H), 3.93 (m, 4 H), 3.95 (m, 2 H), 6.95 (d, $J = 8.5$ Hz, 2 H), 7.03-7.07 (m, 4 H), 7.28 (d, $J = 2.2$ Hz, 2 H), 7.32 (dd, $J = 8.8$ Hz, $J = 2.6$ Hz, 2 H), 7.38 (m, 4 H), 7.42-7.47 (m, 4 H). ^{13}C NMR ($[\text{D}_6]$ acetone, 75 MHz): δ 14.2 (CH_3), 14.3, (CH_3), 23.3 (CH_2), 27.1 (CH_2), 27.2 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 32.2 (CH_2), 32.3 (CH_2), 47.9 (CH_2), 114.7 ($\text{C}_{\text{quat.}}$), 116.8 (CH), 117.0 (CH), 118.1 (CH), 125.1 ($\text{C}_{\text{quat.}}$), 125.6 (CH), 125.6 ($\text{C}_{\text{quat.}}$), 125.6 (CH), 126.2 (CH), 126.4 (CH), 127.6 ($\text{C}_{\text{quat.}}$), 130.0 (CH), 130.9 (CH), 134.8 ($\text{C}_{\text{quat.}}$), 135.3 ($\text{C}_{\text{quat.}}$), 144.7 ($\text{C}_{\text{quat.}}$), 145.0 ($\text{C}_{\text{quat.}}$), 145.5 ($\text{C}_{\text{quat.}}$). MS (FAB+) m/z (%): 1005 ($^{81}\text{Br}^{79}\text{BrM}^+$, 75), 1003 ($^{81}\text{Br}^{79}\text{BrM}^+$, 100), 1001 ($^{79}\text{Br}^{79}\text{BrM}^+$, 47), 918 (13). IR (KBr), $\tilde{\nu}$ 2953 cm^{-1} , 2927, 2854, 1628, 1457, 1416, 1332, 1241, 872, 806. UV/VIS (CH_2Cl_2), λ_{max} (ϵ) 270 nm (70000). Anal. calcd. for $\text{C}_{54}\text{H}_{57}\text{Br}_2\text{N}_3\text{S}_3$ (1004.1): C 64.60, H 5.72, N 4.18, S 9.58, Br 15.92; found: C 64.67, H 5.77, N 4.21, S 9.32, Br 15.63.

3. 10,10'-Bis(*n*-hexyl)-7-phenyl-3,3'-bi(10*H*-phenothiazine) (**6b**)

A solution of 0.49 g (1.00 mmol) of **3d**, 0.12 g (1.00 mmol) of phenyl boronic acid, 46 mg (40 μmol) of $\text{Pd}(\text{PPh}_3)_4$, 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 stirred at room temp, for 72 h and then heated to 50 $^\circ\text{C}$ for 12 h under nitrogen. After cooling to room temp. 0.41 g (1.00 mmol) of **4** were added 10 mL of degassed DME and the reaction mixture was heated at 80 $^\circ\text{C}$ for 18 h. After cooling to room temp. a solution of 0.5 g of Na_2SO_3 in 100 mL of water was added to the reaction mixture. The aqueous phase was extracted with twice (2×50 mL) with diethylether

and 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 0.19 g (30 %) of **6b** as a yellow glassy resin.

^1H NMR ($[\text{D}_6]$ acetone, 300 MHz): δ 0.83-0.88 (m, 6 H), 1.27-1.33 (m, 8 H), 1.41-1.50 (m, 4 H), 1.74-1.87 (m, 4 H), 3.94 (t, $J = 7.2$ Hz, 2 H), 3.96 (t, $J = 7.5$ Hz, 2 H), 6.90-6.95 (m, 1 H), 6.99-7.08 (m, 4 H), 7.13-7.22 (m, 2 H), 7.28-7.33 (m, 1 H), 7.37-7.44 (m, 7H), 7.46-7.49 (m, 1 H), 7.60-7.63 (m, 2 H). ^{13}C NMR ($[\text{D}_6]$ acetone, 75 MHz): δ 15.3 (CH_3), 24.3 (CH_2), 28.1 (CH_2), 28.5 (CH_2), 33.2 (CH_2), 48.8 (CH_2), 48.9 (CH_2), 117.5 (CH), 117.7 (CH), 117.7 (CH), 124.3 (CH), 124.3 (CH), 126.2 (CH), 126.3 (CH), 126.5 (C_{quat}), 126.5 (C_{quat}), 126.8 (CH), 126.9 (CH), 127.5 (CH), 127.5 (CH), 127.7 (CH), 127.8 (CH), 126.5 (C_{quat}), 126.5 (C_{quat}), 126.9 (CH), 127.0 (CH), 127.1 (CH), 127.1 (CH), 127.7 (CH), 127.7 (CH), 128.1 (C_{quat}), 128.8 (CH), 129.0 (CH), 129.3 (C_{quat}), 130.7 (CH), 135.9 (C_{quat}), 136.0 (C_{quat}), 137.1 (C_{quat}), 141.6 (C_{quat}), 145.9 (C_{quat}), 146.2 (C_{quat}), 146.3 (C_{quat}), 147.0 (C_{quat}). MS (FAB+) m/z (%): 640 (M^+ , 100), 555 ($\text{M}^+ - \text{C}_6\text{H}_{16}$, 13), 470 ($\text{M}^+ - 2 \text{C}_6\text{H}_{13}$, 13). IR (KBr): $\tilde{\nu}$ 3027 cm^{-1} , 2953, 2925, 2853, 1601, 1576, 1460, 1332, 1250, 874, 807, 760, 747, 697. UV/Vis (CH_2Cl_2): λ_{max} (ϵ) 288 nm (27000). Anal. calcd. for $\text{C}_{40}\text{H}_{42}\text{N}_2\text{S}_3$ (641.0): C 78.71, H 6.92, N 4.37, S 10.00; found: C 78.50, H 7.03, N 4.36, S 9.90.

4. 7-(4-Formylphenyl)-10,10'-bis(*n*-hexyl)-3,3'-bi(10*H*-phenothiazine) (**6c**)

A solution of 0.49 g (1.00 mmol) of **3d**, 0.15 g (1.00 mmol) of 4-formylbenzene boronic acid, 46 mg (40 μmol) of $\text{Pd}(\text{PPh}_3)_4$, 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 $^\circ\text{C}$ for 28 h under nitrogen. After cooling to room temp. 0.41 g (1.00 mmol) of **4** were added 10 mL of degassed DME and the reaction mixture was heated at 80 $^\circ\text{C}$ for 15 h. After cooling to room temp. a solution of 0.5 g of Na_2SO_3 in 100 mL of water was added to the reaction mixture. The aqueous phase was extracted with twice (2×50 mL) with diethylether and 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 1:15) to give 0.25 g (37 %) of **6c** as an orange glassy resin.

^1H NMR ($[\text{D}_6]$ acetone, 300 MHz): δ 0.83-0.88 (m, 6H), 1.28-1.27 (m, 8H), 1.45-1.52 (m, 4H), 1.76-1.89 (m, 4H), 3.96 (t, $J = 6.9$ Hz, 2 H), 4.01 (t, $J = 7.0$ Hz, 2 H), 6.91-6.97 (m, 1 H), 7.02-7.23 (m, 5 H), 7.39-7.41 (m, 2 H), 7.43-7.48 (m, 2 H), 7.55 (d, $J = 2.2$ Hz, 1 H), 7.61 (dd, $J = 8.5$ Hz, $J = 2.2$ Hz, 1H), 7.86-7.99 (m, 4 H, AA'BB'). ^{13}C NMR ($[\text{D}_6]$ acetone, 75 MHz): δ 15.2 (CH_3), 15.3 (CH_3), 24.3 (CH_2), 28.2 (CH_2), 28.5 (CH_2), 28.5 (CH_2), 33.2 (CH_2), 48.8 (CH_2), 49.0 (CH_2), 117.6 (CH), 117.8 (CH), 117.9 (CH), 117.9 (CH), 124.3 (CH), 126.1 (CH), 126.3, (CH), 126.5 ($\text{C}_{\text{quat.}}$), 126.6 ($\text{C}_{\text{quat.}}$), 126.7 (CH), 127.0 (CH), 127.1 (CH), 127.3 (CH), 127.5 ($\text{C}_{\text{quat.}}$), 127.5 ($\text{C}_{\text{quat.}}$), 128.3 (CH), 128.5 (CH), 129.0 (CH), 129.3 ($\text{C}_{\text{quat.}}$), 131.9 (CH), 135.4 ($\text{C}_{\text{quat.}}$), 135.8 ($\text{C}_{\text{quat.}}$), 136.3 ($\text{C}_{\text{quat.}}$), 137.2 ($\text{C}_{\text{quat.}}$), 145.6 ($\text{C}_{\text{quat.}}$), 146.3 ($\text{C}_{\text{quat.}}$), 147.1 ($\text{C}_{\text{quat.}}$), 147.2 ($\text{C}_{\text{quat.}}$), 147.3 ($\text{C}_{\text{quat.}}$), 193.4 (CH). MS (FAB+) m/z (%): 689 (M^+ , 100), 583 ($\text{M}^+ - \text{C}_6\text{H}_{16}$, 11), 498 ($\text{M}^+ - 2 \text{C}_6\text{H}_{13}$, 11). IR (KBr): $\tilde{\nu}$ 2925 cm^{-1} , 2854, 2046, 1637, 1462, 1247, 807, 583. UV/Vis (CH_2Cl_2): λ_{max} (ϵ) 290 nm (66000). Anal. calcd. for $\text{C}_{43}\text{H}_{44}\text{N}_2\text{OS}_2$ (669.0): C 77.21, H 6.63, N 4.19, S 9.59; found: C 77.17, H 6.74, N 4.19, S 9.59.

References

- (1) *Organikum*, 20th ed.; Becker, H. G. O.; Berger, W.; Domschke, G.; Fanghänel, E.; Faust, J.; Fischer, M.; Gentz, F.; Gewald, K.; Gluch, R.; Mayer, R.; Müller, K.; Pavel, D.; Schmidt, H.; Schollberg, K.; Schwetlick, K.; Seiler, E.; Zeppenfeld, G.; Johann Ambrosius Barth Verlag: Heidelberg, Leipzig, 1996.
- (2) Cymerman-Craig, J.; Rogers, W. P.; Warwick, G. P. *Aust. J. Chem.* **1955**, 8, 252-257.
- (3) Bodea, C.; Terdic, M. *Acad. Rep. Pop. Rom.* **1962**, 13, 81-87. *Chem. Abstr.* **1963**, 59, 11477h.

(4) Krämer, C. S.; Zimmermann, T. J.; Sailer, M.; Müller, T. J. J. *Synthesis* **2002**, 1163-1170.

(5) Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*, Georg Thieme Verlag, Stuttgart, New York, **1991**, pp. 69.

I. ^1H NMR spectra

Recorded in D_6 -acetone

Recorded in D_6 -acetone

Recorded in D₆-acetone

3d

Recorded in D₆-acetone

6a

Recorded in D₆-acetone

Recorded in D₆-acetone

Recorded in D₆-acetone

Recorded in D₆-acetone

II. ^{13}C NMR spectra

Recorded in D₆-acetone

3d

Recorded in D₆-acetone

6a

Recorded in D₆-acetone

Recorded in D₆-acetone

Recorded in D₆-acetone

Recorded in D₆-acetone