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2,3-Disubstituted Benzo[*b*]thiophenes from Diarylalkynes *via* Electrophilic Addition-Cyclization and Palladium-Catalyzed Cross-Coupling

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Abstract: Diarylalkynes are readily transformed in 3-chlorobenzo[*b*]thiophenes in a two-step electrophilic addition-cyclization procedure that runs highly efficiently in solution or in the solid phase. The heteroaromatic carbon-chlorine bond participates in palladium-catalyzed Suzuki–Miyaura or Buchwald–Hartwig cross-couplings to give, in a single step, 2,3-disubstituted derivatives of pharmacological relevance .

Keywords: benzo[*b*]thiophenes; cross-coupling; electrophilic addition; electrophilic substitution; phthalimidesulfenyl chloride; solid phase synthesis

Introduction

Benzo[*b*]thiophenes are of interest because of their frequent occurrence in nature and their wide range of biological and physiological effects.[1] Benzo[*b*]thiophene derivatives currently in pharmaceutical use or development include selective estrogen receptor modulators (SERM),[2] tubulin-binding agent,[3] modulators of multidrug resistance,[4] angiogenesis inhibitors,[5[site-directed thrombin inhibitors,[6] and anti-inflammatory[7] agents. For example, SERMs raloxifen **1a**, arzoxifen **1b** and related derivatives **1c–e** (Figure 1) have already found therapeutic use as effective agents in the prevention of cancer and osteoporosis.

Thus, the classical approaches for either the construction of the pentatomic heteroaromatic fused ring or its functionalization[1] are continuously being complemented by new methods that take advantage of the more recent acquisitions of synthetic organic chemistry, including multi-component reactions,[8] microwave-assisted or/and solid-phase synthesis[9] and cross-coupling catalysis.[10]

Several years ago we reported an easy two-step (one-pot) procedure for the preparation of 3-chlorobenzo[*b*]thiophenes.[11] The method is based on the electrophilic addition of the phthalimidesulfenyl chloride PhtNSCl (Pht = Phthaloyl) to aryl-alkyl- or symmetrical diarylalkynes, to give (*E*)-β-chlorothiovinylphthalimides with high Markovnikov regioselectivity. These compounds under Lewis acid catalysis ($AlCl_3$ and $BF_3{\cdot}OEt_2$ were demonstrated to be the reagents of choice) undergo an intramolecular electrophilic aromatic substitution with closure of the thiophene ring and elimination of the phthalimide residue (Scheme 1).[11]

In this paper, we describe an update of this methodology for the preparation of 2,3-disubstituted benzo[*b*]thiophenes of pharmaceutical interest exploiting the opportunities offered by some of the recent developments in organic synthesis.

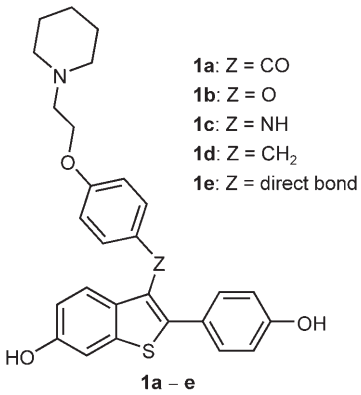
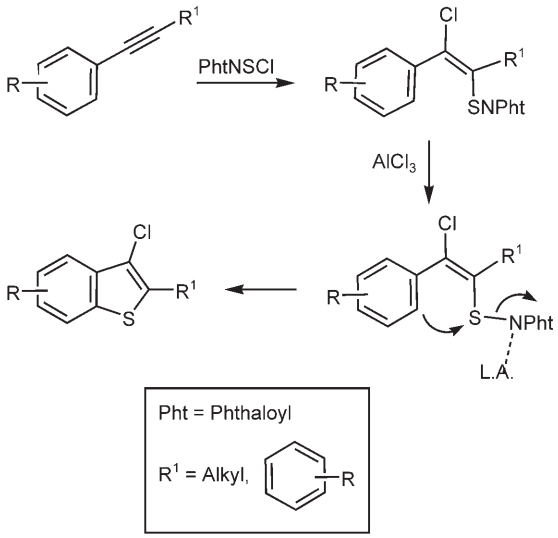


Figure 1. Selected bioactive 2,3-disubstituted benzo[*b*]thiophenes.

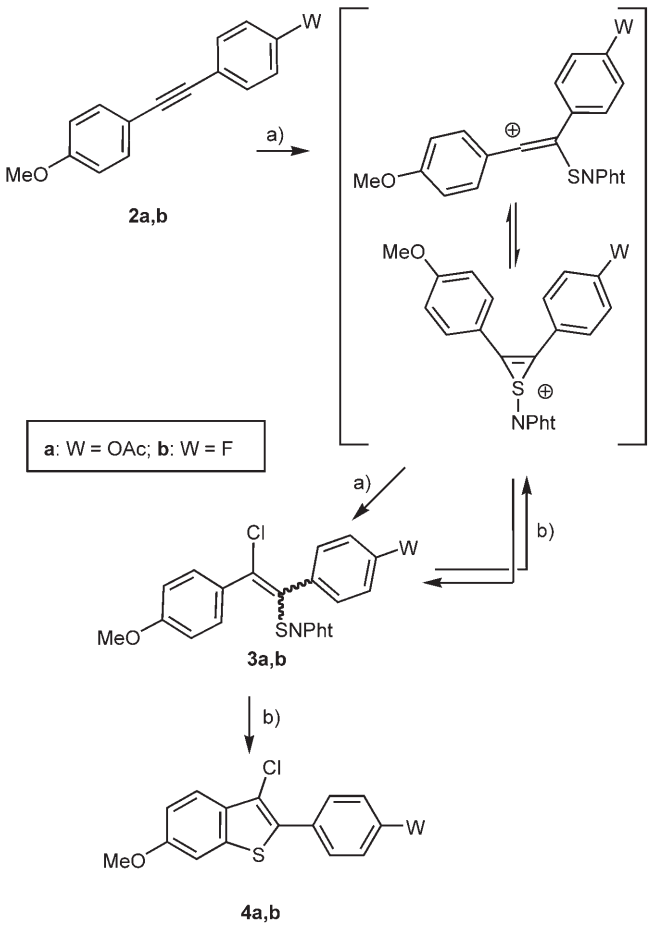


Scheme 1. General procedure for the preparation of 3-chlorobenzo[*b*]thiophenes from aryl-alkyl- and symmetrical diarylalkynes.

Results and Discussion

We started facing the problem of the regiochemistry of the addition of PhtNSCl to unsymmetrical diarylalkynes bearing those groups (i.e., OMe, OH and F) found in the more biologically active derivatives. Alkynes **2a** and **2b**, easily prepared by Sonogashira cross-coupling in up to 90% isolated yield (see Experimental Section), were reacted with PhtNSCl in dry dichloromethane (DCM) at room temperature to give sulfenamides **3a** and **3b** as single regioisomers but as 1:1 and 5:2 mixtures of *E*/*Z* isomers, respectively (Scheme 2). This peculiar behaviour suggests that the electrophilic addition to these electron-donating substituted alkynes occurred through a *p*-methoxy-stabilized open vinyl cation intermediate, instead of, or together with, the predicted thiirenium ion.[12] The open intermediate causes the formation of an *E*/*Z* mixture of diastereoisomeric sulfenamides **3**, but makes certain the complete regioselectivity of the reaction for the favoured attack of the chloride ion to the more stabilized vinyl cation (Scheme 2).

Sulfenamides **3** can be isolated as mixtures of *E*/*Z* diastereoisomers by flash chromatography, however, the successive cyclization to 3-chlorbenzo[*b*]thiophene can be, more conveniently, carried out on crude **3** as obtained after a simple aqueous basic work-up. The intramolecular ring closure to benzothiophene requires that the sulfenamide sulfur and the aromatic ring lay *cis* to each other (see Scheme 1), hence, only the *E* isomer should be consumed in the Lewis acid-catalyzed intramolecular S_EAr. In spite of this, reacting the crude *E*/*Z* mixtures of derivatives **3a** or **3b** with 4 equivs. of $AlCl_3$ in DCM at room temperature, we observed complete consumption of the starting

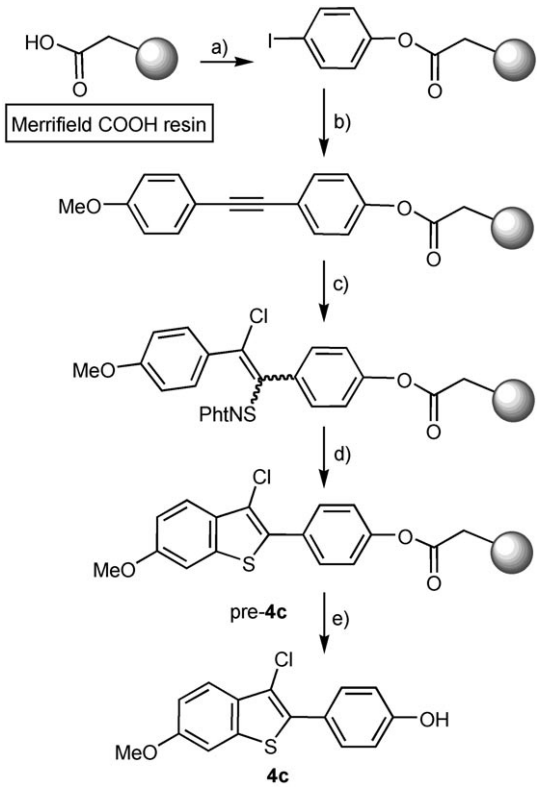


Scheme 2. *Reagents and conditions*: a) 1.1 equivs. PhtNSCl, DCM, room temperature, 3 h; b) 4 equivs. $AlCl_3$, DCM, room temperature, **4a** 4 h, 72%, **4b** 2 h, 68% over two steps.

materials and the thiophenes **4a** and **4b** were isolated in 72% and 68% overall yield, respectively. This can be rationalized considering that, under the reaction conditions required for the cyclization, a *Z*/*E* isomerization takes place allowing the complete consumption of the *Z* isomer as well.

The two steps, addition and cyclization, can also be carried out in a one-pot procedure, but this caused a small decrease (5–15%) of the overall yield of benzothiophenes.

The complete regioselectivity and the straightforwardness of the transformation of alkyne **2a** into benzothiophene **4a** prompted us to verify the value of this methodology in the solid phase. Since the Sonogashira reaction has already been applied for the preparation of diarylalkynes in the solid phase[13] and recently we demonstrated the fruitful use of PhtNSCl in the substitution reaction on solid supported β-keto esters,[14] we envisaged to extend the above described methodology (see Scheme 2) using a carboxylic acid-modified Merrifield resin as starting material, as described in Scheme 3.



Scheme 3. *Reagents and conditions*: a) *i*: 5 equivs. $SOCl_2$, toluene, 60 °C, 2 h (repeated twice); *ii*: 2 equivs. 4-iodophenol, 2 equivs. DIPEA, 0.1 equiv. DMAP, DCM, room temperature, 24 h; b) 2 equivs. 4-ethynylanisole, 3 equivs. Bu_4NOAc, 6 % mol $Pd(OAc)_2$ DMF, room temperature, 24 h; c) 1.5 equivs. PhtNSCl, DCM, room temperature, 16 h; d) 4 equivs. $AlCl_3$, DCM, room temperature, 4 h; e) 5 equivs. NaOMe, THF, room temperature 3 h, 50 % overall.

The supported carboxylic acid was reacted with thionyl chloride followed by esterification with 4-iodophenol in the presence of DIPEA and a catalytic amount of DMAP. The aryl iodide was cross-coupled under Sonogashira conditions with 4-ethynylanisole, and the obtained supported alkyne reacted with PhtNSCl in DCM. A mixture of *E/Z* supported β-chlorothiovinylsulfenamide was obtained and cyclized with $AlCl_3$ to the benzo[*b*]thiophene pre-**4c**. Transesterification with NaOMe in dry THF allowed the release from the resin and the isolation of thiophene **4c** (Scheme 3). The formation of the solid supported reagents and the progress of the reactions were monitored on the resin either by FT-IR, by means of the diagnostic stretching bands exhibited by the ester, the alkyne and the *N*-thiophthalimide functional groups, or by ^1H NMR monitoring mainly the variation of the chemical shift of the methoxy group in the diverse solid supported intermediates (see Experimental Section). Remarkably, 3-chlorobenzo[*b*]thiophene **4c** was isolated, by a simple acid work-up of the solution obtained by washing the resin after transesterification, in 50 % overall yield as a pure compound without any further purification.

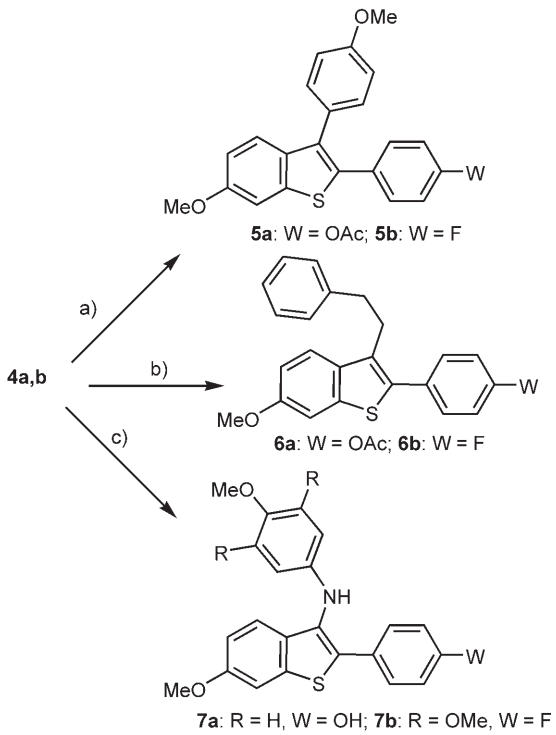
Clearly, this demonstrates that the regioselectivity of the addition as well as the Lewis acid-catalyzed *Z*/*E* equilibration are effective also for solid-supported reagents, and that the six consecutive steps on the resin: a) *i*: formation of the acyl chloride, *ii*: esterification, b) Sonogashira cross-coupling, c), PhtNSCl electrophilic addition, d) $AlCl_3$-catalyzed intramolecular S_EAr and e) transesterification, occurred with an average yield close to 90 % (Scheme 3).

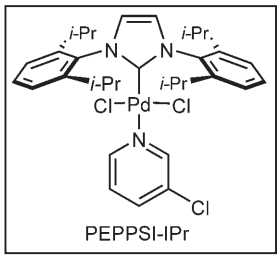
2-Aryl-3-chlorobenzo[*b*]thiophenes **4a–c** can be converted into 2,3-disubstituted derivatives of type **1** using literature procedures like, for example, a reductive dechlorination followed by an S_EAr on the very nucleophilic C-3 position,[1,2a] or an oxidation at sulfur to facilitate a heteroaromatic nucleophilic substitution of the chlorine atom.[3c] Our idea was to use these 3-chlorobenzo[*b*]thiophenes for a direct functionalization *via* a metal-catalyzed cross-coupling, avoiding any additional manipulation.

The use of largely diffuse, easy to handle and to prepare aromatic and heteroaromatic chloro derivatives as efficient partners in cross-coupling reactions is still an open synthetic problem that has found some practical but as yet no general solutions.[15] In any case, examples of chlorothiophenes used as substrates for cross-coupling reactions are scarce, and almost unknown for 3-chlorobenzo[*b*]thiophenes.

Keeping in mind this potential limitation, we started studying the possibility to transform compounds **4** into derivatives like **1** through a metal-catalyzed cross-coupling that was as general and simple as possible. Recently PEPPSI (*p*yridine, *e*nhanced, *p*recatalyst, *p*reparation, *s*tabilization and *i*nitiation) was introduced as a user-friendly air- and moisture-stable catalytic system for a wide-range of cross-coupling reactions,[16] thus we decided to study its usefulness on 3-chlorobenzo[*b*]thiophenes **4**. Indeed, reacting **4a** and **4b** with 4-methoxyphenylboronic acid catalyzed by 2 % mol of PEPPSI-IPr we observed a clean Suzuki–Miyaura coupling affording derivatives **5a** and **5b** in 85 % and 89 % isolated yield (Scheme 4). Gratifyingly, the same catalyst was also effective in the Suzuki–Miyaura coupling carried out with 2-phenylethylboronic acid that, under very similar reaction conditions, allowed the isolation of 3-ethylphenylbenzo[*b*]thiophenes **6a** and **6b** in very good yields (Scheme 4). It is noteworthy that the Suzuki–Miyaura couplings on derivative **4a** occurred without affecting the acetoxy group on the 4′ position.

These successes in forming new sp^2–sp^2 and sp^2–sp^3 carbon-carbon bonds prompted us to verify the ability of PEPPSI-IPr to catalyze the formation of a carbon-nitrogen bond in a Buckwald–Hartwig process. Reacting thiophene **4a** with 4-methoxyaniline and derivative **4b** with 3,4,5-trimethoxyaniline, the expected di-





Scheme 4. *Reagents and conditions*: a) 1.5 equivs. 4-methoxyphenylboronic acid, 2% mol PEPPSI-IPr, 3 equivs. K_2CO_3, toluene, 100°C, **5a**, 3 h, 85%, **5b**, 6 h, 89%; b) 1.5 equivs. 2-phenylethylboronic acid, 2% mol PEPPSI-IPr, 3 equivs. K_2CO_3, toluene, 100°C, **6a**, 7 h 90%, **6b**, 3 h 92%; c) for **7a**: 1.3 equivs. 4-methoxyaniline, 4% mol PEPPSI-IPr, 3 equivs. NaO-*t*-Bu, toluene, 100°C, 5 h, 78%; for **7b**: 1.3 equivs. 2,3,4-methoxyaniline, 4% mol PEPPSI-IPr, 3 equivs. NaO-*t*-Bu, toluene, 100°C, 4 h, 80%.

arylamines **7a** and **7b** were isolated in good yield as reported in Scheme 4. Under these reaction conditions the coupling with acetoxy derivative **4a** occurred with concomitant deacetylation affording the 4′-hydroxy thiophene 7**a** (Scheme 4).

Thus the chlorine atom in the 3-position, provided by the electrophilic addition of PhtNSCl to the alkyne, becomes the tool for the direct introduction of substituents by a palladium-catalyzed cross-coupling reaction, that is particularly simple using PEPSSI-IPr.[17]

In this light we decided to assess this methodology for the preparation of benzothiophenes of pharmaceutical relevance. We were delighted to find that on

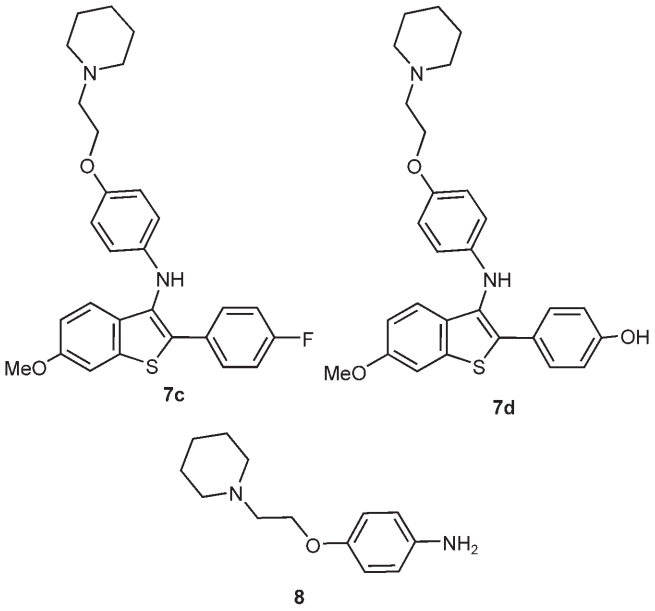


Figure 2. Benzo[*b*]thiophenes of biological relevance prepared by PEPSSI-IR mediated Buckwald-Hartwig cross-coupling of **4b** and **4c** with amine **8**.

reacting amine **8** (Figure 2), prepared by Mitsunobu reaction of 4-acetamidophenol with 1-(2-hydroxyethyl)piperidine, with thiophenes **4b** and **4c**, under the above reported PEPPSI-IPr catalyzed Buckwald-Hartwig conditions, compounds **7c** and **7d** (Figure 2) were isolated in 86% and 75% yield, respectively. In fact, BBr_3 demethylation of derivative **7d** gave dihydroxy derivative **1c** (see Figure 1) known to be active in sub-nanomolar concentration as a SERM.[3c] On the other hand the substitution of the 4′-OH with a 4′-F group, as in **7c**, has been indicated as a simple yet effective way for decreasing the toxicity of dihydroxy compounds, like **1a–c**, caused to their ability to give glutathione adducts followed by oxidation to unsafe quinoid species.[18]

Conclusions

The addition of PhtNSCl to 4,4′-disubstituted unsymmetrical diarylalkynes occurred with complete regioselectivity to give β-chloro-*N*-thiophthalimides as suitable precursors of 3-chlorobenzo[*b*]thiophenes obtained by intramolecular electrophilic substitution catalyzed by $AlCl_3$. The whole procedure, including the Sonogashira synthesis of the starting alkyne, has been successfully applied on the solid phase. Eventually, the C-3 carbon-chlorine bond has been cross-coupled with aryl- or alkyboronic acids and with anilines, using PEPPSI-IPr as catalysis, to give 2,3-disubstituted benzo[*b*]thiophenes of pharmaceutical relevance with overall yields and number of steps comparable

to or better than those of the other available synthetic procedures. The possibility to broaden the cross-coupling reaction of 3-chlorobenzo[*b*]thiophenes is under consideration.

Experimental Section

Cross-coupling reactions were carried out on flame-dried flasks under a positive pressure of dry nitrogen. THF was distilled from sodium in the presence of the blue colour of benzophenone kethyl, toluene was distilled from sodium, and DCM was distilled from CaH_2. All reactions were monitored by TLC on commercially available precoated plates (silica gel 60 F254) and the products were visualized with acid-vanillin solution. Silica gel 60, 230–400 mesh, was used for column chromatography. Petrol refers to light petroleum, bp 40–60 °C. Melting points were measured on a microscopic apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solutions. Residual $CHCl_3$ was used as reference at 7.26 and 77.00 ppm, respectively. FT-IR spectra were recorded in KBr pellets or $CHCl_3$ solutions. Mass spectra were measured with a Shimadzu QP5050. Commercially available reagents, catalysts and ligands were used as obtained from freshly open containers without further purifications. PEPPSI-IPr was purchase from Sigma–Aldrich. Phthalimidesulfenyl chloride was prepared from the corresponding commercially available disulfide (purchase from Chemper snc) as reported elsewhere.[14]

Solid-Phase Synthesis

Carboxylic Merrifield resin was purchased from Novabiochem. It is an 1% cross-linked divinylbenzene-styrene copolymer of 100–200 mesh with a loading of 1.4 mmol g^{-1}. Solid-phase reactions were carried in securely sealed vials and the resin suspensions transferred by plastic pipettes. Solid phase work-up was carried out by means of the plastic syringe technique. Flat-bottom PE syringes were equipped with sintered Teflon filters, Teflon tubing and valves which allow suction to be applied to the syringe from below. The resins were washed with the solvent used for the reaction and sequentially with DCM, MeOH, diethyl ether and again DCM and the shrunken beads were dried under vacuum over KOH before further transformations and analyses. Functionalized resins were analyzed with FT-IR and/or MAS solid-phase NMR. MAS solid-phase NMR were acquired on a 400 MHz Varian MercuryPlus spectrometer using a PFGID-Varian Nanoprobe (pulsed field gradient, indirect detection), at 25 °C using $CDCl_3$ as solvent with a CPMG modified sequence to minimize the resin signals.

Addition of PhtNSCl to Alkynes 2a and 2b

To a solution of alkyne (1.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise, at 0 °C, a solution of phthalimidesulfenyl chloride (1.1 mmol) in dry CH_2Cl_2 (8 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h then diluted with CH_2Cl_2 (10 mL), and washed with saturated $NaHCO_3$ solution (2×30 mL) and water (2×30 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give **3a** and **3b** as mixtures of *E*/*Z* diastereoisomers in 1:1 (δ OMe = 3.68 and 3.84 ppm) or 5:2 ratio (δ OMe_{major} = 3.68 ppm, OMe_{minor} = 3.83 ppm), respectively.

Aluminium Trichloride Cyclization to Benzo[*b*]thiophenes 4a and 4b

To a solution of thiophthalimide **3**, as a mixture of *E*/*Z* diastereoisomers, (1.0 mmol) in dry CH_2Cl_2 (15 mL), $AlCl_3$ (4.0 mmol) was added under a nitrogen atmosphere. After stirring at room temperature for 2–4 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), and washed with saturated $NaHCO_3$ solution (2×30 mL) and water (2×30 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the crude product was purified by flash chromatography to provide the desired benzo[*b*]-thiophene.

4-(3-Chloro-6-methoxybenzo[*b*]thiophen-2-yl)phenyl acetate (4a): The product was isolated, after column chromatography (eluent: CH_2Cl_2/petroleum ether 4:1), as a pale-brown solid; yield: 72%; mp 121–123 °C; IR (KBr): ν = 2941, 1759 (C=O), 1608, 1474, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (s, 3H), 3.89 (s, 3H), 7.08 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.17–7.21 (m, 2H), 7.25 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.75–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.14, 55.68, 104.80, 115.12, 116.39, 121.84, 123.02, 130.18, 131.78, 132.46, 138.08, 150.56, 158.41, 169.28; MS: *m*/*z* (%) = 332 (M^{+}, 44), 290 (100), 275 (72); anal. calcd. for $C_{17}H_{13}ClO_3S$: C 61.35, H 3.94; found: C 61.25, H 3.81.

3-Chloro-2-(4-fluorophenyl)-6-methoxybenzo[*b*]thiophene (4b): The product was isolated, after column chromatography (eluent: petroleum ether/CH_2Cl_2 4:1), as a white solid; yield: 68%; mp 86–87 °C; IR (KBr): ν = 2929, 1608, 1496, 1233 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.89 (s, 3H), 7.08 (dd, *J* = 2.2, 9.0 Hz, 1H), 7.13–7.18 (m, 2H), 7.25 (s, 1H), 7.70–7.75 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.68, 104.82, 115.13, 115.60, 115.82, 116.29, 123.01, 128.57, 130.86, 130.93, 131.73, 132.30, 137.99, 158.40, 161.40, 163.88; MS: *m*/*z* (%) = 292 (M^{+}, 100), 277 (90), 249 (40); anal. calcd. for $C_{15}H_{10}ClFOS$: C 61.54, H 3.44; found: C 61.84, H 3.45.

Solid-Phase Synthesis of 4-(3-Chloro-6-methoxybenzo[*b*]thiophen-2-yl)phenol (4c)

Commercial Merrifield resin (1.0 mmol) was swelled in dry toluene (2 mL) under mechanical stirring for 30 min, then $SOCl_2$ (5.0 mmol) was added and the mixture was heated at 60 °C for 2 h. The same procedure was repeated to ensure the complete halogenation: IR (KBr): ν = 1770 and 1731 (C=O), 870 (C–Cl) cm^{-1}.

The solid supported acyl chloride (1.0 mmol) was swelled in dry CH_2Cl_2 (4 mL) under mechanical stirring. After 30 min, DMAP (0.1 mmol), 4-iodophenol (2.0 mmol) and DIPEA (2.0 mmol) were added in sequence and stirring was continued for 24 h at room temperature to afford the ester-supported resin: IR (KBr): ν = 1737 (C=O) cm^{-1}.

An oven-dried Schlenk flask was charged with the ester-resin (1.0 mmol), Bu_4NOAc (3.0 mmol), $Pd(OAc)_2$ (6 mol%) and DMF (5 mL) under a nitrogen atmosphere.

After 10 min of stirring 4-ethynylanisole (2.0 mmol) was added and stirring was continued at room temperature under nitrogen for 24 h to give the alkyne-resin: IR (KBr): $\nu = 2207$ (C≡C), 1734 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 3.73$ (s, OMe).

Alkyne-resin (1.0 mmol) was swelled in dry CH_2Cl_2 (3 mL) under mechanical stirring for 30 min. To the suspension a solution of phthalimidesulfenyl chloride (1.5 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise at 0 °C under a nitrogen atmosphere, and stirring was continued for 16 h at room temperature to obtain a 2:1 mixture of *E/Z* supported *N*-thiophthalimides: IR (KBr): $\nu = 1787$, 1742 and 1714 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 3.63$ (s, OMe_{minor}), 3.81 (s, OMe_{major}), 7.50–7.80 (m, H_{arom}Pht).

The *N*-thiophthalimide-modified resin (1.0 mmol) was swelled in dry CH_2Cl_2 (5 mL) under mechanical stirring. After 30 min, $AlCl_3$ (4.0 mmol) was added and stirring was continued for 4 h at room temperature to afford the benzo[*b*]thiophene resin pre-**4c**: IR (KBr): $\nu = 1734$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 3.70$ (s, OMe).

Supported benzothiophene pre-**4c** (1.0 mmol) was swelled in dry THF (3.5 mL) under mechanical stirring for 30 min, then a solution of sodium methoxide 1.35 M (5.0 mmol) in MeOH was added and the mixture was stirred for 3 h at room temperature. The resin was filtered and washed with several portions of CH_2Cl_2 and MeOH. The organic phase was washed with saturated NH_4Cl solution and water, and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided derivative **4c** as a pure white solid; yield: 50%; mp 157–159 °C; IR (KBr): $\nu = 3422$ (O–H), 3008, 1608, 1479, 1216 cm^{-1}; ^1H NMR [$(CD_3)_2CO$, 400 MHz]: $\delta = 3.88$ (s, 3H), 6.97–7.01 (m, 2H), 7.10 (dd, $J = 2.4$, 8.8 Hz, 1H), 7.45 (d, $J = 2.4$ Hz, 1H), 7.61–7.65 (m, 2H), 7.67 (d, $J = 8.8$ Hz, 1H), 8.76 (s, 1H); ^{13}C NMR [$(CD_3)_2CO$, 100 MHz]: $\delta = 56.04$, 105.92, 115.11, 116.00, 116.57, 123.17, 124.36, 131.16, 132.44, 134.70, 138.57, 158.83, 159.36; MS: *m/z* (%) = 290 ($M^{\cdot+}$, 100), 275 (91), 247 (27); anal. calcd. for $C_{15}H_{11}ClO_2S$: C 61.96, H 3.81; found: C 61.91, H 3.82.

General Procedure for the PEPPSI-IPr-Catalyzed Suzuki–Miyuara Cross-Coupling Reactions

An oven-dried Schlenk flask was charged with 3-chlorobenzo[*b*]thiophene (1.0 mmol), boronic acid (1.5 mmol), K_2CO_3 (3.0 mmol), PEPPSI-IPr catalyst (2 mol%) and dry toluene (8 mL), under a nitrogen atmosphere. The mixture was stirred at 100 °C under nitrogen until complete consumption of the starting material as judged by TLC (3–7 h). Upon cooling, the reaction mixture was diluted with diethyl ether (20 mL), washed with brine (3×30 mL), and dried over Na_2SO_4. Concentration in vacuum afforded the desired coupling product that was chromatographed on silica gel.

4-{6-Methoxy-3-(4-methoxyphenyl)benzo[*b*]thiophen-2-yl}phenyl acetate (5a): The product was isolated, after column chromatography (eluent: CH_2Cl_2), as a white solid; yield: 85%; mp 160–162 °C; IR (KBr): $\nu = 2929$, 1753 (C=O), 1602, 1468, 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.29$ (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.93–7.01 (m, 5H), 7.23–7.27 (m, 2H), 7.29–7.35 (m, 3H), 7.46 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 21.10$, 55.20, 55.62, 104.57, 114.19, 114.37, 121.42, 124.09, 127.60, 130.33, 131.39, 132.22, 132.69, 135.17, 135.26, 140.02, 149.79, 157.64, 158.92, 169.25; MS: *m/z* (%) = 404 ($M^{\cdot+}$, 76), 362 (100), 347 (64); anal. calcd. for $C_{24}H_{20}O_4S$: C 71.27, H 4.98; found: C 71.44, H 5.07.

General Procedure for the PEPPSI-IPr-Catalyzed Buchwald–Hartwig Cross-Coupling Reactions

Under nitrogen, 3-chlorobenzo[*b*]thiophene (1.0 mmol), aniline (1.3 mmol), NaO-*t*-Bu (3.0 mmol), PEPPSI-IPr catalyst (4 mol%) and dry toluene (6 mL) were added to an oven-dried Schlenk flask. The resulting mixture was stirred at 100 °C for the desired time until complete consumption of the starting material as judged by TLC, (4–24 h). Upon cooling, the reaction mixture was diluted with diethyl ether (20 mL), washed with brine (3×30 mL), and dried over Na_2SO_4. The crude amine was purified by flash chromatography to provide the desired coupling product.

4-(6-Methoxy-3-{4-[2-(piperidin-1-yl)ethoxy]phenylamino}benzo[*b*]thiophen-2-yl)phenol (7d): The product was isolated by flash chromatography (eluent: CH_3OH/EtOAc 1:1) as a brown solid; yield: 75%; mp 174–176 °C; IR ($CHCl_3$): $\nu = 3583$ (O–H), 3393 (N–H), 2941, 1606, 1507 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.42$–1.50 (m, 2H), 1.60–1.67 (m, 4H), 2.51–2.53 (m, 4H), 2.76–2.80 (m, 2H), 3.84 (s, 3H), 4.00–4.04 (m, 2H), 5.32 (s, 1H), 6.57–6.66 (m, 4H), 6.76–6.80 (m, 2H), 6.86 (dd, $J = 2.4$, 8.8 Hz, 1H), 7.24 (d, $J = 2.4$ Hz, 1H), 7.29 (d, $J = 8.8$ Hz, 1H), 7.37–7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 23.93$, 25.21, 54.71, 55.56, 57.80, 65.33, 105.12, 113.66, 115.30, 116.01, 116.26, 122.84, 124.38, 128.58, 129.47, 130.22, 130.95, 137.73, 140.16, 151.78, 156.79, 157.14; MS: *m/z* (%) = 474 ($M^{\cdot+}$, 26), 112 (100), 98 (89); anal. calcd. for $C_{28}H_{30}N_2O_3S$: C 70.86, H 6.37, N 5.90; found: C 70.64, H 6.70, N 5.70.

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References

[1] a) R. K Russell, J. B. Press, in: *Comprehensive Heterocyclic Chemistry II*, (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier, Amsterdam, **1996**, Vol. 2, p 679; b) Y. Z. Tony, J. O'Toole, C. S. Proctor, *Sulfur Rep.* **1999**, *22,* 1–47;.

[2] a) C. D. Jones, M. G. Jevnikar, A. J. Pike, M. K. Peters, L. J. Black, A. R. Thompson, J. F. Falcone, J. A. Clemens, *J. Med. Chem.* **1984**, *27*, 1057–1066; b) R. A. Magarian, L. B. Overacre, S. Singh, K. L. Meyer, *Curr. Med. Chem.* **1994**, *1*, 61–86; c) A. D. Palkowitz, A. L. Glasebrook, K. J. Thrasher, K. L. Hauser, L. L. Short, D. L. Phillips, B. S. Muehl, M. Sato, P. K. Shetler, G. J. Cullinan, T. R. Pell, H. U. Bryant, *J. Med. Chem*, **1997**, *40*, 1407–1416; d) U. Schopfer, P. Schoeffter, S. F. Bischoff, J. Nozulak, D. Feuerbach, P. Floersheim, *J. Med. Chem.* **2002**, *45,* 1399–1401.

[3] a) K. G. Pinney, A. D. Bounds, K. M. Dingeman, V. P. Mocharla, G. R. Pettit, R. Bai, E. Hamel, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1081–1086; b) S.-X. Zhang, K. F. Bastow, Y. Tachibana, S.-C. Kuo, E. Hamel, A. Mauger, V. L. Narayanan, K.-H. Lee, *J. Med. Chem.* **1999**, *42*, 4081–4087; c) Z. Chen, V. P. Mocharla, J. M. Farmer, G. R. Pettit, E. Hamel, K. G. Pinney, *J. Org. Chem.* **2000**, *65,* 8811–8815; d) B. L. Flynn, P. Verdier-Pinard, E. Hamel *Org. Lett.* **2001**, *3*, 651–654; e) T. Brown, H., Jr. Holt, M. Lee, *Top. Heterocycl. Chem.* **2006**, *2*, 1–51.

[4] B. H. Norman, A. H. Dantzig, J. S. Kroin, K. L. Law, L. B. Tabas, R. L. Shepard, A. D. Palkowitz, K. L. Hauser, M. A. Winter, J. P. Sluka, J. J. Starling, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3381–3386.

[5] a) D. H. Boschelli, J. B. Kramer, D. T. Connor, M. E. Lesch, D. J. Schrier, M. A. Ferin, C. D. Wright, *J. Med. Chem.* **1994**, *37*, 717–718; b) R. R. Cobb, K. A. Felts, T. C. McKenzie, G. C. N. Parry, N. Mackman, *FEBS Lett.* **1996**, *382*, 323–326; c) A. Gualberto, G. Marquez, M. Garballo, G. L. Youngblood, S. W. Hunt, III, A. S. Baldwin, F. Sobrino, *J. Biol. Chem.* **1998**, *273*, 7088–7093.

[6] a) D. J. Sall, J. A. Bastian, S. L. Briggs, J. A. Buben, N. Y. Chirgadze, D. K. Clawson, M. L. Denney, D. D. Giera, D. S. Gifford-Moore, R. W. Harper, K. L. Hauser, V. J. Klimkowski, T. J. Kohn, H. Lin, J. R. McCowan, A. D. Palkowitz, G. F. Smith, K. Takeuchi, K. J. Thrasher, J. M. Tinsley, B. G. Utterback, S. B. Yan, M. Zhang, *J. Med. Chem.* **1997**, *40*, 3489–3493; b) K. Takeuchi, T. J. Kohn, J. A. Bastian, N. Y. Chirgadze, M. L. Denney, R. W. Harper, H. Lin, J. R. Mccowan, D. S. Gifford-Moore, M. E. Richett, D. J. Sall, G. F. Smith, M. Zhang, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 759–764.

[7] a) C. D. Wright, S. F. Stewart, P. J. Kuipers, M. D. Hoffman, L. J. Devall, J. A. Kennedy, M. A. Ferin, D. O. Theuson, M. C. Conroy, *J. Leukocyte Biol.* **1994**, *55*, 443–451; b) M. R. Bleavins, F. A. de La Igelsia, J. A. McCay, L. White, Jr., L. Kimber, A. E. Munson, *Toxicology* **1995**, *98*, 111–123.

[8] T. Aoyama, T. Takido, M. Kodomari, *Synlett* **2005**, 2739–2742.

[9] T. Besson, V. Thiéry, *Top Heterocycl Chem*, **2006**, *1*, 59–78.

[10] a) D. Yue, R. C. Larock, *J. Org. Chem.* **2002**, *67,* 1905–1909; b) I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 4473–4475.

[11] G. Capozzi, F. de Sio, S. Menichetti, C. Nativi, P. L. Pacini, *Synthesis* **1994**, 521–525.

[12] G. Capozzi, G. Modena, L. Pasquato, in: *The Chemistry of Functional Groups: The Chemistry of Sulfenic Acids and Their Deriavtives*, (Ed.: S.Patai), Wiley, Chichester, **1990**, p 430 and references cited therein.

[13] a) M. Erdélyi, A. Gogoll, *J. Org. Chem.* **2003**, *68*, 6431–6434; b) S. Bräse, J. H. Kirchhoff, J. Köbberling, *Tetrahedron* **2003**, *59*, 885–939.

[14] S. Menichetti, M. Mori, C. Nativi, *Tetrahedron* **2005**, *61*, 5005–5010.

[15] a) M. Harris, S. L. Buckwald, *J. Org. Chem.* **2000**, *65*, 5327–5333; b) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122,* 4020–4028; c) C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123,* 2719–2724; d) M. A. Fernández-Rodríguez, Q. Shen, J. F. Hartwig, *Chem. Eur. J.* **2006**, *12*, 7782–7796.

[16] a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743–4748; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749–4755; c) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, 13, 150–157.

[17] Disappointingly, despite the wide range of reaction conditions tested, adapting catalysts, co-catalysts, ligands, included PEPPSI-IR, and bases, neither cross-couplings on the solid-phase supported chlorobenzo[*b*]-thiophene pre-**4c**, nor carbonylative Suzuki–Miyaura reactions, with direct access to raloxifen-like derivatives (see compound **1a**, Figure 1), were successfully.

[18] H. Liu, J. Liu, R. B. van Breemen, G. R. J. Thatcher, J. L. Bolton, *Chem. Res. Toxicol.* **2005**, *18,* 162–173.

