Pergamon

Tetrahedron Letters 40 (1999) 5155–5159

TETRAHEDRON LETTERS

Synergistic methodologies for the synthesis of 3-aroyl-2-arylbenzo[*b*]thiophene-based selective estrogen receptor modulators. Two concise syntheses of raloxifene

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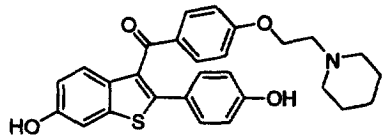
Received 15 April 1999; accepted 14 May 1999

Abstract

Difunctionalized benzo[*b*]thiophene intermediates are prepared which allow fully independent elaboration of the 2-aryl position or the tether position of benzo[*b*]thiophene-based selective estrogen receptor modulators (SERMs). Two concise syntheses of the SERM raloxifene (Evista®) are presented.

Raloxifene (**1**) is a selective estrogen receptor modulator (SERM)[1] which has recently been approved for use in Europe and the United States for the prevention of osteoporosis.[2] SERMs are characterized by their ability to antagonize estrogen receptors found in mammary and uterine tissue, while acting as agonists on receptors associated with bone and lipids.[3] The combination of these effects is thought to provide a uniquely advantageous therapeutic profile for the post-menopausal female population, providing health benefits on skeletal and cardiovascular systems without the undesirable side effects and risks associated with estrogen or hormone replacement therapy.[1b]



raloxifene, 1

Expansion of the structure–activity relationship (SAR) of this class of 3-aroyl-2-aryl-substituted benzo[*b*]thiophenes has identified numerous additional novel compounds.[4] The recently reported use of this class of compounds as thrombin inhibitors[5] has further underscored their therapeutic significance. The SAR efforts around this class of compounds were accompanied by concomitant development of new synthetic methodologies. Direct 3-acylation of substituted 2-dimethylaminobenzo[*b*]thiophenes with

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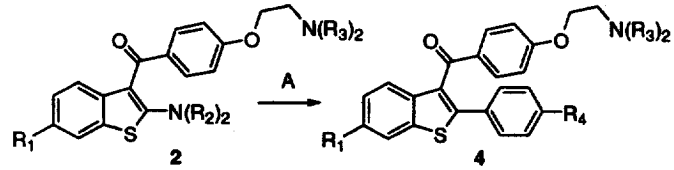
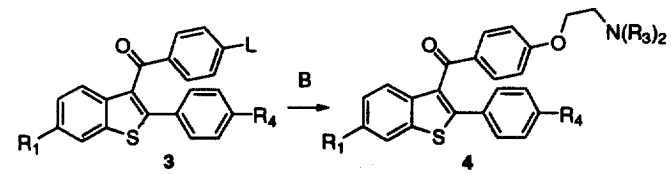
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00955-7

para-substituted benzoyl chlorides delivered compounds **2**, which received aryl Grignard reagents at the 2-position to afford compounds **4** (Eq. 1), which were readily transformed into the desired SERMs.[4c,6a–b] Similarly, Lewis acid-mediated acylation of 2-arylbenzo[*b*]thiophenes with suitably *para*-substituted benzoyl chlorides provided advanced intermediates **3** for variation of the tether region of the parent compound **1** via nucleophilic aromatic substitution (S_NAR) with 2-aminoalkoxides and related nucleophiles (Eq. 2), followed by deprotection.[7] We report here the synthesis and reactions of difunctionalized compounds **5** which incorporate both of these methodological capabilities, enabling fully independent synthetic elaboration at either site, for the rapid assembly of 3-aroyl-2-arylbenzo[*b*]thiophene-based SERMs. The utility of this combination of capabilities is further illustrated in two concise syntheses of raloxifene.

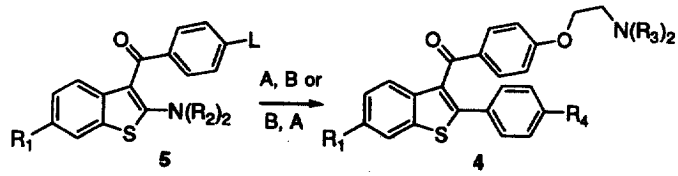


(1)

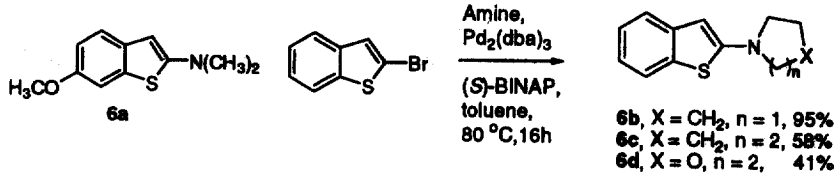


(2)

The envisioned compounds **5** would incorporate 3-aroyl-2-dialkylamino substitution on the benzo[*b*]thiophene as well as an S_NAr leaving group at the *para*-position of the 3-aroyl group (Eq. 3). Access to these compounds was realized using the recently reported direct acylation of 2-dialkylaminobenzo[*b*]thiophenes.[4c,6a–b] 2-Dimethyl-amino-6-methoxybenzo[*b*]thiophene **6a** was prepared via a 2-step literature procedure.[8] Dialkylamine-based enamines **6b–6d** were prepared from 2-bromobenzo[*b*]thiophene[9] via palladium-catalyzed reaction with the indicated dialkylamine in good yields (Eq. 4).[10] Direct, uncatalyzed acylation of compounds **6** with *p*-bromo- or *p*-fluorobenzoyl chlorides proceeded smoothly within a few hours at 100°C, and afforded the crystalline compounds **5** in good yields (Eq. 5). Notably, acylation of **6a** with *p*-fluorobenzoyl chloride afforded **5a** at room temperature after several hours.

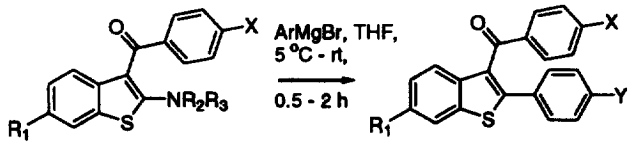


(3)

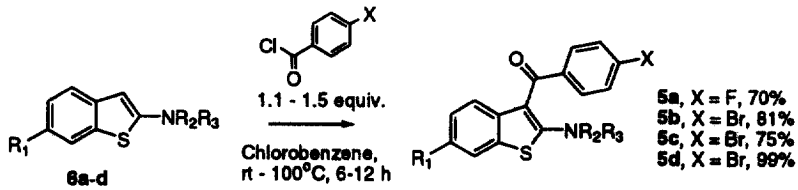


(4)

Table 1
Grignard reaction with compounds 5

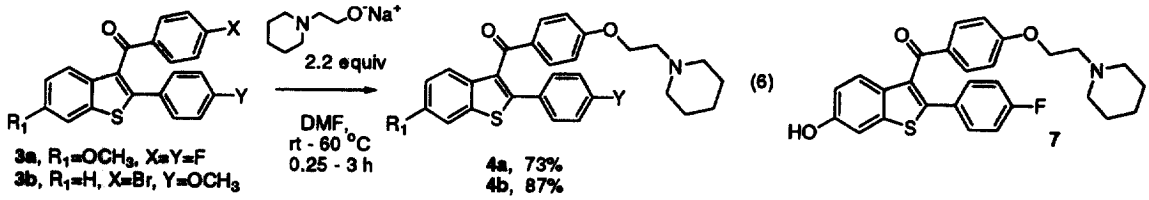


Compound	Grignard	Product (Yield)
5a	*p*-Fluoro	3a, Y=F, (95)
5b	*p*-Methoxy	3b, Y=OCH_3, (77)
5c	*p*-Methoxy	3c, Y=OCH_3 (67)
5d	*p*-Methoxy	3d, Y=OCH_3 (34)



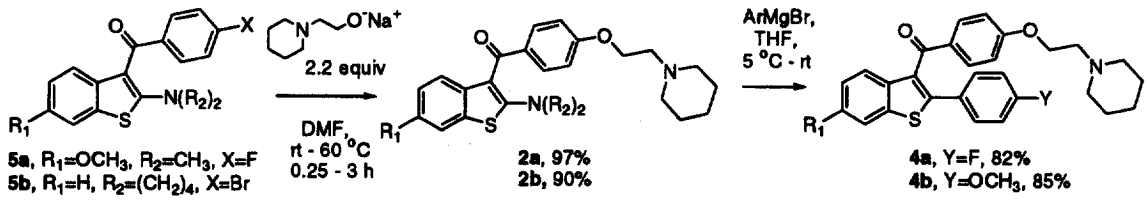
(5)

While in principle nucleophilic attack could proceed indiscriminately at either of the two electrophilic sites (in addition to reaction at carbonyl), it was gratifying to observe that reaction of compounds **5** with aryl magnesium bromides (1.5 equiv., THF, 5–23°C) proceeded exclusively at the 2-position to afford the 2-aryl substituted species **3** (Table 1). The absence of any carbonyl overaddition products in these reactions suggested that the enolate obtained on Michael addition remained stable and eliminated the dialkylamine moiety during reaction quench. High yields of Michael adducts in the presence of excess Grignard reagent (2–4 equiv.) have been noted in similar systems.[6] From inspection of the results found in Eq. 5 and Table 1, compounds **3a** and **3b** were selected for further study. When subjected to the sodium alkoxide of 1-(2-hydroxyethyl)piperidine to install the prototypical ethoxypiperidine SERM tether, both **3a** and **3b** underwent smooth S_NAr addition to afford methyl ether-protected compounds **4a** and **4b** (Eq. 6). The ease with which this displacement occurred (2.2 equiv. alkoxide, rt, DMF, 0.25 h for **3a**, 60°C, DMF, 3 h for **3b**) stood in contrast with the more forcing conditions generally expected for S_NAr substitution on aromatics containing only a carbonyl activating group, paralleling our recently reported findings.[7,11] In the case of **4a**, deprotection ($AlCl_3$, propanethiol, rt, 2 h, 68%) afforded compound **7**, previously identified as a potent SERM;[4c,e] compound **4b** has been previously deprotected to the corresponding phenol.[4c]



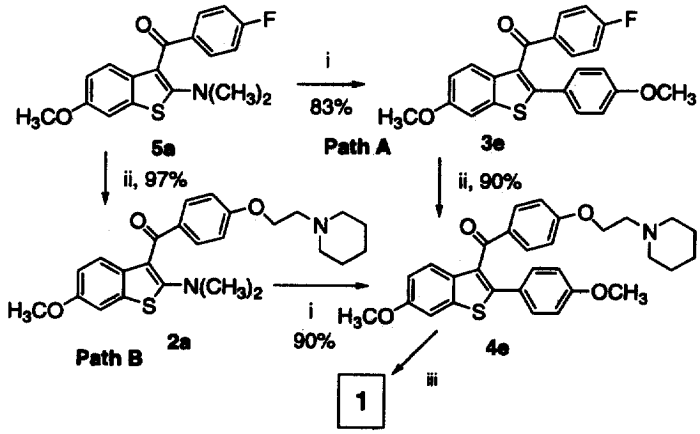
Reversing the order of synthetic operations, reaction of compounds **5** with the sodium alkoxide of 1-(2-hydroxyethyl)piperidine (conditions as before) also proceeded with equal facility and regioselectivity to provide compounds **2**. When compounds **2** were subjected to Grignard reagents (1.2–3.0 equiv., THF, 5–23°C, 1–3 h), displacement at the 2-position proceeded efficiently in high yield to provide an

alternative entry into the manifold of compounds **4**, establishing the flexibility of intermediates **5** for use in their construction (Scheme 1).



Scheme 1.

The value of the Michael addition–elimination/S_NAr methodology using difunctionalized intermediates **5** was illustrated in two concise syntheses of raloxifene (Scheme 2). Thus, starting from 2-dimethylamino-6-methoxybenzo[*b*]thiophene **6a**, acylation as previously noted afforded **5a**. Reaction of **5a** with *p*-methoxyphenylmagnesium bromide (83%) followed by reaction with 1-(hydroxyethyl)piperidine sodium alkoxide (90%) afforded methyl ether-protected raloxifene **4e** via **3e** (path A). Reversing the order of nucleophile addition proceeded with equal efficiency; treatment of **5a** with 1-(hydroxyethyl)piperidine sodium alkoxide (97%), followed by *p*-methoxyphenylmagnesium bromide (90%) again afforded **4e** via **2a** (path B). The efficiency inherent in these syntheses was evident; beginning from **6a**, successive regions of the final compound were added, with atom loss limited to leaving groups (Cl, NR_2 and F). Methyl ether deprotection of **4d** has been previously accomplished ($AlCl_3$, ethanethiol, 78%).[2a] Thus, formal overall yields to **1** were 40% (Path A) and 48% (Path B) from **6c**.



Scheme 2. Syntheses of raloxifene **1** via intermediate **5a**. Conditions: (i) *p*-MeO-Ar-MgBr, THF, 5–23°C, 1–2 h; (ii) NaH, DMF, 1-(2-hydroxyethyl)piperidine (2.2 equiv.), rt, 0.25–0.5 h; (iii) lit.[2a], 78%

The orthogonal reactivity of the two electrophilic sites on difunctionalized intermediates **5** permits the choice of sequence of substitution in the synthesis of 3-aroyl-2-arylbenzo[*b*]thiophene-based SERMs without consequence to subsequent chemistry, defining the synergy of the combination of methods. The accumulative nature of the chemistry is inherently efficient, demonstrated particularly in the syntheses of raloxifene. Further application of this chemistry to the synthesis of additional 3-aroyl-2-arylbenzo[*b*]thiophenes may be anticipated.[12]

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