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Bromination of 3-substituted benzo[*b*]thiophenes: access to Raloxifen intermediate

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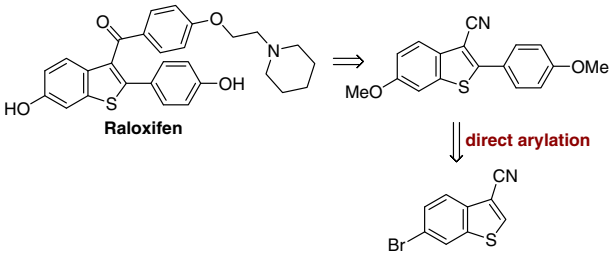
ABSTRACT

A practical route to prepare halogeno-derivatives is described, starting from easily available 3-cyano-benzo[*b*]thiophene. Main efforts have been devoted to the optimization of the experimental procedures (solvent, bromination) to promote selectivity. Synthetic studies investigate the potential access to an advanced intermediate of Raloxifen.

Raloxifen, a 2-arylbenzo[*b*]thiophene marketed by Eli Lilly on the trademark Evista®, displayed excellent properties as a selective estrogen receptor modulator. Its therapeutic benefit is devoted to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis or presenting a high class of risk for invasive breast cancer.[1] During the last five years, the laboratory has been interested in the reactivity of benzo[*b*]thiophenes especially developing new pallado-catalyzed direct arylation on C-2 position.[2] In this Letter, we wish to report the optimization and studies related to the access of 6-bromo-3-cyanobenzo[*b*]thiophene, envisioned as a synthetic intermediate of Raloxifen (Scheme 1).

The electrophilic aromatic substitution (EAS) is a classical functionalization method of aromatic compounds based on the relative high electronic density of aromatic systems. EAS requires activation of the electrophile (strongly dependent of the reagents) and occurs in a two-step mechanism: after addition of the in situ generated electrophilic species on the aromatic ring, a cyclohexadienyl carbocation ring is formed (named as σ complex). The arenium ion (Wheland complex), evolves rapidly to regenerate the aromaticity of the system. The benzo[*b*]thiophene nucleus is composed of two fused aromatic rings with the thiophene scaffold which is electronically enriched by the presence of the sulphur atom, reacting thus quickly in comparison with the benzene ring. Some strategies to functionalize the benzene moiety through electrophilic aromatic substitution have been already described in literature. Activation by electro-donating group promoted regioselective substitution on electronically enriched benzene.[3] Other cases reported the mono-functionalization of benzene requiring substituents in C-2 and/or C-3 positions.[4,5] The most representative work was developed by Dickinson with an electrophilic bromination of 2-bromo-3-methyl-benzo[*b*]thiophene allowing a mixture of regioisomers (C-4 and C-6 positions) followed by a debromination of the C-2 position by a halogen-lithium exchange/hydrolysis sequence. An inseparable mixture of 6-bromo-3-methylbenzo[*b*]thiophene and 4-bromo-3-methylbenzo[*b*]thiophene in a ratio 4:1 was obtained within 62% global yield.[6]



Scheme 1. Retrosynthetic access to Raloxifen.

In this Letter, the laboratory describes some strategies to functionalize the benzenic part through electrophilic aromatic substitution remaining free the C-2 position and to promote the methodology to target intermediates that could be involved in

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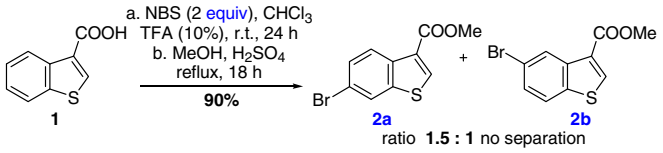


Scheme 2. Bromination on 3-benzo[*b*]thiophene carboxylic acid.

the synthesis of therapeutic drug Raloxifen. Thus, the preliminary researches investigated the bromination of the benzo[*b*]thiophene-3-carboxylic acid **1**. Treatment with *N*-bromosuccinimide (2 equiv) led to the formation of two regioisomers functionalized at the C-6 and C-5 positions respectively in a 1.5:1 ratio (Scheme 2). The reaction was conducted in chloroform associated with 10% of trifluoroacetic acid, enhancing the solubility of the starting material and favoring the activation of the electrophilic bromine. The acidic conditions promoted the reactivity of NBS as 2 equiv were required to fulfill complete disappearance of 3-benzo[*b*]thiophene carboxylic acid. The presence of a carboxylic acid group provided attractive mesomeric effect (-M) to decrease the density of thiophene ring and to avoid the C-2 halogenation. No trace of 2-bromo-3-benzo[*b*]thiophene carboxylic acid was detected. Unfortunately, both regioisomers were impossible to separate by flash column chromatography even after derivatization into their corresponding esters **2a** and **2b**.

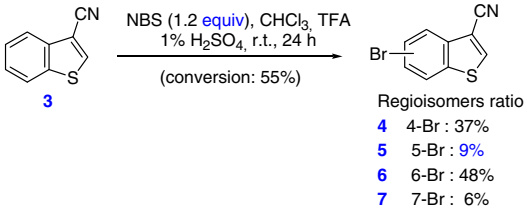
The reactivity of the benzo[*b*]thiophene to EAS and the functionalization of the positions were predicted by the work of Taylor.[7] Concerning the benzenic ring, the established order of preferred position is the following: **C-6** > **C-5** > **C-4** > **C-7**. The results obtained are in accordance with this order as the C-6 and C-5 brominated derivatives were only obtained with a rather favorable proportion in C-6 position.

Increase of the number of equivalents of NBS (5.5 equiv) on compound **1** provided, after esterification the 5,6-dibrominated compound with a modest yield of 23% (two steps). The carboxylic acid group allowed the access to new halogenated derivative of benzo[*b*]thiophene pattern with a control of the bromination in favor of the benzenic ring. Some major drawbacks were faced: separation problems and low yield which encouraged us to focus on 3-cyano-benzo[*b*]thiophene derivative **3**.

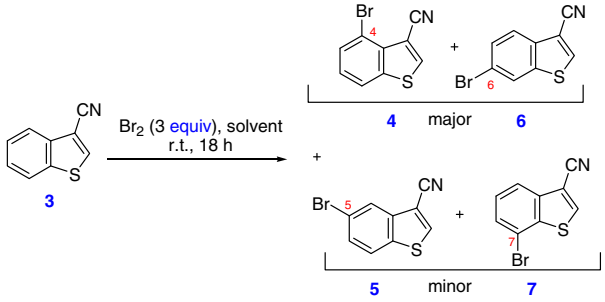
In a presence of a slight excess of NBS (1.2 equiv), the formation of four mono-brominated regioisomers was observed with 45% of recovery of starting material (Scheme 3).

The ^{1}H NMR analysis allowed us to assign the proportion of all the regioisomers, respectively, 37% (Br in C-4), 9% (in C-5), 48% (in C-6) and 6% (in C-7). Nevertheless, the conversion remained low and the introduction of additional quantity of NBS (until 2 equiv) ran to failure (several di-brominated derivatives, partial conversion). The dibromination, on a kinetically aspect, appears to be faster than the first bromination step.

The brominating agent was thus replaced by molecular bromine, supposed to be less electrophilic in comparison with NBS (Scheme 4).[8] The purpose of using Br_2 is to find a balance between efficient conversion and selectivity. First experiment



Scheme 3. Bromination on 3-cyanobenzo[*b*]thiophene.



Scheme 4. Regioselectivity studies on bromination.

carried out on 3-cyano-benzo[*b*]thiophene **3** with 3 equiv of Br_2 in $CHCl_3$ provided a global conversion of 75% in mono-brominated compounds **4**, **5**, **6**, **7** (isolated yield: 60%). More interesting was the presence of compounds **4** and **6** in major quantity (in comparison with compounds **5** and **7** isolated in minor quantity).

The influence of the solvent was mainly investigated screening a wide variety of polar, apolar, protic, aprotic characteristics. Starting material **3** was dissolved in the appropriate solvent (0.5 M), in the presence of 3 equiv of bromine at room temperature during 24 h.[9] The ^{1}H NMR analysis assigned the relative ratio of all the regioisomers **4**, **5**, **6**, **7** (Table 1).

In view of the results obtained by analysis of the crude reaction mixture by NMR, the solvent seems to influence moderately the impact of the bromination on the different C-4, C-5, C-6 and C-7 positions. Only DMF increases significantly the general selectivity of the reaction to 15.7/1 (major vs minor) in comparison with other solvents (average selectivity 6/1). But DMF was not the most efficient for the selectivity 6-Br/4-Br. Valuable information was also obtained with acetonitrile providing the best ratio 6-Br/4-Br of 2.6 and to a certain extent, nitromethane also suggested interesting selectivity. Considering the donating capacity of both solvents in the classification of Gutmann (DN_{MeCN}: 14.1; DN_{DMF}: 26.6), the solvatation of the bromine species, the stabilization of σ complexes could be some factors explaining the difference of regioselectivity. Table 2 summarized the influence of the Br_2 concentration using 3-cyano-benzo[*b*]thiophene **3** dissolved at 0.5 M in the appropriate solvent. As already described above, DMF and MeCN were the most efficient and selective solvents for the bromination reaction. Best yields were finally obtained with 5 equiv of Br_2 in DMF or acetonitrile (Table 2).[10]

Classical aromatic electrophilic brominations by bromine are under kinetic control: the presence of the C-4 brominated derivative **4** as secondary major product (instead of the C-5 brominated derivative **5**, in accordance to Taylor's[7] prediction) may come from an enhanced stability of the Wheland complex intermediate. The arenium intermediates associated to the four brominated regioisomers were studied (Table 3). We evaluated their global energies after geometrical optimization with Hyperchem® (ab-initio method, 3-21G algorithm, RMS gradient = 0.001).

The difference of energy (compared to **σ6**) is higher with **σ5** and **σ7** (>3 kcal/mol) while that of **σ4** is relatively low (>1 kcal/mol). The theoretical stability order is: $\sigma_{\mathbf{6\text{-}Br}} > \sigma_{\mathbf{4\text{-}Br}} > > \sigma_{\mathbf{5\text{-}Br}} > \sigma_{\mathbf{7\text{-}Br}}$ and this is in appropriateness with experimental results pointing out the compounds **4** and **6** as major products of the reaction. The carboxylic acid, an electro-withdrawing group as nitrile function, should also orientate the substitution in favor of C-6 and C-4 positions. The bulky influence of CO_2H probably led to destabilized σ complex in C-4 position. This un-stabilization may induce a modification of the stability order of the σ complexes

Table 1
Solvent optimization conditions

Solvent	% 4-Br **4**	% 5-Br **5**	% 6-Br **6**	% 7-Br **7**	Ratio major/minor	Ratio 6-Br/4-Br
$CHCl_3$	34	7	51	8	5.7	1.5
Et_2O		No conversion			–	–
$Cl(CH_2)_2Cl$	31	7	53	9	5.3	1.7
$MeNO_2$	28	8	58	6	6.1	2.1
AcOH	33	7	52	8	5.7	1.6
MeCN	**24**	**8**	**63**	**5**	6.7	**2.6**
DMF	**39**	**4**	**55**	**2**	**15.7**	1.4
$HmimPF_6$	38	6	49	7	6.7	1.3

Table 2
Overview of optimized isolated yields

Solvent	Br_2 (equiv)	Yield 6-Br (%)	Yield 4-Br (%)	Yield (%)
$CHCl_3$	3.5	32	22	54
$Cl(CH_2)_2Cl$	4.0	41	20	61
DMF	**5.0**	**54**	**30**	**87**
MeCN	**5.0**	**60**	**22**	**82**

as following: $\sigma_{6\text{-Br}} > \sigma_{5\text{-Br}} > > \sigma_{4\text{-Br}} > \sigma_{7\text{-Br}}$ and should be an explanation of the major formation of 6-bromo- and 5-bromobenzo[*b*]thiophene carboxylic acids.

In the aim of promoting the bromination methodology, developed in our laboratory, the 6-bromo-3-cyanobenzo[*b*]thiophene **6** was converted into derivative **8** in the Miyaura conditions in the presence of bis(pinacolato)diboron (1.2 equiv). Boronic ester **8** was directly oxidized by hydroxylamine[11] in basic medium providing phenol **9** in 74% within two steps.[12] Subsequent alkylation with iodomethane provided in excellent yield methyl ether **10**.[13] Direct arylation of benzo[*b*]thiophene in C-2 position was performed in the presence of 4-bromoanisole (2 equiv), $Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %) as a catalytic system and potassium carbonate as a base affording synthetic intermediate **11** of Raloxifen (Scheme 5).[14]

In summary, we have developed expertize on the synthesis of new halogenated benzo[*b*]thiophenes by electrophilic aromatic substitution. The presence of an electro-withdrawing group on the nucleus promoted the mono-bromination as well as the orientation of the substitution on the benzenic part. The proportion of isomers is strongly dependent on the experimental conditions (nature of the substituent in C-3 position, strong effect solvent) but in adequation with the theoretical predictions. The major compound **6** was obtained with a good isolated yield of 60% and should be an excellent building block for more complex molecules of therapeutic interest such as Raloxifen.

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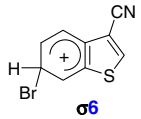
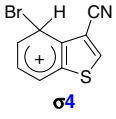
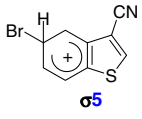
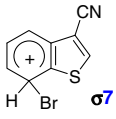
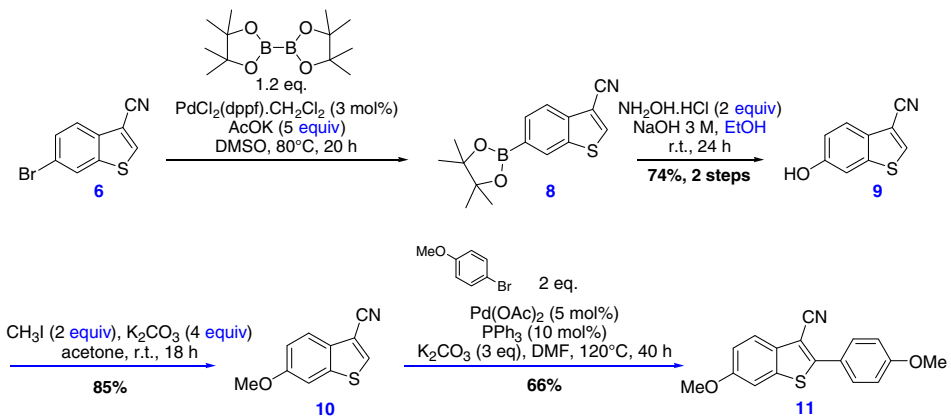
Table 3
Molecular modeling tool for the four arenium intermediates with Hyperchem

σ Intermediate	 **σ6**	 **σ4**	 **σ5**	 **σ7**
E (kcal/mol)	−2102952.289	−2102951.676	−2102949.215	−2102947.734
With **σ6**	–	613 cal/mol	3074 cal/mol	4555 cal/mol



Scheme 5. Access to the synthetic intermediate **12** of Raloxifen.

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9. *General procedure for the synthesis of bromo-benzo[b]thiophene-3-carbonitriles derivatives:*
   To a stirred solution of benzo[*b*]thiophene-3-carbonitrile (1.23 g, 7.7 mmol) in appropriate anhydrous solvent (15 mL) were slowly added 3 equiv of bromine (1.2 mL, 23.1 mmol). The resulting mixture was stirred at room temperature overnight. If the reaction was not complete (as observed by TLC or ^{1}H NMR), additional bromine was added (0.5 equiv per 0.5 equiv) until total consumption of the starting material. Then the mixture was partitioned between CH_2Cl_2 (120 mL) and 10% aqueous $NaHCO_3$ solution (120 mL). To this biphasic solution was added dropwise, under vigorous stirring, saturated aqueous $Na_2S_2O_3$ solution until discoloration of the organic medium. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (2×50 mL). The combined extract was dried ($MgSO_4$), filtered and concentrated *under vacuum*. The resulting residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc 93:7) to afford the pure desired product.
10. *Physical data for major compounds **4** and **6**:*
    *4-Bromo-benzo[b]thiophene-3-carbonitrile (**4**).* Solvent: anhydrous *N,N*-dimethyformamide; isolated yield: 30%; white solid; mp: 159–161 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 7.9 Hz, 1 H), 7.69 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.86 (dd, *J* = 7.9, 1.0 Hz, 1 H), 8.26 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.0 (C), 115.2 (C), 117.2 (C), 122.4 (CH), 127.1 (CH), 130.9 (CH), 134.7 (C), 140.2 (C), 140.9 (CH) ppm.
    *6-Bromo-benzo[b]thiophene-3-carbonitrile (**6**).* Solvent: acetonitrile; isolated yield: 60%; white solid; mp: 148–150 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 8.5, 1.0 Hz, 1 H), 7.87 (d, *J* = 8.5 Hz, 1 H), 8.07 (d, *J* = 1.0 Hz, 1 H), 8.10 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.2 (C), 113.9 (C), 120.5 (C), 123.7 (CH), 125.5 (CH), 129.7 (CH), 136.1 (C), 138.0 (CH), 140.0 (C) ppm.
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12. *Experimental procedure and physical data for compound **9**:*
    A Schlenk tube was charged with 6-bromo-benzo[*b*]thiophene-3-carbonitrile **6** (238 mg, 1 mmol), $PdCl_2$(dppf).CH_2Cl_2 (24 mg, 0.03 mmol), bis(pinacolato) diboron (305 mg, 1.2 mmol), AcOK (491 mg, 5 mmol) and anhydrous DMSO (3 mL) under argon atmosphere. The mixture was heated at 80 °C for 20 h and, after cooling, partitioned between Et_2O (50 mL), H_2O (40 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated, and aqueous layer was extracted twice (2×50 mL) with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuum* and afforded **8** as a pale brown solid: mp 121–123 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.31 (s, 12 H), 7.82 (d, *J* = 7.5 Hz, 1 H), 7.96 (d, *J* = 7.5 Hz, 1 H), 8.48 (s, 1 H), 8.97 (s, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 24.6 (4 CH_3), 84.0 (2 C), 105.2 (C), 114.2 (C), 121.1 (CH), 126.0 (C), 130.1 (CH), 131.2 (CH), 138.0 (C), 139.0 (C), 142.8 (CH) ppm.
    The corresponding residue **8** was dissolved in EtOH (10 mL). Then NH_2OH.HCl (140 mg, 2 mmol) followed by 3 M aqueous NaOH solution (1 mL) was added. After stirring for 24 h at room temperature, the mixture was dissolved in H_2O (30 mL), neutralized to pH 7 with CH_3COOH and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered and evaporated *in vacuum*. Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 80:20) gave **9** (130 mg, 74% yield in two steps) as a white solid: mp 178–180 °C (CH_2Cl_2/pentane). ^{1}H NMR (300 MHz, acetone-d_6) δ = 7.17 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.50 (d, *J* = 2.3 Hz, 1 H), 7.78 (d, *J* = 8.6 Hz, 1 H), 8.34 (s, 1 H), 8.96 (s, 1 H) ppm. ^{13}C NMR (75 MHz, acetone-d_6) δ = 107.0 (C), 108.8 (CH), 115.0 (C), 117.2 (CH), 123.5 (CH), 131.2 (C), 136.5 (CH), 141.3 (C), 157.4 (C) ppm.
13. *Experimental procedure and physical data for compound **10**:*
    To a stirred solution of 6-hydroxy-benzo[*b*]thiophene-3-carbonitrile **9** (110 mg, 0.63 mmol) in anhydrous acetone (6.3 mL) were added, under argon atmosphere, K_2CO_3 (348 mg, 2.52 mmol) and iodomethane (78 μL, 1.26 mmol). The mixture was stirred for 24 h at room temperature and partitioned between H_2O and CH_2Cl_2. The organic layer was separated, and aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuum*. The resulting residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc 70:30) to give **10** (101 mg, 85% yield) as a white solid: mp 88–90 °C (CH_2Cl_2/pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.90 (s, 3 H, OMe), 7.16 (dd, *J* = 8.9, 2.3 Hz, 1 H), 7.34 (d, *J* = 2.3 Hz, 1 H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.94 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 55.8 (CH_3), 105.1 (CH), 106.8 (C), 114.6 (C), 116.3 (CH), 123.2 (CH), 131.3 (C), 135.0 (CH), 140.3 (C), 158.8 (C) ppm.
14. *Experimental procedure and physical data for compound **11**:*
    A Schlenk tube was charged with benzo[*b*]thiophene **10** (1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (26 mg, 0.10 mmol), K_2CO_3 (415 mg, 3 mmol) under argon atmosphere and sealed with a rubber septum. Then anhydrous *N,N*-dimethylformamide (1 mL) and 4-bromoanisole (2 mmol) were added and the mixture was heated at 120 °C for 40 h. After cooling, the mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was separated, and aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuum*. The resulting residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc 80:20) to afford 6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophene-3-carbonitrile **11** (195 mg, 66%); white solid; mp 129–131 °C (CH_2Cl_2/pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.88 (s, 3 H), 3.90 (s, 3 H), 7.02 (d, *J* = 9.0 Hz, 2 H), 7.12 (dd, *J* = 8.9, 2.3 Hz, 1 H), 7.28 (d, *J* = 2.3 Hz, 1 H), 7.80 (d, *J* = 8.9 Hz, 1 H), 7.82 (d, *J* = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 55.6 (CH_3), 55.8 (CH_3), 100.3 (C), 105.0 (CH), 114.8 (2 CH), 115.7 (C), 115.9 (CH), 123.1 (CH), 124.3 (C), 129.5 (2 CH), 133.2 (C), 138.5 (C), 152.6 (C), 158.5 (C), 161.2 (C) ppm.