Published in final edited form as:
Tetrahedron Lett. 2010 December 15; 51(50): 6485–6488. doi:10.1016/j.tetlet.2010.09.137.

A new approach to desketoraloxifene analogs from oxygen-bearing 3-iodobenzo[*b*]thiophenes prepared via iodocyclization

Chul-Hee Cho[†], **Dai-Il Jung**[†,‡], and **Richard C. Larock**[†,*]

[†]Department of Chemistry, Iowa State University, Ames, Iowa 50011

[‡]Department of Chemistry, Dong-A University, Saha-Gu, Busan 604-714, Korea

Abstract

A formal total synthesis of the benzothiophene selective estrogen receptor modulator (SERM) desketoraloxifene and analogs has been accomplished from alkynes bearing electron-rich aromatic rings by electrophilic cyclization using I_2. This approach affords oxygen-bearing 3-iodobenzo[*b*]thiophenes in excellent yields, which are easily further elaborated using a two-step approach involving Suzuki-Miyaura and Mitsunobu coupling reactions.

Keywords

Iodocyclization; 3-iodobenzothiophene; benzothiophene SERM; desketoraloxifene

Early cancer drug discovery efforts focused on the design of small molecule nonsteroidal estrogen receptor (ER) ligands with antagonist properties against breast and other reproductive tissues.[1] Tamoxifen (I, Figure 1) is the archetypal selective estrogen receptor modulator (SERM).[2–4] It was the first marketed drug to be realized from these efforts and, while this compound and its active metabolite, 4-hydroxytamoxifen (II, Figure 1), are effective antiestrogens on estrogen receptor positive breast tissue, they subsequently were discovered to have undesirable estrogenic properties on the endometrium.[5] A third triphenylethylene compound, toremifene (III, Figure 1), has also been approved for the treatment of breast cancer, although it too has been reported to have undesirable uterine stimulatory activity.[6] Because more potent and safer chemotherapeutic agents are needed, due to the potential side effects of tamoxifen I, considerable attention has been paid to the development of less toxic SERMs.[7] Many SERMs in clinical use and clinical development are also highly susceptible to oxidative metabolism by electrophilic, redox active quinoids simply because they are based on polyaromatic phenol scaffolds.[8,9]

A benzothiophene SERM, raloxifene (**IV**, Figure 1), is in clinical use for the prevention and treatment of postmenopausal osteoporosis and is currently in clinical trials for the chemoprevention of breast cancer.[4,10] Another benzothiophene SERM, arzoxifene (**V**, Figure 1), is a structural analog of raloxifene in which the carbonyl hinge has been replaced by an ether linkage and the 4′-hydroxy group is methylated. This SERM is currently in

* larock@iastate.edu .

Supplementary data Supplementary data associated with this article can be found, in the online version, at doi:########.

clinical trials for the treatment of breast cancer and, since it has similar structural characteristics to tamoxifen **I**, has the potential to form quinoids.[7,11]

Interestingly, removal of the ketone moiety in raloxifene results in a benzothiophene analog SERM desketoraloxifene (**VI**, Figure 1), which is more planar and conformationally more similar to 4-hydroxytamoxifen (**II**). Desketoraloxifene (**VI**) has been found to be a much stronger activator of the Activator Protein-1 (AP-1) site by ERα than ERβ, and mimics 4-hydroxytamoxifen (**II**) more than raloxifene (**IV**).[10,12,13] With this information in hand, a set of desketoraloxifene analogs **3**/**4** was designed based on the structures of 4-hydroxytamoxifen (**II**) and raloxifene (**IV**).

Previously, we have developed a general synthesis of 2,3-disubstituted benzo[*b*]thiophenes by the palladium/copper-catalyzed cross-coupling of various *o*-iodothioanisoles and terminal alkynes, followed by electrophilic cyclization under mild reaction conditions (Scheme 1).[14] Very recently, a simple and efficient method for the parallel synthesis of multi-substituted benzo[*b*]thiophenes has also been described *via* known palladium-catalyzed couplings for generation of a diverse set of building blocks starting from 3-iodobenzo[*b*]thiophenes.[15,16]

We wish to report here a new efficient method for the preparation of oxygen-functionalized 3-iodobenzo[*b*]thiophenes **1** by electrophilic cyclization using I_2 and their further elaboration to desketoraloxifene analogs **3**/**4** (Scheme 2 and Table 1). The 3-iodobenzo[*b*]thiophenes **1**, having oxygen substituents at the C-5 and/or C-6 benzothiophene positions, are promising precursors to a wide variety of desketoraloxifene analogs **3**/**4**.

Results and Discussion

Our first goal was the efficient preparation of a variety of oxygen-bearing 3-iodobenzo[*b*]thiophenes **1** (Scheme 2). In this series, we proposed to initially change the substituents at the C-2, C-3, C-5, and C-6 positions of the benzothiophene ring system. This decision was based on the structure of desketoraloxifene (**VI**), which has a *para*-phenol at the 2-position, a basic aliphatic amine chain at the 3-position and an hydroxyl group at the 6-position of the benzothiophene ring system.

The cyclization proceeds smoothly when the substituent on the distal end of the alkyne is an electron-rich methoxy-aryl group. These 3-iodobenzo[*b*]thiophenes **1** are easily further elaborated using a two-step approach involving Suzuki-Miyaura and Mitsunobu coupling reactions to give desketoraloxifene analogs **3**. The first step, the palladium-catalyzed Suzuki-Miyaura coupling of the 3-iodobenzo[*b*]thiophenes **1** with a tetrahydropyranyl (THP) ether-protected boronic acid, *e.g.p*-THPO$C_6H_4B(OH)_2$, for 6–8 h, followed by aqueous HCl deprotection, afforded the desired phenolic oxygen products **2**[15] in high yield (Scheme 2).

In the second step, amine-coupled SERM precursors have been produced by reaction of the phenolic oxygen species **2** with 1-(2-hydroxyethyl)piperidine under Mitsunobu reaction conditions,[17] using Ph_3P and diethyl azodicarboxylate (DEAD), to afford the desketoraloxifene analogs **3** in good yields. The use of multimethoxy-substituted desketoraloxifene analogs **3** affords considerable diversity. The final step in our synthesis delivers hydroxy-substituted desketoraloxifene analogs **4** using BBr_3. The results are summarized in Table 1.

As illustrated in Table 1, entry 10, desketoraloxifene (**VI**) itself has been synthesized using the approach outlined. The desired dimethoxy-substituted desketoraloxifene analog **3e** was obtained from compound **2e** using 1-(2-hydroxyethyl)piperidine under the general Mitsunobu coupling conditions in 83% yield. Compound **3e** was then converted by

demethylation using BBr_3 to the corresponding desketoraloxifene **4e** (**VI**) in 78% yield. In a similar manner a variety of desketoraloxifene analogs **3** and **4** have been prepared in good yields and a minimum of steps.

In summary, a number of benzothiophene SERM analogs and the desketoraloxifene analogs **3**/**4**[18] have been successfully synthesized starting from various oxygen-bearing 3-iodobenzo[*b*]thiophenes **1** by a two-step approach involving sequential Suzuki-Miyaura and Mitsunobu couplings. We believe that this approach to oxygen-bearing 3-iodobenzo[*b*]thiophenes **1** should readily afford many other functionalized desketoraloxifene analogs **3**/**4** using known chemistry and parallel synthesis strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institute of General Medical Sciences (GM070620 and GM079593) and the National Institutes of Health Kansas University Chemical Methodologies and Library Development Center of Excellence (GM069663) for support of this research; Johnson Matthey, Inc. for donation of tetrakis(triphenylphosphine)palladium(0) and Frontier Scientific, Inc. for donation of 4-[(tetrahydro-2H-pyran-2-yl)oxy]benzeneboronic acid.

References and notes

(1). Lerner LJ, Holthaus JF, Thompson CR. Endocrinology 1958;63:295. [PubMed: 13574085]

(2). Harper MJ, Walpole AL. Nature 1966;212:87. [PubMed: 5965580]

(3). Jordan VC. Nat. Rev. Drug Discovery 2003;2:205.

(4). Jordan VC, Phelps E, Lindgren JU. Breast Cancer Res. Tr 1987;10:31.

(5). Killackey MA, Hakes TB, Pierce VK. Cancer Treat. Rep 1985;69:237. [PubMed: 3971394]

(6). Robinson SP, Goldstein D, Witt PL, Borden EC, Jordan VC. Breast Cancer Res. Tr 1990;15:95.

(7). Liu H, Liu J, van Breemen RB, Thatcher GRJ, Bolton JL. Chem. Res. Toxicol 2005;18:162. [PubMed: 15720120]

(8). Macgregor JI, Jordan VC. Pharmacol. Rev 1998;50:151. [PubMed: 9647865]

(9). Bolton JL, Yu L, Thatcher GRJ. Methods Enzymol 2004;378:110. [PubMed: 15038960]

(10). Weatherman RV, Carroll DC, Scanlan TS. Bioorg. Med. Chem. Lett 2001;11:3129. [PubMed: 11720858]

(11). Suh N, Glasebrook AL, Palkowitz AD, Bryant HU, Burris LL, Starling JJ, Pearce HL, Williams C, Peer C, Wang Y, Sporn MB. Cancer Res 2001;61:8412. [PubMed: 11731420]

(12). Grese TA, Sluka JP, Bryant HU, Cullinan GJ, Glasebrook AL, Jones CD, Matsumoto K, Palkowitz AD, Sato M, Termine JD, Winter MA, Yang NN, Dodge JA. Proc. Nat. Acad. Sci. U.S.A 1997;94:14105.

(13). Carta G, Knox AJS, Lloyd DG. J. Chem. Inf. Model 2007;47:1564. [PubMed: 17552493]

(14). Yue D, Larock RC. J. Org. Chem 2002;67:1905. [PubMed: 11895409]

(15). Cho C-H, Neuenswander B, Lushington GH, Larock RC. J. Comb. Chem 2009;11:900. [PubMed: 19569714]

(16). Cho C-H, Neuenswander B, Larock RC. J. Comb. Chem 2010;12:278. [PubMed: 20055500]

(17). Mitsunobu O, Yamada Y. Bull. Chem. Soc. Japan 1967;40:2380.

(18). General procedure for iodocyclization using I_2 to form compounds 1. To a solution of 5.0 mmol of the alkyne and 20 mL of CH_2Cl_2 was added gradually 1.2 equiv of I_2 dissolved in 30 mL of CH_2Cl_2. The reaction mixture was allowed to stir at room temperature for up to 10 min. The reaction was monitored by TLC to establish completion. The remaining I_2 was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by EtOAc (2 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to

yield the crude product, which was purified by flash chromatography using EtOAc/hexanes as the eluent to afford the corresponding products **1**.3-Iodo-5-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (1a). The product was obtained as a pale yellow solid (94% yield): mp 114–115 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.90 (s, 3H), 6.95–7.00 (m, 3H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.58–7.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 55.8, 78.8, 108.4, 114.0 (×2), 115.7, 123.0, 127.1, 131.1 (×2), 131.3, 143.2, 143.5, 158.6, 160.2; HRMS calcd for $C_{16}H_{13}IO_2S$ [M^+], 395.9681, found 395.9684.General procedure for Suzuki-Miyaura coupling to form compounds 2. To a solution of **1** (1.0 mmol) and 5 mol % $Pd(PPh_3)_4$ in toluene (10 mL) was added K_2CO_3 (2.5 mmol) under an Ar atmosphere. To the resulting mixture was added *p*-$THPOC_6H_4B(OH)_2$ (1.5 mmol) dissolved in ethanol (2 mL) and water (0.5 mL) and the reaction mixture heated to 80 °C for 6–8 h with vigorous stirring. After concentration of the solvent under reduced pressure, 10% aq HCl was added to the crude product in THF (0.1 M) at room temperature and stirred for 1 h. The mixture was then extracted by EtOAc (2 × 20 mL), and the aqueous phase was also extracted with EtOAc or CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography using EtOAc/hexanes as the eluent to afford the corresponding products **2**.3-(4-Hydroxyphenyl)-5-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (2a). The product was obtained as a pale yellow oil (89% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.78 (s, 3H), 5.12 (br s, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.96–7.03 (m, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 55.8, 105.8, 114.0 (×2), 114.3, 115.9 (×2), 122.9, 127.1, 128.3, 130.8 (×2), 131.1, 131.85 (×2), 131.89, 140.7, 142.4, 155.0, 157.8, 159.2; HRMS calcd for $C_{22}H_{18}O_3S$ [M^+], 362.0977, found 362.0983.General procedure for the Mitsunobu reaction to form compounds 3. To a solution of **2** (0.2 mmol), triphenylphosphine (PPh_3) (0.4 mmol), and alkylaminoethanol (0.3 mmol) in anhydrous THF (2 mL) was added diisopropyl azodicarboxylate (DIAD) (0.3 mmol) with stirring at 0–5 °C. The resulting solution was stirred at room temperature for 24–32 h (monitored by TLC until completion) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using methanol/ethyl acetate/hexanes as the eluent to afford the corresponding products **3**.6-Methoxy-2-(4-methoxyphenyl)-3-{4-[2-(1-piperidinyl)ethoxy]phenyl}benzo[*b*]thiophene (3e). The product was obtained as a pale yellow oil (83% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.50 (m, 2H), 1.58–1.66 (m, 4H), 2.55 (br s, 4H), 2.81 (t, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 4.15 (t, *J* = 6.0 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.90–6.97 (m, 1H), 6.92 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 4H), 7.32 (d, *J* = 2.3 Hz, 1H), 7.44 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 26.1 (×2), 55.3 (×2), 55.4, 55.9, 58.2, 66.1, 104.8, 114.0 (×2), 114.3, 114.9 (×2), 124.0, 127.2, 128.2, 130.7 (×2), 131.6 (×2), 131.7, 135.5, 136.4, 139.9, 157.5, 158.2, 159.0; HRMS calcd for $C_{29}H_{31}NO_3S$ [M^+], 473.2025, found 473.2029.General procedure for the demethylation of 3e to form 6-hydroxy-2-(4-hydroxyphenyl)-3-{4-[2-(1-piperidinyl)ethoxy]phenyl}benzo[*b*]thiophene (desketoraloxifene, 4e). To a solution of compound **3e** (0.095 mmol, 45 mg) in anhydrous CH_2Cl_2 (2 mL) cooled in an ice water bath under N_2 was added BBr_3 (0.38 mL, 0.38 mmol) while stirring. The solution turned orange in color. This solution was stirred for 3 h after slowly warming to room temperature. The reaction was quenched with satd aq $NaHCO_3$ (2 × 2 mL) and the product was extracted with 5% $CH_3OH/CHCl_3$ (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by column chromatography using 5–10% $CH_3OH/CHCl_3$ as the eluent to provide 33 mg (78%) of desketoraloxifene (**4e**) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34–1.43 (m, 2H), 1.48–1.57 (m, 4H), 2.72 (br s, 2H), 3.35 (br s, 4H), 4.10 (t, *J* = 5.7 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.84 (dd, *J* = 2.2, 8.7 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 9.62 (s, 1H), 9.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.7, 25.3 (×2), 54.3 (×2), 57.2, 65.3, 107.0, 114.6, 114.7 (×2), 115.3 (×2), 123.2, 124.6, 127.4, 130.1 (×2), 130.7, 131.0 (×2), 133.5, 134.8, 138.8, 155.1, 156.9, 157.6; HRMS calcd for $C_{27}H_{27}NO_3S$ [M^+], 445.1712, found 445.1725.

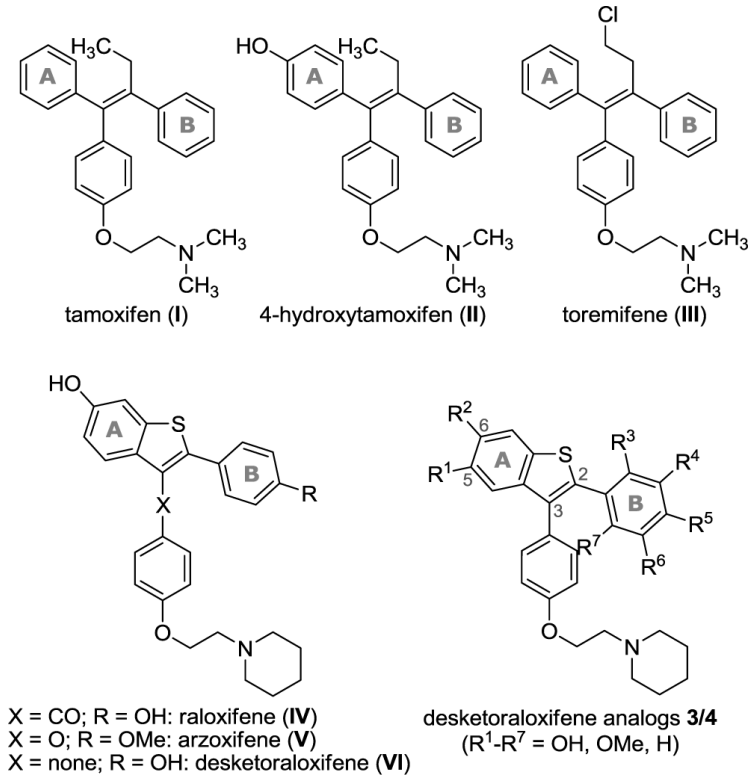
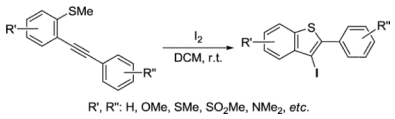


Figure 1.

Chemical structures of tamoxifen (**I**), 4-hydroxytamoxifen (**II**), toremifene (**III**) and representative synthetic benzothiophene SERMs [*e.g.* raloxifene (**IV**), arzoxifene (**V**), and desketoraloxifene (**VI**)] with A and B rings corresponding to tamoxifen.



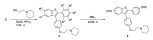
R', R": H, OMe, SMe, SO_2Me, NMe_2, *etc*.

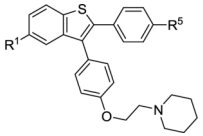
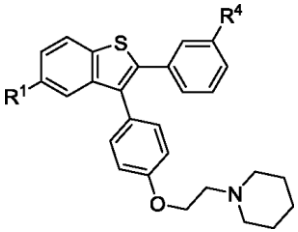
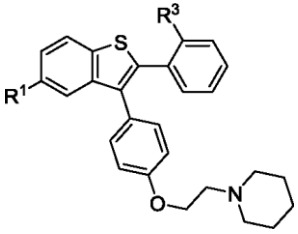
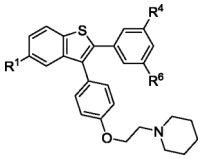
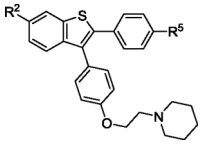
Scheme 1.

Scheme 2.

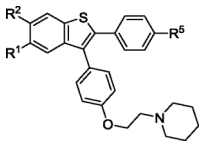
Table 1

Synthesis of desketoraloxifene analogs **3** and **4**[a]



Entry	2	R	Product	3/4	Yield (%)[d]
1	**2a**	R^1,R^5 = OMe		**3a**	89
2	**2a**	R^1,R^5 = OH		**4a** [b]	58
3	**2b**	R^1,R^4 = OMe		**3b**	86
4	**2b**	R^1,R^4 = OH		**4b** [b]	61
5	**2c**	R^1,R^3 = OMe		**3c**	87
6	**2c**	R^1,R^3 = OH		**4c** [b]	52
7	**2d**	R^1,R^4,R^6 = OMe		**3d**	83
8	**2d**	R^1,R^4,R^6 = OH		**4d** [c]	39
9	**2e**	R^2,R^5 = OMe		**3e**	83
10	**2e**	R^2,R^5 = OH		**4e (VI)** [b]	78

Tetrahedron Lett. Author manuscript; available in PMC 2011 December 15.

Entry	2	R	Product	3/4	Yield (%)[d]
11	**2f**	R^1,R^2,R^5 = OMe		**3f**	76
12	**2f**	R^1,R^2,R^5 = OH		**4f** [c]	41

[a] Reagents and conditions: i. *Mitsunobu coupling*: **2** (0.2 mmol), alkylaminoethanol (1.5 equiv), DIAD (1.5 equiv), PPh_3 (2.0 equiv), THF (2.0 mL), rt, 24–36 h. ii. *Demethylation*: **3** (0.1 mmol), BBr_3, CH_2C1_2 (1.0 mL), rt, N_2, 3 h.

[b] 4.0 Equiv of BBr_3 used.

[c] 6.0 Equiv of BBr_3 used.

[d] Isolated yields after column chromatography. All isolated products were characterized by ^1H and ^{13}C NMR spectroscopy (see the Supporting Information).