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Expeditious Synthesis of 3-Aryl Benzothiophene A Raloxifene Intermediate

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ABSTRACT

A cyclodehydration of aryl thioacetyl compound with aluminum chloride to form 3-Aryl-6-methoxy thiofurans was an important step in the synthesis of raloxifene hydrochloride. Aryl thioacetyl compound was prepared in a single step from 3-methoxy benzenethiol and 4-methoxy phenacylbromide.

Keywords: Raloxifene hydrochloride; Cyclodehydration; Aluminum chloride

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INTRODUCTION

Benzo (b) thiophene derivatives are identified as an important class of compounds in many pharmaceutical areas. They exhibit a wide variety of biological properties, such as antiallergic [1], and ocular hypotensive activities [2]. Raloxifen, a 2-arylbenzo[b]thiophene marketed by Eli Lilly on the trademark Evista, displayed excellent properties as a selective estrogen receptor modulator (SERM). 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 [3-10]. After lung cancer, breast cancer in women is the most common cancer in the world with more than a million new cases diagnosed every year [11]. Estrogens, acting through the estrogen receptor, are important drivers of breast cancer growth (Figure 1). Much progress has been made in the fight against breast cancer with the development of anti-estrogen agents, such as raloxifene hydrochloride (1) [12].

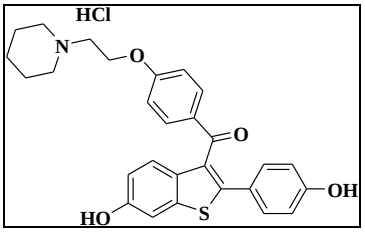


Figure 1: Raloxifene HCl (1)

EXPERIMENTAL SECTION

Materials and Instruments

Most of the reagents used in this work were obtained from commercial suppliers and were of LR/AR grade. Melting points were determined using open capillary tubes on POLMON melting points apparatus (Model-96) and are uncorrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded by using a Bruker 400 Spectrometer with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR Spectrophotometer as KBr pellets or with the neat products. Mass spectra were recorded on an API 2000 LCMS/MS Applied Bio Systems MDS Sciex spectrometer. Microanalysis was performed on a Perkin-Elmer 240CHN elemental analyzer.

Analytical TLC was conducted on E-Merck 60F254 aluminium-packed plates of silica gel (0.2 mm). Developed plates were visualized by using UV light or in an iodine chamber. HPLC was performed by using a Shimadzu 2010 instrument.

1-(4-Methoxy-phenyl)-2-(3-methoxy-phenylsulfanyl)-ethanone (3):

To a solution of 3-methoxy benzenethiol (2) (400 g, 2.8 mol) and ethanol 800 mL at 0-5°C 20% KOH solution (160 g, 2.8 mol) was added drop wise for 1 h, stirred for 10 min and 2-Bromo-1-(4-methoxy-phenyl)-ethanone (652 g, 2.85 mol) was added portion wise at 0-5°C for 1.5 h. After completion of the addition, reaction mass was allowed to RT and stirred for 2 h. After completion of the reaction (monitored by TLC) DM water (1.0 Ltr) was added and stirred for 30 min at RT. Product is filtered and the solid was washed with water (200 mL), to obtain crude product. Crude product was recrystallized from methanol to yield the desired product, off white color solid 3. (695 g, 84% yield, 98.66% purity); mp 53-55.4°C; IR (in KBr, cm^{-1}): 3310, 2888, 1608, 1248; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.92 (d, *J* = 8.84 Hz, 2H), 7.17 (t, *J*=7.8 Hz, 1H), 6.96-6.90 (q, 4H), 6.75-6.72 (m, 1H), 4.24 (s, 2H); 3.85 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 192.71, 163.83, 159.84, 136.50, 131.04, 129.86, 128.34, 122.01, 115.17, 113.89, 112.70, 55.36, 55.27, 40.72; Mass for $C_{16}H_{16}O_3S$ [M+1] 289.1.

6-Methoxy-3-(4-methoxy-phenyl)-benzo[b]thiophene (4):

To a stirred solution of aluminum chloride (111.6 g, 0.83 mol) and dichloromethane (DCM) (1500 mL) at 0-5°C 1-(4-Methoxy-phenyl)-2-(3-methoxy-phenylsulfanyl)-ethanone (3) in DCM (200 g, 0.769 mol in 600 mL DCM) was added over 45 min at 0-5°C. After completion of the addition the resulting mixture was stirred for 30 h at RT. After completion of the reaction (monitored by TLC) the reaction mixture was quenched in to 10% aq HCl solution (500 mL) and extracted with DCM (2 × 200 mL). Organic layer was washed with DM water (300 mL) and dried over sodium sulfate and concentrated under vacuum, to get the crude product. To this crude product was added methanol (300 ml) and stirred for 15 min at 5-10°C. The product was filtered and washed with methanol (30 mL) to yield the desired product in white color (4). (170 g, 90% yield, 99.27% purity); mp 95-98.7°C; IR (in KBr, cm^{-1}): 3368, 2832, 1894, 1600, 1469, 1232; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.76 (d, *J* = 8.84 Hz, 1H), 7.50 (d, *J* = 8.48 Hz, 2H), 7.37 (d, *J*=2.0 Hz, 1H), 7.15 (s, 1H), 7.01 (d, *J* = 8.35 Hz, 3H), 3.89, (s, 3H, OCH_3)3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 159.14, 157.49, 142.12, 137.37, 132.25, 129.71, 128.71, 123.58, 119.88, 114.39, 114.17, 105.26, 55.64, 55.38; Mass for $C_{16}H_{14}O_2S$ [M+1] 271.2.

6-Methoxy-2-(4-methoxy-phenyl)-benzo[b]thiophene (6):

Methanesulfonic acid (61 g, 0.63 mol) was added to a solution of 6-Methoxy-3-(4-methoxy-phenyl)-benzo[b]thiophene (4) (170 g, 0.63) in toluene (700 mL) at RT, and the mixture was stirred at 90°C for 4 h. After completion of the reaction (monitored by TLC) heptane (280 mL) was added at 90 °C and the resulting mixture was stirred for 1 h at 90°C, followed by 3 h at 80°C. After 3 h 2-Propanol (490 mL) was added and stirred for 30 min, the mixture was then cooled to 0°C, stirred for 1 h and filtered, washed with toluene and 2-propanol mixture 190 mL (70/30 v/v), and dried overnight at 60°C under vacuum to yield the desired product (6) (136.0 g, 80% yield, 99.7% purity); mp 196-197°C; IR (in KBr, cm^{-1}): 3410, 2963, 1883, 1605, 1249, 816; ^{1}H NMR (400 MHz, DMSO) (δ ppm): 7.61 (t, *J* = 7.84 Hz, 3H), 7.33 (s, 1H), 7.29 (d, *J* = 1.3 Hz, 1H), 6.98-6.93 (m, 3H), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO) (δ ppm): 159.47, 157.19, 141.53, 140.62, 134.92, 127.43, 127.28, 123.90, 117.76, 114.36, 114.32, 104.90, 55.63, 55.40; Mass for $C_{16}H_{14}O_2S$ [M+1] 271.2.

[4-(2-Chloro-ethoxy)-phenyl]-[6-methoxy-2-(4-methoxy-phenyl)-benzo[b]thiophen-3-yl]-methanone (8):

To a stirred solution of 6-Methoxy-2-(4-methoxy-phenyl)-benzo[b]thiophene (135 g, 0.5 mol) (6) and dichloromethane (DCM) (700 mL) at 0-5°C, 4-(2-Chloro-ethoxy)-benzoyl chloride (7) [13,14] in DCM (131.4 g, 0.0.6 mol in 300 mL DCM) was added over 45 min, after 30 min aluminum chloride (7) (100 g, 0.75 mol) was added portion wise for 15 min at 0-5°C. Resulting mixture was stirred for 2 hr at 0-5°C. After completion of the reaction (monitored by TLC), reaction mixture was quenched in to 10% aq HCl solution (500 mL) and extracted with DCM (2 × 200 mL). Organic layer were washed with DM water (500 mL) and dried over sodium sulfate and concentrated under vacuum, to get the crude product. To this crude product methanol (250 mL) was added and stirred for 15 min, filtered and washed with methanol to obtain the desired product 8 (193.5 g, 85% Yield, 98.71% HPLC purity); mp 119-121.6°C; IR (in KBr, cm^{-1}): 3421, 2836, 2042, 1912, 1633, 1594 1246, 1030, 826; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.77 (d, *J* = 8.69 Hz, 2H), 7.53 (d, *J* = 8.9 Hz, 1H), 7.32 (d, *J* = 8.96 Hz, 3H), 6.96 (d, *J* = 6.76 Hz, 1H), 6.76 (t, *J* = 6.98 Hz, 3H), 4.20 (t, *J* = 5.72 Hz, 2H), 3.88 (s, 3H), 3.78 (t, *J* = 5.74 Hz, 2H), 3.74 (s,

3H); ^{13}C NMR (100 MHz, DMSO) (δ ppm): 193.14, 162.19, 159.78, 157.68, 142.80, 140.08, 133.92, 132.39, 130.99, 130.41, 130.30, 125.96, 124.05, 114.84, 114.20, 114.08, 104.51, 67.95, 55.65, 55.27, 41.58; Mass for $C_{25}H_{21}ClO_4S$ [M+1] 454.9.

[6-Methoxy-2-(4-methoxy-phenyl)-benzo[b]thiophen-3-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone (9):

Under nitrogen atmosphere, to a mixture of 8 (175 g, 0.38 mol) and DMF (500 mL) Piperidine (110 g, 1.29 mol) was added at RT, stirred at 80-85°C for 4 h. The reaction was monitored by TLC, after completion of the reaction the mixture was cooled to RT and concentrated under vacuum. The residue was dissolved in ethyl acetate (500 mL) and washed with saturated bi carbonate solution (700 mL) and DM water 500 mL. The organic layer was separated and deride over sodium sulfate and concentrated under vacuum, to get the product free base.

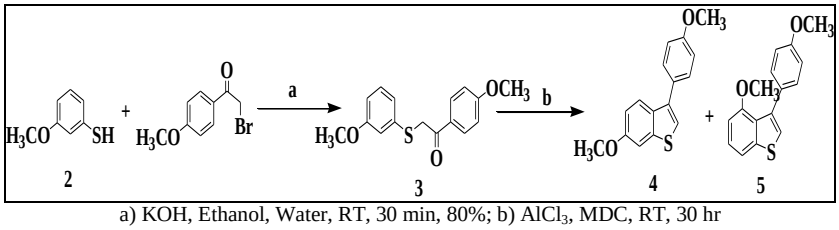
Base product was diluted in IPA 300 mL, added 18% IPA HCl at 5-10°C for 30 min, stirred for 30 min at 10-15°C, filtered the solid and washed with IPA (100 mL), to get the desired product 9. (155 g, 74% Yield, 98.85% HPLC purity); mp 111-113.8°C; IR (in KBr, cm^{-1}): 3421, 2859, 1599, 1251, 826; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 11.0 (s, 1H, HCl), 7.72 (d, *J* = 8.72 Hz, 3H), 7.32 (d, *J* = 8.72 Hz, 3H), 7.0 (t, *J* = 2.36 Hz, 3H), 6.89 (d, *J* = 8.68 Hz, 2H), 4.47 (t, *J* = 4.4 Hz, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 3.44-3.33 (m, 4H), 2.99-2.91 (m, 2H), 1.84-1.65 (m, 5H), 1.36-1.33 (m, 1H); ^{13}C NMR (100 MHz, DMSO) (δ ppm): 192.92, 162.34, 160.0, 157.88, 141.35, 139.89, 133.63, 132.24, 130.66, 130.50, 130.15, 125.65, 123.74, 115.58, 115.26, 114.93, 105.68, 63.11, 56.06, 55.72, 54.86, 52.97, 22.71, 21.63; Mass for $C_{30}H_{31}NO_4S$ [M+1] 504.2.

Raloxifene HCl (1)

Ethanethiol (23.8 g, 0.37 mol) was added to a solution of aluminum chloride (34.7 g, 0.26 mol) and EDC (200 ml) at 0-5°C for 15 min, after 10 min added a solution of 8 (20 g, 0.037 mol, in 50 ml EDC) for 20 min at 0-5°C, stirred for 3 h at RT. Reaction monitored by TLC, after completion of the reaction, cooled to 0-5°C and added THF for 30 min and resulting mixture was quenched in to ice water solution (800 ml), after 15 min added Con HCL (40 ml), stirred for 10 hr at RT, the solid was filtered and washed with water, get the crude product, purification in methanol and DMF yielded the desired product 1. (13.5 g, 66% Yield, 99.91% HPLC purity); mp 250-253.4°C; IR (in KBr, cm^{-1}): 3144, 2687, 1642, 1597, 1431, 1169, 838; ^{1}H NMR (400 MHz, DMSO) (δ ppm): 10.61 (s, 1H), 9.93 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.11 Hz, 1H), 7.17 (d, *J* = 7.28 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.89 (dd, J_1 = 1.64 Hz, J_2 = 1.76 Hz, 1H), 6.71 (d, *J* = 8.4, 2H), 1.76 (m, 4H),1.64 (m, 1H), 1.36 (m, 1H); ^{13}C NMR (100 MHz, DMSO) (δ ppm): 193.08, 162.78, 162.13, 158.42, 156.02, 141.11, 139.71, 132.67, 132.38, 130.79, 130.17, 130.01, 124.17, 123.72, 116.23, 115.75, 115.12, 107.63, 63.02,54.95, 53.04, 36.25, 31.23, 22.76, 21.60; Mass for $C_{28}H_{28}ClNO_4S$ [M+1] 474.1(- HCL).

RESULTS AND DISCUSSION

In this paper we wish to report the synthesis of raloxifene intermediate i.e. 6-Methoxy-3-(4-methoxy-phenyl)-benzo[b]thiophene 4 from 1-(4-Methoxy-phenyl)-2-(3-methoxy-phenylsulfanyl)-ethanone 3 in high yields, and reloxifene drug. Synthesis of several 2,3-arylbenzo[*b*]thiophenes was reported by the cyclodehydration of arylthioacetones with P_2O_5, PPA or $ZnCl_2$ [15]. Seongkon et al. [16] reported a method for synthesis of 4 via the cyclodehydration of 3 in the presence of $BF_3{\cdot}OEt_2$ and obtained a mixture of 4 and 5 (para: ortho) with 75:25 ratio. Later Vicenz JT et al. [17] reported a process with an Amberlyst 15 [18] catalyzed cyclodehydration to get 4 and 5 with 80: 20 ratio. Our methodology is simple and practical. We first prepared the known 3 by reacting of 3-methoxythiophenol 2 with 4-methoxy phenacylbromide in the presence base [19-22]. The cyclization is being critical with isomer ratio of 80: 20 of 4 and 5. We focused on to improve the ratio to >90:10. Different cyclization conditions were studied (Table 1) and found that aluminum chloride and methylene chloride combination at room temperature achieved a better ratio. Compound 4 prepared by this method is identical to the reported one in literature. The sequence of reactions are shown in Scheme 1.

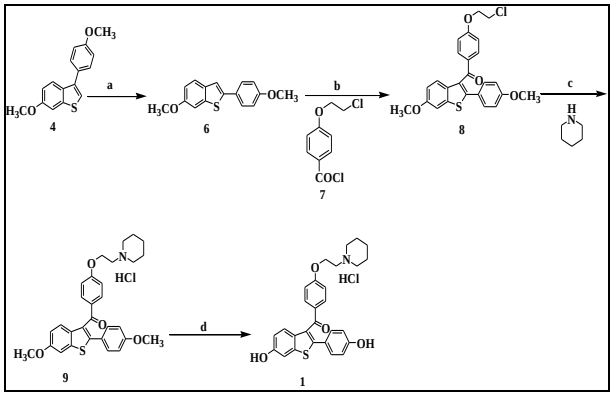


a) KOH, Ethanol, Water, RT, 30 min, 80%; b) $AlCl_3$, MDC, RT, 30 hr

Scheme 1: Synthesis of 4 and 5

Table 1: Reagent and solvent optimization study for the syntheses of 4

Entry	reagent	Solvent	Temp in °C	Product HPLC %	
				4	5
a	PPA	_	80°C	77.25	15.65
b	$BF_3{\cdot}OEt_2$	MDC	RT	74.44	18.42
c	Amberlyst 15	Toluene	110°C	82.2	15.18
d	PTSA	Toluene	100°C	55.39	11.28
e	$FeCl_3$	EDC	RT	ND	ND
f	$SnCl_2$	MDC	RT	22.8	5.7
g	Eaton's reagent	Toluene	70°C	60.28	22.31
h	$AlCl_3$	MDC	RT	92.21	4.14
i	$AlCl_3$	EDC	RT-Reflux	60.92	23.44
j	$AlCl_3$	THF	RT-Reflux	ND	ND
k	$AlCl_3$	2-Me THF	RT-Reflux	36.66	4.28
l	$AlCl_3$	Dioxane	RT-Reflux	ND	ND
m	$AlCl_3$	DMF	RT-Reflux	ND	ND
n	$AlCl_3$	DMSO	RT-Reflux	ND	ND
o	$AlCl_3$	Ethylacetate	RT-Reflux	ND	ND
p	$AlCl_3$	Toluene	RT-Reflux	ND	ND



a) MSA, Toluene, IPA, 90°C, 4 hr; b) $AlCl_3$, MDC, RT, 2 hr; c) DMF, 80°C, 4 hr; d) Ethane thiol, $AlCl_3$, EDC, THF, RT

Scheme 2: Synthesis of raloxifene hydrochloride (1)

The next critical step is for the synthesis of reloxifene is the rearrangement of 4 to 6, we optimized the process of this rearrangement with methane sulfonicacid and toluene at 90°C. Conversion of 6 to drug reloxifene 1 was done as per reported procedure. The sequence of reactions are performed are given in Scheme 2.

CONCLUSION

In conclusion we have developed a method for the preparation of reloxifene intermediate in high yields and the drug in best yields compared to the earlier methods.

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