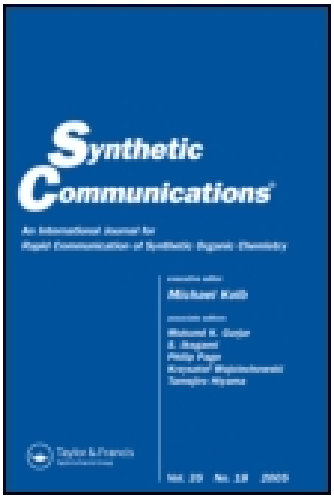

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PIPERIDINE NUCLEOPHILIC SUBSTITUTION WITHOUT SOLVENT: AN EFFICIENT SYNTHESIS OF RALOXIFENE

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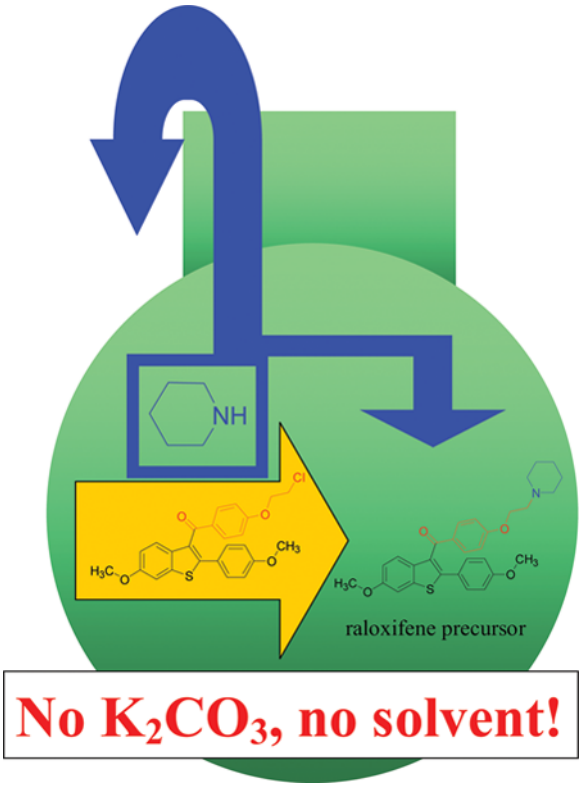
GRAPHICAL ABSTRACT



Abstract *Mild and high-yielding synthesis is described for raloxifene via piperdine nucleophilic substitution of a new raloxifene intermediate 3-aroyl-2-aryl-substituted benzo[b] thiophenes, which is obtained by acylation of para-substituted benzoyl chlorides and*

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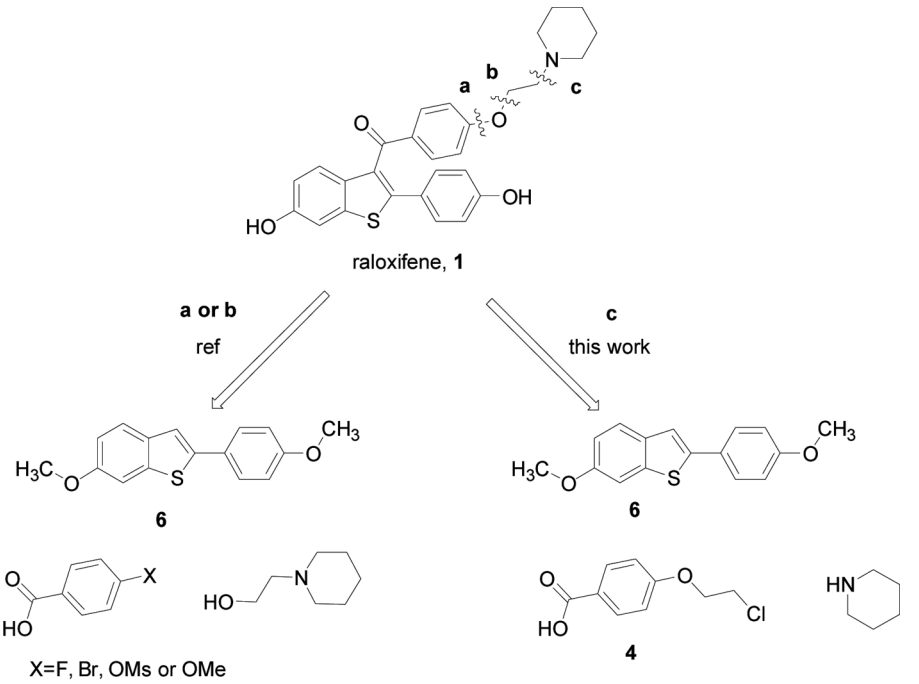
2-arylbenzo[b]thiophenes. The key step is solvent free and offers valuable advantages, such as low cost, and is suitable for industrial production.

Keywords Friedel–Crafts acylation; green chemistry; nucleophiles; raloxifene; SERM

INTRODUCTION

Raloxifene (**1**) is a selective estrogen receptor modulator (SERM), which acts in a tissue-specific fashion as estrogen receptor antagonist in some tissues (uterine and mammary tissues) but as agonist in others (bone and cardiovascular systems). It was approved in 1997 by the U.S. Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women and in 2007 for the chemoprevention of breast cancer in postmenopausal women at high risk for invasive breast cancer.[1,2]

It is currently a large volume product, and the recent work of novel formulations and drug delivery systems could have increased bulk demand for the drug. Several manufacturing routes to raloxifene are well developed.[3] Schmid reported the synthesis of raloxifene or its side-chain analogs via nucleophilic aromatic displacement of aroylbenzohiophenes (Scheme 1, route a). Acylation of substituted *p*-benzoyl chlorides with benzothiophene **6** gives aroylbenzohiophene, following nucleophilic aromatic substitution with oxygen-based nucleophiles to introduce the side piperdino-ethanol chain.[4–7] Jones and coworkers reported the Friedel–Crafts

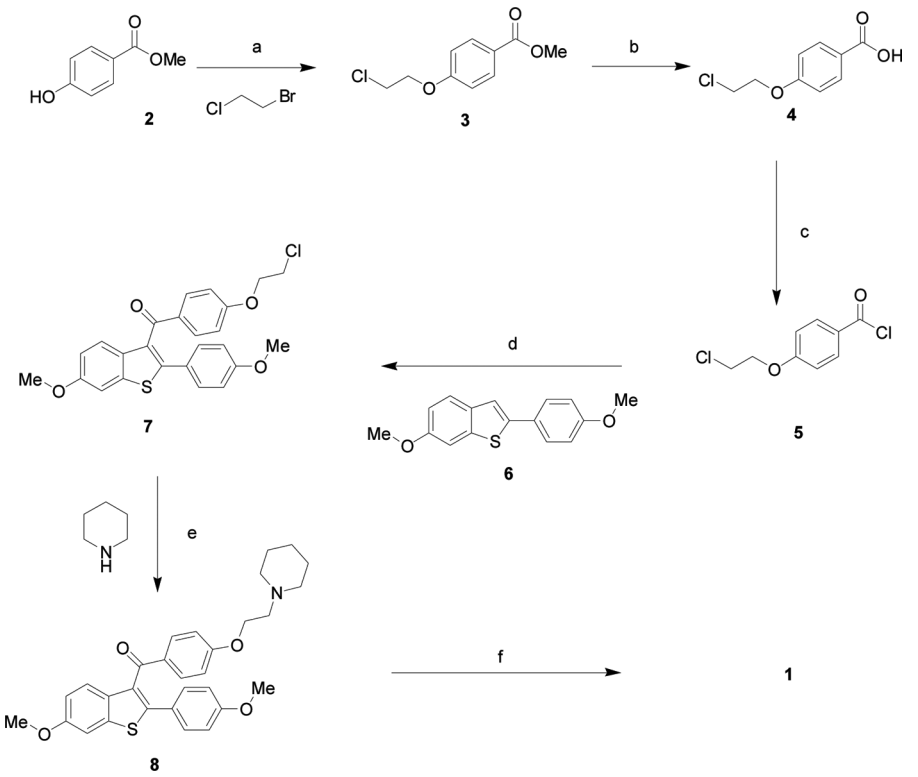


Scheme 1. Current manufacturing routes to raloxifene.

acylation of benzothiophene **6** with 4-[2-(1-piperidino)ethoxy]benzoly chloride has been utilized for the raloxifene (route b).[8,9] Generally routes a and b both need a strong basic condition (NaH, DMF or Cs_2CO_3, CuI) to introduce the piperdinoethanol side chain, generating large aqueous waste streams. Thus an environmentally friendly route of manufacture would be developed not only to the increase bulk demand of the drug but also to meet the needs of green chemistry. We report here that route c, using difunctionalized coumpunds **5** as key intermediate, which incorporates both in the acylation reaction and piperidine nucleophilic substitution, might meet this need.

RESULTS

The improved synthesis of raloxifene **1** was accomplished as shown in Scheme 2. Methyl p-hydroxybenzoate **2**, 1-bromo-2-chloroethane, and K_2CO_3 were refluxed in acetone, yielding compound **3** in 94% yield. Without prior purification, **3** was hydrolyzed to the corresponding p-substituted benzoyl acids **4** in 100% yield. The application of general reaction conditions of methanol as solvent and



Scheme 2. Reagents and conditions: (a) K_2CO_3, 1-bromo-2-chloroethane, acetone, reflux, 91%; (b) HCl, THF, 100%; (c) $SOCl_2$, CH_2Cl_2; (d) $AlCl_3$, CH_2Cl_2, 50 °C, 95% from **3**; (e) piperidine, 94%; and (f) $AlCl_3$, CH_2Cl_2, 50 °C, 90%.

hydrochloric as acid would afford the substitution impurity 4-(2-methoxy-ethoxy)-benzoic acid. To control this impurity during reaction, various solvents such as alcohol, ethyl acetate, acetone, and tetrahydrofuran (THF) were screened, and THF gave the best result from the view of impurity formation and yield. Compound **4** is a solid and was easily isolated from THF by adding water. Then **4** was transferred to acid chlorides **5** and substantially reacted with benzothiophene **6** using $AlCl_3$ in dichloromethane at 50 °C to afford aroylated benzothiophene **7** in two steps, with yield of 95% (79% from method A[8] and 65.5% from method B[3]).

With the requisite **7** in hand, we next examined piperidine nucleophilic substitution to produce the desired beno[b]thien-3-yl ketones **8**. In general using reaction conditions A (acetone, NaI, K_2CO_3, reflux, 70%) and B (acetonitrile, NaI, K_2CO_3, reflux, 85%), impurity formation was observed from the beginning of the reaction. We screened various conditions and were delighted to found that using excess piperidine at reflux temperature gave negligible impurity formation. Piperidine was not only reagent but also solvent. The isolated product **8** was stable and was converted into the desired raloxifene **1** as reported.

In conclusion, we have developed a viable alternative route for the synthesis of raloxifene. The new synthesis would have been better able to support the increase in bulk demand for this drug for the chemoprevention of breast cancer and novel formulations. Our synthetic route has several advantages: the use of difunctionalized coumpunds **5** as key intermediate makes Friedel–Crafts acylation and nucleophilic substitution highly efficient. The using of piperine as reagent and solvent avoids the large waste streams derived from neutralization reaction of sodium hydride. The cost of the new route is less than the current route of manufacture.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on AM400 (Bruker) instruments in $CDCl_3$. Chemical shifts were calibrated using a solvent peak or tetramethylsilane as an internal reference. All reactions were carried out under a nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride immediately prior to use. All chemicals were distilled or recrystallized before use, where necessary.

Preparation of [4-(2-Chloro-ethoxy)-phenyl]-[6-methoxy-2-(4-methoxy-phenyl)-benzo[b]thiophen-3-yl]-methanone (7)

Under an N_2 atmosphere, **5** was added to a mixture of **6** (20.25 g, 75 mmol) and $AlCl_3$ (13.30 g, 100 mmol) in DCM (2 mL), and the mixture was stirred for 12 h. The reaction was monitored by TLC (*n*-hexane/EtOAc, 4:1). After the reaction was judged complete, the reaction mixture was allowed to cool. The crude mixture was poured into H_2O and extracted with EtOAc. The organic layer was separated and concentrated. The residue was crystallized from EtOAc to give the product **7** (32.26 g, 95%): yellow solid crystals; mp 119–120 °C; IR (KBr) ν_{max}: 2960, 2835, 1647, 1599, 1472, 1251, 1169, 1032, 830 cm^{-1};^{1}H NMR (400 MHz, CDCl3) δ 7.76 (d, $J = 8.8$ Hz, 2H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.31 (s, 1H), 6.95 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.75 (dd, $J = 9.2$, 7.2 Hz, 4H), 4.20 (t, $J = 4.0$ Hz,

2H), 3.87 (s, 3H), 3.78 (t, $J = 6.0$ Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 193.1, 162.1, 159.7, 157.6, 142.7, 139.9, 133.8, 132.3, 130.9, 130.2, 130.1, 125.9, 123.9, 114.8, 114.1, 113.9, 104.4, 67.8, 55.6, 55.2, 41.5; MS (EI) m/z (%):452 (M^+, 100.0), 437 (13.0), 297 (25.0), 183 (39.0), 121 (44.0). HRMS m/z (EI) calcd. for $C_{25}H_{22}ClO_4S$: (M+H) +: 453.0927; found: 453.0933.

Preparation of [6-Methoxy-2-(4-methoxy-phenyl)-benzo[b] thiophen-3-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone (8)

Under an N_2 atmosphere, a mixture of **7** (8.50 g, 19 mmol) and piperdine (30 ml) was stirred under reflux for 12 h. The reaction was monitored by TLC (*n*-hexane/EtOAc, 4:1). After the reaction was judged complete, the reaction mixture was allowed to cool. The mixture was concentrated for recovery of piperidine. EtOAc was added and the residue was washed with saturated $NaHCO_3$ aqueous solution. The organic layer was separated and concentrated to give the product **8** (8.80 g, 94%): yellow viscous oil; IR (KBr) ν_{max}: cm^{-1} 2933, 1645, 1597, 1535, 1501, 1470, 1249, 1164, 1030, 827; ^{1}H NMR (400 MHz, CDCl3) δ7.76 (d, $J = 8.8$ Hz, 2H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 2.4$ Hz, 1H), 6.94 (dd, $J = 8.8$, 2.0 Hz, 1H), 6.75 (dd, $J = 7.2$, 5.2 Hz, 4H), 4.08 (t, $J = 6.0$ Hz, 2H), 3.86 (s, 3H), 3.73 (s, 3H), 2.71 (t, $J = 6.0$ Hz, 2H), 2.46 (s, 4H), 1.60–1.54 (m, 4H), 1.43–1.41 (m, 2H).^{13}C NMR (100 MHz, CDCl3) δ 193.2, 163.0, 159.7, 157.6, 142.4, 140.1, 133.9, 132.3, 130.6, 130.4, 130.2, 126.0, 124.0, 114.8, 114.2, 114.1, 104.5, 66.3, 57.7, 55.6, 55.2, 55.1, 25.9, 24.1. MS (EI) m/z (%): 501 (M^+, 100.0), 452 (12.0), 402 (21.0), 297 (24.0), 98 (100.0). HRMS m/z (EI) calcd. for $C_{30}H_{32}NO_4S$: (M+H) +: 502.2052; found: 502.2055.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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