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Nucleophilic Aromatic Substitution on 3-Aroyl-2-Arylbenzothiophenes. Rapid Access to Raloxifene and Other Selective Estrogen Receptor Modulators

Christopher R. Schmid,* James P. Sluka and Kristin M. Duke

Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285-4813

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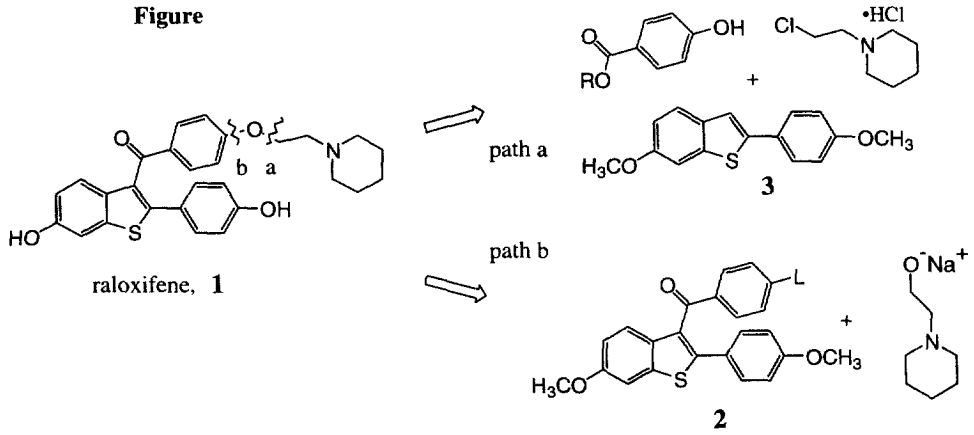
Abstract: Versatile, mild and high yielding methods for nucleophilic aromatic substitution of 2-dialkylamino-1-ethoxides and related nucleophiles on 3-aroyl-2-arylbenzothiophene nuclei are presented. A short synthesis of raloxifene is detailed.

The therapeutic potential of selective estrogen receptor modulators (SERMs) in the treatment of post-menopausal disorders has become increasingly recognized.[1] SERMs act in a tissue-specific fashion to antagonize estrogen receptors in uterine and mammary tissues, while acting as agonists in receptor sites associated with bone and cardiovascular systems.[2] In particular, raloxifene (**1**, Evista®) has recently received approval in the United States and Europe for the prevention of osteoporosis.[3]

Figure



Extensive structure activity relationship (SAR) studies on benzothiophene-based SERMs have been undertaken,[4] highlighting the importance of new synthetic methodology to enable continued SAR exploration. One area left unexplored to date would target the ethoxypiperidino tether region in these species. Identification of new methodology for the installation of the tether region would not only aid in ongoing SAR studies, but also potentially impact the selection of a route of manufacture for raloxifene. Accordingly, research into alternatives for attachment of the tether region of benzothiophene-based SERMS was initiated. Our findings detail a facile nucleophilic aromatic substitution (S_NAr) approach to the synthesis of SERM species from commercially

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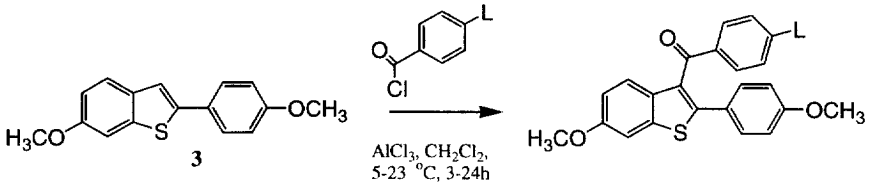
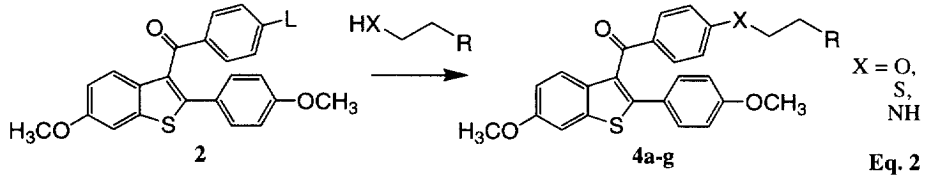
available 1-hydroxyethyl-2-dialkylamines and readily accessed 3-aroyl-2-arylbenzothiophenes. A short synthesis of raloxifene using this methodology is also reported.

Previous synthetic approaches to **1** and other SERMs relied on alkylation of methyl- or ethyl-4-hydroxybenzoate with electrophiles such as β-chloroethylpiperidine hydrochloride, followed by formation of the acid chloride and condensation with an appropriate 2-arylbenzothiophene catalyzed by Lewis acid (in the case of **1**, Figure, path a).[3a] Our approach relied instead on construction of the aryl carbon-heteroatom bond via nucleophilic aromatic substitution (S_NAr) of a 2-dialkylamino-1-ethoxide or other nucleophile on a suitably derivatized aromatic nucleus (Figure, path b). This approach lead retrosynthetically to **2**, where L was a leaving group appropriate for S_NAr chemistry. Selection of substituent L was based both on the anticipated success of the substrate in S_NAr displacement as well as the commercial availability of the corresponding *p*-substituted benzoyl chloride required for its synthesis. Fluoro, nitro and bromo were thus selected as substituents, and compounds **2** were synthesized by reacting the corresponding *p*-substituted benzoyl chloride with benzothiophene **3**[3a] under standard Lewis acid acylation conditions (1.1-1.5 equiv $AlCl_3$, Eq. 1). Chromatography delivered **2a**, **2b**, and **2c** in yields of 74, 18, and 65% respectively.[6]



Eq. 1

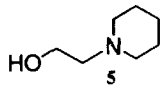
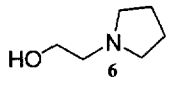
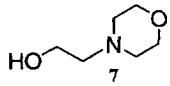
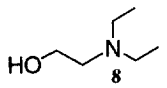
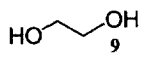
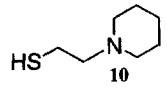
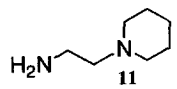
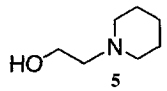
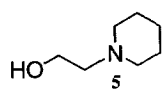
Compounds **2** were then reacted with various nucleophiles to afford the methyl ether-protected SERM precursors **4** (Eq. 2).



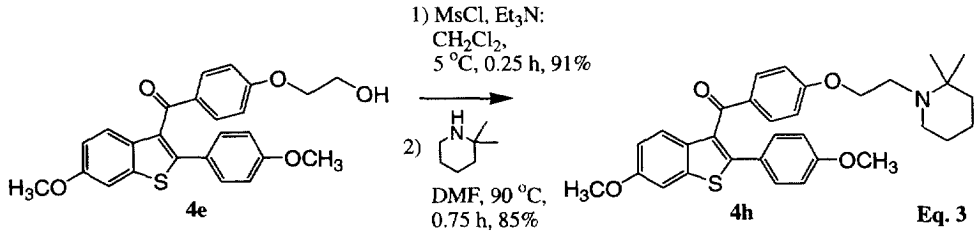
Eq. 2

Results of S_NAr reactions of benzothiophenes **2** with various nucleophiles are presented in the Table. The ease with which substitution occurred on **2a** with oxygen-based nucleophiles **5-8** was unanticipated; substitutions of this type are generally associated with more aggressive conditions when only one activating substituent is present on the aromatic ring.[7] Here, formation of alkoxide (2.0 equiv, 2.2 equiv NaH, DMF, rt) followed by reaction with **2a** (1 equiv) gave complete consumption of starting material within about 15 minutes at room temperature to afford products **4a-4d** in high yield. Nitro-substituted **2b** and bromo-substituted **2c** gave comparable results under the same conditions when reacted with 1-hydroxyethylpiperidine **5**. The thio-substituted species **4f** was obtained under similarly mild conditions. In the case of aza analogue **4g** (X = NH), anion forming conditions with NaH and DMF failed to deliver the desired product; instead, recently reported conditions for S_NAr substitution using indole nucleophiles were successfully employed (KF/Al_2O_3, DMSO, 18-C-6).[8, 9] Methyl ether deprotection on compounds **4** has been previously accomplished by several means ($AlCl_3$/PrSH,[10] BBr_3[4c]) to afford the desired SERMs.

Table: Synthesis of Protected SERMs 4 via S_NAr on Benzothiophenes 2

Substrate	Nucleophile	Conditions	Compound	Yield (%)
2a	 5	NaH, DMF, rt, 15 min	4a	90
2a	 6	NaH, DMF, rt, 15 min	4b	87
2a	 7	NaH, DMF, rt, 15 min	4c	87
2a	 8	NaH, DMF, rt, 15 min	4d	88
2a	 9	3:1 DMF:Et(OH)$_2$, NaH, 90 °C, 1 h	4e	84
2a	 10	Et_2O, NaH, DMF, 40 °C, 1 h	4f	98
2a	 11	37% KF/Al_2O_3, DMSO, 120 °C, 12 h[9]	4g	72
2b	 5	NaH, DMF, rt, 15 min	4a	78
2c	 5	NaH, DMF, 50 °C, 3 h	4a	81

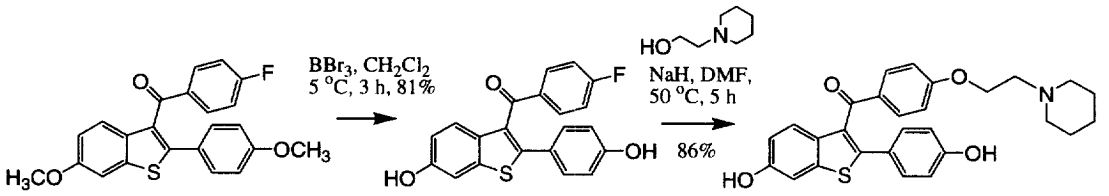
Compound **4e**, from reaction of ethylene glycol with **2a**, could be elaborated into the additional protected SERM **4h** via mesylation followed by displacement with 2,2-dimethylpiperidine, further demonstrating the potential scope of compounds available by this method (Eq. 3).



Eq. 3

Finally, the S_NAr chemistry could be successfully performed on deprotected (i.e. phenol) substrates as well, allowing the order of substitution and deprotection to be reversed. This was demonstrated in a short, direct synthesis of raloxifene (Eq. 4). Thus **2a** was deprotected (BBr_3, dichloromethane, 81%), providing bis-phenol **12**. Reaction with excess sodium hydride (4.4 equiv) and **5** (4 equiv) afforded raloxifene in 86% yield after

chromatography.



The methodology detailed here enables rapid and high yield access to benzothiophene-based SERMs via easily-accessed advanced synthetic intermediates, providing an additional valuable entry into SERM species, while also extending the scope of application of S_NAr chemistry. The synthesis of raloxifene presented here further demonstrates the flexibility of the approach.

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