Facile Synthesis of Functionalized Oligophenothiazines via One-Pot Bromine–Lithium Exchange–Borylation–Suzuki Coupling (BLEBS)

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Abstract: The bromine–lithium exchange in bromophenothiazines followed by transmetalation with trimethyl borate and addition of palladium catalyst, 1.2 equivalents of a base, and an aryl halide yields the cross-coupling products in moderate to very good yields.

Key words: borylations, cross-coupling, heterocycles, metalation, oligomers, one-pot reactions

Phenothiazines constitute a pharmaceutically important class of heterocycles with a broad spectrum of pharmacological activity. Most interestingly, phenothiazines are also able to cleave DNA upon photochemical induction. As a consequence of the low oxidation potential, these tricyclic nitrogen–sulfur heterocycles readily form stable radical cations and their physiological activities can also be attributed to this circumstance. Furthermore, the first reversible oxidations are accompanied by characteristic, deep colored radical cation absorptions. Thus, phenothiazine derivatives have become valuable spectroscopic probes in molecular and supramolecular arrangements for photoinduced electron transfer (PET) studies and as functional motifs in materials science. The prospect of incorporating highly redox active fragments like phenothiazines into conjugated chains could constitute a so far unknown class of redox addressable molecular wires, and in particular, for redox manipulation of single molecules with nanoscopic scanning techniques. Recently, as part of our program to synthesize and investigate wire-like oligophenothiazines, we communicated the syntheses, structures, and first cyclic voltammetry measurements of directly linked phenothiazinyl dyads and triads that can be regarded as models for polymers with electronically coupled electrophores. Retrosynthetic analysis with fragmentations based upon Suzuki arylations suggested the use of boronates. Although several one-pot procedures with Negishi, Stille, and Kumada cross-coupling reactions have been reported, practical one-pot preparations of boronates from electron-rich heterocycles by halogen–lithium exchange followed by subsequent Suzuki–Miyaura cross-coupling have remained largely unexplored. Here, we report a straightforward access to functionalized arylated phenothiazines, phenothiazinyl dyads and triads by a one-pot bromine–lithium exchange–borylation–Suzuki (BLEBS) sequence.

In contrast to stepwise protocols which inevitably lead to reduced yields during workup or chromatography, we set out to develop a one-pot synthesis of arylphenothiazines and oligophenothiazines by a BLEBS sequence. Therefore, in the BLEBS reaction, a THF solution of a bromophenothiazine was cooled to –78 °C (dry ice/acetone bath) and treated with n-butyllithium. Then, trimethyl borate was added and the reaction mixture was allowed to come to room temperature. Finally, an aryl halide, catalytic amounts of [Pd(PPh3)4], and 1.2 equivalents of potassium tert-butoxide were added and the mixture was heated overnight affording the corresponding cross-coupling products in moderate to good yields (Scheme 1, Table 1).

Scheme 1 One-pot BLEBS sequence
The conventional two-step synthesis of the desired aryl phenothiazines and oligophenothiazines requires the preparation and isolation of the phenothiazine pinacol boronate or boronic acid. Either the rather expensive tetramethyl dioxaborolane is coupled by palladium catalysis according to Masuda’s procedure with a suitable bro- 
mophenothiazine, or, by bromine-lithium exchange of followed by trapping with trialkyl borate and subsequent 
synthesis. This makes the BLEBS protocol generally suitable for coupling with base sensitive 
aryl halides. Further studies with other heterocyclic 
substrates and the extension of this one-pot methodology 
are currently underway.

All reactions involving water-sensitive compounds were carried out in flame-dried Schlenk glassware under N₂ or argon. Reagents and catalysts were purchased reagent grade and used without further purification. Solvents were dried and distilled according to standard procedures. The phenothiazine compounds 1a, 1b, 2a, and 2d were synthesized according to literature procedures. Flash column chromatography: silica gel 60, mesh 230–400, Merck, TLC: silica gel plates (60 F₂₅₄, Merck, Darmstadt).

**Scheme 2** Attempted one-pot palladium-catalyzed borylation–Suzuki coupling using bis(pinacolato)diboron

1H, 13C, and DEPT spectra were recorded on Bruker ARX 250, Bruker DRX 300 or Bruker DRX 500 spectrometers in CD₂Cl₂ or acetone-d₆ as solvent, unless otherwise stated. The assignments of quaternary C, CH, CH₂, and CH₃ were made on the basis of DEPT spectra. Mass spectra were recorded with JEOL JMS-700 und Finnigan TSQ 700 spectrometers. Elemental analyses were carried out in the microanalytical laboratory of the Organisch-Chemisches Institut, Universität Heidelberg.

**BLEBS Sequences on Bromophenothiazines: General Procedure (GP)**

To a well-stirred mixture of bromophenothiazine 1 (1 equiv) dissolved in anhyd THF and cooled down to –78 °C, was added dropwise a 1.6 M hexane solution of n-BuLi (1.1 equiv) via a syringe. After stirring for 5 min at –78 °C, trimethyl borate (1.2 equiv) was dropped slowly into the mixture and it was allowed to come to r.t. Then, aryl halide (1.2 equiv), Pd(PPh₃)₄ (4 mol%), and r-BuOK (1.2 equiv) were added and the solution was stirred for 14 h at 67 °C. After cooling down to r.t., the mixture was diluted with CH₂Cl₂ (150 mL) andaq sat. Na₂SO₃ (100 mL). The organic phase was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried (MgSO₄) and the solvents were removed under vacuum. The residue was purified with flash chromatography yielding in the phenothiazines 3a–f as yellow or orange oils or resins.

**7-Bromo-10,10-dihexyl-10H,10'H-3,3'-biphenothiazine (3a)**

Prepared according to the GP and purified by flash chromatography (hexane–acetone, 25:1); yield: 2.70 g (83%); yellow resin.

IR (KBr): 2952, 2925, 2853, 1600, 1575, 1457, 1250 cm⁻¹.
One-Pot Synthesis of Oligophenothiazines

1H NMR (300 MHz, acetone-d6): 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), 7.62–7.32 (m, 2 H), 7.35 (s, \( J = 2.2 \) Hz, 2 H), 7.39–7.44 (m, 2 H).

13C NMR (75 MHz, acetone-d6): δ = 14.2 (CH3), 23.2 (CH2), 27.1 (CH), 27.1 (CH), 27.4 (CH), 27.5 (CH), 32.1 (CH), 32.2 (CH), 47.8 (CH), 47.9 (CH), 114.7 (Cq), 116.6 (CH), 116.7 (CH), 117.0 (CH), 118.0 (CH), 123.2 (CH), 125.0 (Cq), 125.6 (CH), 126.0 (Cq), 126.1 (CH), 126.3 (CH), 127.6 (Cq), 128.0 (CH), 128.7 (CH), 130.0 (CH), 130.9 (CH), 134.7 (Cq), 135.3 (Cq), 144.7 (Cq), 145.3 (Cq), 145.4 (Cq), 146.0 (Cq).

MS (FAB+): \( m/z \) (%) = 644.2 (M+, 100), 599.1 (M+ – C6H13, 40), 474.0 (M+ – 2 C6H13, 35).

UV/Vis (CH2Cl2): \( \lambda_{max} (e) \) = 268 (44000), 284 (320000), 326 nm (16400), 362 nm (11800).

7-Bromo-10,10'-dihexyl-7'-((10-hexyl-10H-phenothiazin-3-yl)-10H,10'H-3,3'-biphenothiazine (3b)
Prepared according to the GP and purified by flash chromatography (hexane–acetone, 25:1); yield: 1.11 g (77%); yellow resin.

Table 1 One-Pot BLEBS Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bromophenothiazine 1</th>
<th>Aryl halide 2</th>
<th>Coupling product 3 (yield of BLEBS protocol, %)</th>
<th>Yield (%) of the conventional two-step protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>3a (83)</td>
<td>40**c</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2a</td>
<td>3b (77)</td>
<td>53**b</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2b</td>
<td>3b (72)</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2c</td>
<td>3b (54)</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2d</td>
<td>3b (69)</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>2d</td>
<td>3f (62)</td>
<td>58**a</td>
</tr>
</tbody>
</table>

1H NMR (300 MHz, CDCl3): δ = 8.58 (m, 9 H), 1.29 (m, 12 H), 1.46 (m, 6 H), 1.81 (m, 6 H), 3.95 (m, 6 H), 6.94 (m, 2 H), 7.04 (m, 4 H), 7.21 (m, 3 H), 7.33 (m, 2 H), 7.48 (m, 8 H), 7.39–7.44 (m, 2 H).

13C NMR (75 MHz, CDCl3): δ = 14.2 (CH3), 23.0 (CH3), 23.0 (CH3), 26.9 (CH3), 27.0 (CH3), 27.2 (CH3), 27.2 (CH3), 31.8 (CH3), 31.9 (CH3), 47.9 (CH3), 47.9 (CH3), 114.6 (Cq), 115.8 (Cq), 115.9 (Cq), 116.0 (Cq), 116.1 (Cq), 117.0 (CH), 122.7 (CH), 124.7 (Cq), 124.8 (Cq), 125.0 (Cq), 125.0 (Cq), 125.2 (Cq), 125.3 (CH), 125.3 (CH), 125.5 (CH), 125.5 (CH), 125.6 (CH), 125.8 (CH), 127.1 (Cq), 127.7 (Cq), 127.9 (Cq), 130.3 (Cq), 133.4 (Cq), 134.4 (Cq), 134.5 (Cq), 143.4 (Cq), 144.4 (Cq), 144.7 (Cq), 144.8 (Cq), 145.3 (Cq).

MS (FAB+): m/z (%) = 925 (M+ 100), 840 (M+ – C6H13, 26), 755 (M+ – 2 CH3, 10), 640 (M+ – 3 CH3, 12).

UV/Vis (CH3Cl2): λ_max (ε) = 246 (39000), 274 (35900), 304 (14400), 352 nm (10800).

Anal. Calcd for C2H5NO3S (431.6): C, 75.14; H, 6.77; N, 3.25; S, 7.43. Found: C, 75.02; H, 6.83; N, 3.44; S, 7.45.

10,10′-Dihexyl-10H,10′H-3,3′-biphenothiazine-7-carbaldehyde (3c)

Prepared according to the GP and purified by flash chromatography (hexane/acetonitrile, 20:1); yield: 0.41 g (69%); orange oil.

IR (KBr): 2953, 2926, 2854, 1685, 1602, 1579, 1461, 1415, 1377, 1335, 1310, 1279, 1244, 1198, 1144, 1014, 747 cm−1.

1H NMR (300 MHz, CDCl3): δ = 0.86–0.90 (m, 6 H), 1.28–1.35 (m, 8 H), 1.40–1.47 (m, 4 H), 1.75–1.86 (m, 4 H), 3.84 (t, J = 7.6 Hz, 2 H), 3.88 (t, J = 7.3 Hz, 2 H), 6.87–6.94 (m, 5 H), 7.13 (dd, J = 7.8, 1.2 Hz, 1 H), 7.16–7.19 (m, 1 H), 7.28 (dd, J = 5.7, 2.1 Hz, 2 H), 7.31 (t, J = 2.3 Hz, 1 H), 7.34 (t, J = 2.3 Hz, 1 H), 7.56 (d, J = 2.0 Hz, 1 H), 7.63 (dd, J = 8.4, 2.0 Hz, 1 H), 9.77 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 14.32 (CH3), 14.33 (CH3), 23.17 (CH3), 23.19 (CH3), 27.0 (CH3), 27.1 (CH3), 27.2 (CH3), 27.4 (CH3), 32.0 (CH2), 32.1 (CH2), 48.0 (CH2), 48.6 (CH2), 115.4 (CH), 116.0 (CH), 116.2 (CH), 116.8 (CH), 122.9 (CH), 124.6 (Cq), 124.8 (Cq), 125.0 (Cq), 125.4 (Cq), 125.5 (Cq), 125.7 (CH), 125.8 (CH), 125.9 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 130.7 (CH), 131.7 (Cq), 133.4 (Cq), 135.8 (Cq), 142.9 (Cq), 145.1 (Cq), 145.6 (Cq), 150.9 (Cq), 190.3 (CH).}

10,10′-Dihexyl-10H-10′H-3,3′-biphenothiazin-3-yl)-10H,10′H-3,3′-biphenothiazine-7-carbaldehyde (3d)

Prepared according to the GP and purified by flash chromatography (hexane/acetonitrile, 20:1); yield: 0.37 g (62%); orange resin.

IR (KBr): 2954, 2927, 2858, 1684, 1603, 1579, 1459, 1416, 1336, 1234, 1199, 1148, 1006, 874, 807, 747 cm−1.

1H NMR (300 MHz, CDCl3): δ = 0.86–0.91 (m, 9 H), 1.28–1.35 (m, 12 H), 1.39–1.49 (m, 6 H), 1.75–1.86 (m, 6 H), 3.82–3.91 (m, 6 H), 6.87–6.94 (m, 7 H), 7.11–7.19 (m, 2 H), 7.28–7.36 (m, 8 H), 7.56 (d, J = 1.9 Hz, 1 H), 7.63 (dd, J = 8.4, 1.9 Hz, 1 H), 9.71 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 14.32 (CH3), 14.34 (CH3), 14.35 (CH3), 23.17 (CH3), 23.20 (CH3), 27.0 (CH3), 27.22 (CH3), 27.36 (CH3), 27.37 (CH3), 27.4 (CH3), 32.1 (CH2), 48.0 (CH2), 48.6 (CH2), 115.3 (CH), 115.9 (CH), 116.0 (CH), 116.0 (CH), 116.1 (CH), 116.8 (CH), 122.9 (CH), 124.6 (Cq), 124.8 (Cq), 125.0 (Cq), 125.4 (Cq), 125.5 (Cq), 125.7 (CH), 125.8 (CH), 125.9 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 130.7 (CH), 131.7 (Cq), 133.4 (Cq), 135.8 (Cq), 142.9 (Cq), 145.1 (Cq), 145.6 (Cq), 150.9 (Cq), 190.3 (CH).

MS (FAB+): m/z (%) = 876 (19), 875 (44), 874 (M + H+, 78), 873 (M+, 100), 872 (31), 802 (M+ – C6H13, 14), 790 (20), 789 (M+ + H – C6H13, 32), 788 (M+ – C6H13, 24), 704 (M+ – H – C6H13, 12), 703 (M+ – C6H13, 9), 620 (12), 619 (M+ – H + C6H13, 19), 618 (M+ – C6H13, 20).

(c) For nanoscale materials, see papers in the dedicated issue of Acc. Chem. Res. 1999, 32, 387–454; issue 5.


(a) Krämer, C. S.; Zimmermann, T. J.; Sailer, M.; Müller, T. J. J. Synthesis 2002, 1163.


