KF/Al_2O_3/PEG-400: An Efficient Catalytic System for the Fiesselmann-Type Synthesis of Thiophene Derivatives

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Abstract: A simple and mild protocol has been developed for the synthesis of novel steroidal and nonsteroidal thiophene derivatives from β-halo-α,β-unsaturated aldehydes using KF/Al_2O_3/PEG-400 as an efficient catalytic system. The β-halo-α,β-unsaturated aldehydes are synthesized from the corresponding ketones using Vilsmeier formylation reaction and converted into β-halo-α,β-unsaturated nitriles. The synthetic protocol is subsequently applied to the synthesis of 3-aminothiophene derivatives using β-halo-α,β-unsaturated nitriles.

Key words: Fiesselmann synthesis, KF/Al_2O_3/PEG-400, thiophene, unsaturated aldehyde, unsaturated nitrile

Thiophene and its derivatives constitute the core structures of many natural products[1] and pharmaceutically active agents,[2] and they have become a subject of considerable interest in material chemistry.[3] Materials containing thiophene core units have been reported to exhibit significant lateral dipole moments that help to contribute to physical parameters such as increased dielectric anisotropy and dielectric biaxiality.[4] They find commercial applications in organic light-emitting diodes, organic field-effect transistors, and organic photovoltaic cells.[5] In medicinal chemistry, thiophene derivatives are known to exhibit biological activity as BACE1 inhibitors,[6] anti-inflammatory agents,[7] anti-HIV PR inhibitors,[8] and anti-breast cancer agent.[9] Moreover, thiophene-2-carboxylic acid derivatives are reported as one of the most potent G protein-coupled receptor 35 (GPR35) agonists.[10] Additionally, 3-aminothiophene-2-carboxylic acid and its derivatives are pharmaceutically important precursors, such as in the synthesis of articaine (Figure 1), which is used for local dental anesthetic purposes.[11]

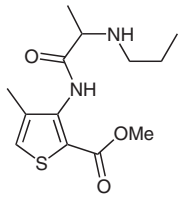

Figure 1 Local dental anesthetic articanine

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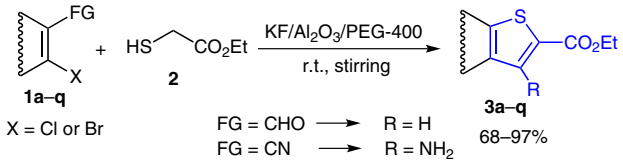
Fiesselmann thiophene synthesis has been well studied in the case of ethyl thioglyconate and β-halo-α,β-unsaturated aldehydes.[12] The formation of the thiophene is known to take place via a domino process involving Michael addition, followed by an internal Knoevenagel reaction in the presence of bases such as sodium in ethanol,[13] sodium hydride,[14] pyridine/triethylamine,[14,15] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[16] However, most of these processes have the disadvantage of having stringent reaction conditions, such as strongly basic conditions, low reaction temperatures,[14] longer reaction times,[14] or use of toxic pyridine as reaction medium.[15]

Furthermore, the majority of these synthetic protocols are based on annulations of the thiophene moiety to nonsteroidal building blocks without adequate emphasis on steroidal systems. On the other hand, the studies on steroidal heterocycles emerge as an important area of research and enormous efforts have been made in the synthesis of novel heterosteroids because of their inherent biological activity.[17] To the best of our knowledge, there is only one example available in the literature for the incorporation of a thiophene moiety in the steroidal core. For example, Kumar et al.[14] reported the synthesis of A-ring fused steroidal thiophene from a 3-chloro-2-aldehyde and ethyl thioglyconate in the presence of pyridine/triethylamine to give a mixture of cyclized thiophene product with appreciable uncyclized intermediate. However, a very strong base such as sodium hydride in refluxing toluene was employed subsequently to afford the cyclized product from uncyclized intermediate.

Nonetheless, solid-supported recyclable catalysts have emerging advantages, such as enhanced reactivity, selectivity, mild conditions, avoidance of cumbersome aqueous workup conditions, and a decrease in solvent waste.[18] The catalyst KF/Al_2O_3 is an interesting solid-supported base and well-known green catalytic system, which tends to replace organic as well as inorganic bases in a variety of reactions.[19] On the other hand, polyethylene glycol (PEG-400) is a nontoxic, nonvolatile, and recyclable solvent used in organic synthesis.[20] In continuation of our research interests on β-halo-α,β-unsaturated aldehydes,[21] herein we report KF/Al_2O_3/PEG-400 as an efficient recyclable catalytic system for the Fiesselmann-type synthesis of steroidal and nonsteroidal thiophenes and their amino derivatives. This synthetic protocol is a domino process that involves the reaction of easily accessible A- and D-ring annulated β-halo-α,β-unsaturated aldehydes with ethyl thioglyconate at room temperature. For the synthesis of

3-aminothiophene derivatives, β-halo-α,β-unsaturated nitriles were used as starting substrates, these were derived from β-halo-α,β-unsaturated aldehydes in a one-pot reaction.[22] The present synthetic protocol utilizes inexpensive and readily available KF/Al_2O_3 as a heterogeneous catalyst in the green solvent PEG-400 for the one-step synthesis of thiophene and its derivatives in high yields (Scheme 1).



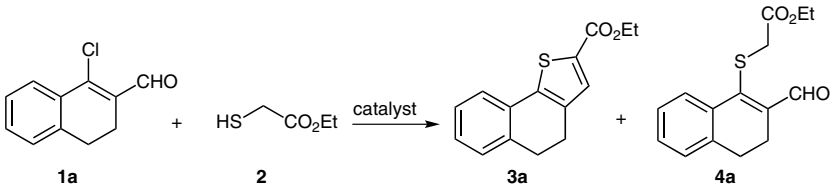
Scheme 1 Synthesis of steroidal and nonsteroidal thiophene derivatives

Initially, we chose 1-chloro-3,4-dihydronaphthalene-2-carbaldehyde (**1a**) as the starting material to perform the optimization studies for the products **3a** and **4a** employing different catalytic conditions (Table 1).

In the absence of a catalyst, the reaction of **1a** with **2a** did not proceed (entry 1) and the use of solid-phase KF/Al_2O_3 (40%) afforded a poor yield of the product (entry 2). On the other hand, the KF/Al_2O_3 catalyzed reaction in acetonitrile and methanol led to good yields of **3a** in shorter reaction times (entries 3 and 4). However, our attempt to utilize the recovered KF/Al_2O_3 afforded uncyclized Michael adduct **4a** as the major product even under the conditions of enhanced loading capacity of the catalytic system (entries 6 and 8). When we used PEG-400 as the reaction media, the thiophene synthesis was efficiently accomplished within a short period of time at room temperature (entries 10 and 11). The recovered catalyst could be used consecutively for another three times to afford product **3a** in high yield (entries 12–14). Interestingly, the use of potassium hydroxide (4 molar equiv) in place of the catalytic system, afforded **3a** in 48% yield along with the mixture of undesired products.

A series of steroidal and nonsteroidal thiophene derivatives were synthesized under the optimized reaction conditions (Table 2). For the synthesis of D-ring fused thiophene, a mixture of 3β-acetoxy-17-bromo-16-formyl-

Table 1 Optimization of the Synthesis of Thiophene **3a**[a]

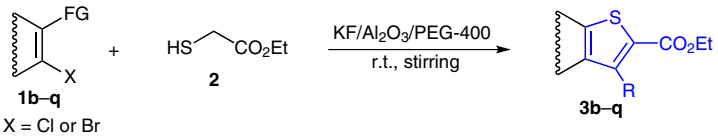


Entry	Catalyst System	Loading (g)	No. of recycle	Yield[b] (%) **3a**	**4a**
1	–	–	–	–[c]	–[c]
2[d,e]	KF/Al_2O_3	0.2	0	40	–[c]
3	KF/Al_2O_3/MeCN	0.2	0	57	–[c]
4	KF/Al_2O_3/MeOH	0.2	0	51	trace
5	KF/Al_2O_3/MeCN	0.5	0	68	–[c]
6	KF/Al_2O_3/MeCN	0.5	1	10	61
7	KF/Al_2O_3/MeOH	0.5	0	67	–[c]
8	KF/Al_2O_3/MeOH	0.5	1	trace	65
9	KF/Al_2O_3/THF	0.5	0	60	15
10	KF/Al_2O_3/PEG-400	0.2	0	71	–[c]
11	KF/Al_2O_3/PEG-400	0.5	0	97	–[c]
12	KF/Al_2O_3/PEG-400	0.5	1	80	–[c]
13	KF/Al_2O_3/PEG-400	0.5	2	77	–[c]

[a] Reaction conditions: **1a** (1.0 mmol), ethyl thioglyconate (1.0 mmol), KF/Al_2O_3 (40%), solvent (3 mL), r.t., 45 min.
[b] Isolated yield.
[c] Not detected.
[d] Neat.
[e] Overnight, r.t.

androsta-5,16-diene (**1j**, 1 mmol) and ethyl thioglyconate (**2**, 1 mmol) was stirred in the presence of KF/Al_2O_3 (40%, 0.5 g) and PEG-400 (3 mL) at room temperature to afford ethyl 3β-acetoxyandrosta-5,16-dieno[17,16-*b*]thiophene-5′-carboxylate (**3j**) in 88% yield (entry 9). The product **3j** was characterized by physical and high-resolution spectral data. When the same reaction was carried out with a chloro-formyl steroid, for example, 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene (**1k**), we obtained the desired product **3j** in 85% yield. However, the chloro-formyl substrate required more reaction time in comparison to the bromo-formyl substrate (entries 9 and 10). The starting materials **1j**,**k** were conveniently prepared from 3β-acetoxyandrost-5-en-17-one using the Vilsmeier reaction.[21] Similarly, steroidal A- and D-ring annulated β-halo-α,β-unsaturated aldehydes **1l**,**m**,**o** were accomplished, respectively, from the Vilsmeier reaction of commercially available estrone and cholesterol. The reaction of each β-halo-α,β-unsaturated aldehydes **1l**,**m**,**o** with ethyl thioglyconate (**2**) afforded corresponding thiophenes **3l**,**m**,**o**, respectively in high yields (entries 11, 12, and 14). The synthesis of A- and D-ring fused steroidal bisthiophene **3p** was accomplished from androst-4-ene-3,17-dione by initial reduction to androstane-3,17-dione followed by Vilsmeier formylation reaction to 3,17-dibromo-2,16-diformylandrosta-2,16-diene (**1p**). The reaction of **1p** with two equivalents of ethyl thioglyconate afforded the desired diethyl androsta-2,16-dieno[3,2-*b*:17,16-*b*′]bisthiophene-5′,5″-dicarboxylate (**3p**) in 75% yield (entry 15). Similarly, the nonsteroidal β-bromo-α,β-unsaturated aldehyde analogue, for example, 2-bromocyclohex-1-enecarbaldehyde (**1b**) reacted with **2** under the catalytic conditions to afford ethyl 4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate (**3b**) in 88% yield. In order to broaden the scope of our reaction, we used eight-membered and acyclic β-chloro-α,β-unsaturated aldehydes **1d** and **1f** to synthesize corresponding thiophene derivatives **3d** and **3f** in high yields (entries 3 and 5).

Table 2 KF/Al_2O_3/PEG-400-Catalyzed Synthesis of Steroidal and Nonsteroidal Thiophene Derivatives **3**[a]



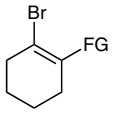
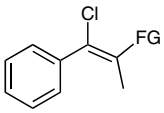
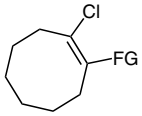
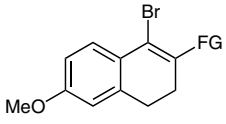
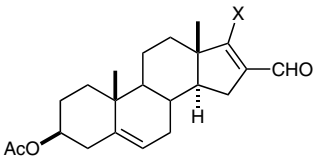
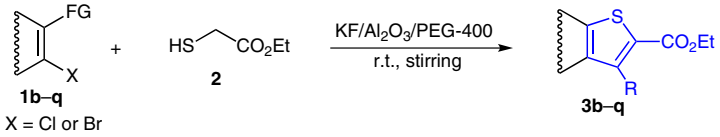
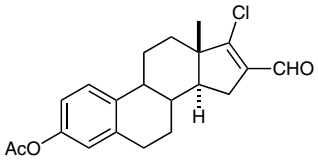
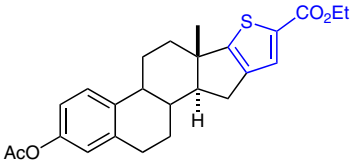
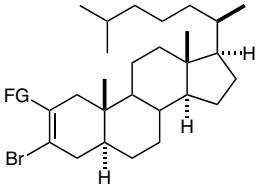
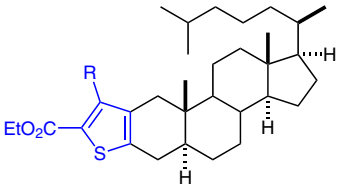
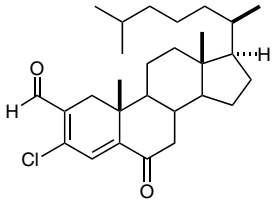
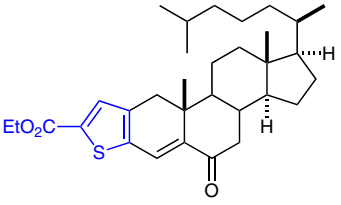
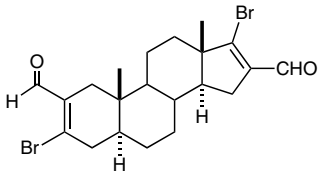
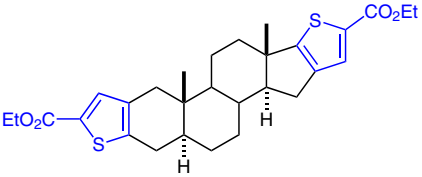
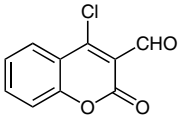
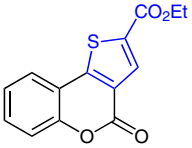
Entry	Substrate	Product		Time (min)	Yield[b] (%)
1		FG = CHO **1b**	R = H **3b**	30	88
2		FG = CN **1c**	R = NH_2 **3c**	45	85
3		FG = CHO **1d**	R = H **3d**	70	70
4		FG = CN **1e**	R = NH_2 **3e**	90	68
5		FG = CHO **1f**	R = H **3f**	60	85
6		FG = CN **1g**	R = NH_2 **3g**	80	88
7		FG = CHO **1h**	R = H **3h**	30	95
8		FG = CN **1i**	R = NH_2 **3i**	50	92
9		X = Br **1j**	**3j**	40	88
10		X = Cl **1k**		90	85

Table 2 KF/Al_2O_3/PEG-400-Catalyzed Synthesis of Steroidal and Nonsteroidal Thiophene Derivatives **3**[a] (continued)



Entry	Substrate		Product		Time (min)	Yield[b] (%)
11		**1l**		**3l**	70	90
12		FG = CHO **1m**		R = H **3m**	50	89
13		FG = CN **1n**		R = NH_2 **3n**	70	85
14		**1o**		**3o**	70	70
15		**1p**		**3p**	90	75
16		**1q**		**3q**	60	80

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), KF/Al_2O_3 (0.5 g of 40%), PEG-400 (3 mL), r.t.
[b] Isolated yield.

Ethyl 4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (**3q**) was synthesized from 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (**1q**) in 80% yield. 3-Aminothiophene derivatives **3c**,**e**,**g**,**i**,**n** were synthesized from β-halo-α,β-unsaturated nitriles **1c**,**e**,**g**,**i**,**n** that were derived from their corresponding β-halo-α,β-unsaturated aldehydes **1b**,**d**,**f**,**h**,**m**, respectively (Table 2).

The mechanism of the basicity of KF/Al_2O_3 is not clear. Weinstock et al.[23] reported that KF/Al_2O_3 derives its basicity from the formation of potassium hydroxide in the initial preparation of the solid supported material by reaction of potassium fluoride with alumina. However, Ando et al.[24] reported that there are three basic species for the basicity of KF/Al_2O_3; (a) the presence of active fluoride, (b) [Al–O^-] ions that generate OH^-, and (c) cooperation of F^- and [Al–OH]. It may be presumed that PEG 400, adsorbed on surface of alumina, may chelate with K^+ to form a chelate cation, with subsequent release of F^- as the balance ion.[25] The three basic species generated through a cooperative action of potassium fluoride on the surface of alumina and PEG 400 would take part in Michael addition of thioglyconate to β-halo-α,β-unsaturated aldehyde to afford intermediate **4a**. The intermediate **4a** subsequently undergoes Knoevenagel condensation under the basic conditions to form the desired product **3a**. To establish the mechanism, the intermediate **4a** was isolated and independently treated with KF/Al_2O_3/PEG-400, to give the final product **3a** in excellent yield.

In conclusion, we have developed a simple and mild protocol for the synthesis of novel steroidal and nonsteroidal

thiophene derivatives from the reaction of β-halo-α,β-unsaturated aldehydes using KF/Al_2O_3/PEG-400 as an efficient catalytic system. In addition, the synthetic strategy is also highly compatible for the generation of 3-aminothiophene derivatives from β-halo-α,β-unsaturated nitriles. This synthetic protocol is advantageous because of merits such as high conversions, simplicity of operation, and cost efficiency, and it can be used for the synthesis of thiophene fused steroidal derivatives. Our protocol will facilitate the generation of libraries of compounds of potential biological significance in medicinal chemistry and drug discovery.

Melting points were recorded in open capillary (Pyrex) tubes with a Buchi-540 micro melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1640 FT-IR spectrophotometer as a thin film using $CHCl_3$ or as a KBr pellet. All NMR spectra were recorded on Bruker Advance DPX 300 MHz spectrometer downfield from TMS (δ = 0.0) using the residual solvent signal at δ = 7.26 (^{1}H) or δ = 77 (^{13}C) as internal standard. Hydrogenation reactions were done in a Parr Hydrogenation apparatus (model: Baldor). ESI-MS (LC) were recorded on a Bruker Daltonic Data analysis 2-0 spectrometer. EI-MS (GC) were recorded on a Trace DSQ GC-MS instrument (Thermo Electron, Austria) through a direct insertion probe (DIP). Elemental analysis was done using Perkin-Elmer series II CSNS/O Model 2400 machine calibrated against standard acetanilide. Yields refer to chromatographically purified compounds, unless otherwise stated.

Preparation of KF/Al_2O_3 (40%)
In a 100-mL round-bottom flask, KF (4 g) was dissolved in H_2O (25 mL) and neutral alumina (6 g, 100–200 mesh) was added. The mixture was vigorously stirred for 10 min and then H_2O was removed under reduced pressure. The resultant solid KF/Al_2O_3 was dried at 100 °C for 5 h in an oven and kept in a desiccator.

Thiophenes 3; General Procedure
A mixture of β-halo-α,β-unsaturated aldehyde (1 mmol, 1 equiv), ethyl thioglyconate (1 mmol, 1 equiv), and KF/Al_2O_3 (0.5 g) were taken in PEG-400 (3 mL) and stirred at r.t. When the reaction was complete ((TLC monitoring), the product was extracted with EtOAc–hexanes (10:90, 3 × 10 mL) and the residue, KF/Al_2O_3/PEG-400, was separated and dried under vacuum for reuse. The upper organic phase was dried and concentrated under reduced pressure. The product was purified by column chromatography.

The same experimental procedure was followed for the synthesis of 2-aminothiophene derivatives from β-halo-α,β-unsaturated nitriles.

Ethyl 4,5-Dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (3a)
White solid; yield: 251 mg (97%); mp 78–81 °C; R_f = 0.6 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 2934, 1702, 1433, 1272, 1073, 759 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 1 H), 7.34 (m, 2 H), 7.15 (m, 2 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 2.87 (m, 2 H), 2.74 (m, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 162.5, 143.1, 137.7, 135.4, 133.6, 130.7, 130.5, 128.3 (2 C), 127.2, 123.6, 61.1, 29.7, 23.8, 14.4.

MS (ESI): *m*/*z* = 258.1 [M$^+$].

Anal. Calcd for $C_{15}H_{14}O_2S$ (258.34): C, 69.74; H, 5.46. Found: C, 69.70; H, 5.48.

Ethyl 4,5,6,7-Tetrahydrobenzo[*b*]thiophene-2-carboxylate (3b)
Light yellow gum; yield: 185 mg (88%); R_f = 0.5 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 1733, 1706, 1463, 1282, 1263, 1070 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 2.76 (t, *J* = 5.7 Hz, 2 H), 2.61 (t, *J* = 5.6 Hz, 2 H), 1.82 (m, 4 H), 1.33 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 162.6, 143.9, 136.2, 134.0, 129.4, 60.7, 25.4, 25.3, 23.2, 22.6, 14.1.

MS (ESI): *m*/*z* = 210 [M$^+$].

Anal. Calcd for $C_{11}H_{14}O_2S$ (210.29): C, 62.83; H, 6.71. Found: C, 62.85; H, 6.74.

Ethyl 3-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate (3c)
Off-white solid; yield: 191 mg (85%); mp 58–61 °C; R_f = 0.4 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 3459, 3359, 2932, 2869, 1666, 1606, 1495, 1445, 1289, 1125, 768 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.34 (br s, 2 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 2.68 (m, 2 H), 2.31 (m, 2 H), 1.83 (m, 4 H), 1.33 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 164.9, 152.3, 143.1, 128.8, 97.4, 59.7, 25.6, 22.9, 22.4, 21.7, 14.6.

MS (LCMS): *m*/*z* = 227.3 [M$^+$ + 2].

Anal. Calcd for $C_{11}H_{15}NO_2S$ (225.31): C, 58.64; H, 6.71; N, 6.22. Found: C, 58.61; H, 6.74; N, 6.25.

Ethyl 4-Methyl-5-phenylthiophene-2-carboxylate (3d)
Light yellow gum; yield: 172 mg (70%); R_f = 0.45 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 2980, 1706, 1450, 1280, 1244, 1189, 1072, 761, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (s, 1 H), 7.51–7.29 (m, 5 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 2.30 (s, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 162.0, 145.0, 136.6, 133.7, 133.5, 130.6, 128.7, 128.4, 127.9, 60.8, 14.7, 14.1.

MS (ESI): *m*/*z* = 246 [M$^+$].

Anal. Calcd for $C_{14}H_{14}O_2S$ (246.32): C, 68.26; H, 5.73. Found: C, 68.21; H, 5.75.

Ethyl 3-Amino-4-methyl-5-phenylthiophene-2-carboxylate (3e)
Colorless gum; yield: 178 mg (68%); R_f = 0.25 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 3466, 3362, 2983, 2926, 1736, 1669, 1606, 1444, 1300, 1154, 1026, 758, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (m, 5 H), 5.47 (br s, 2 H), 4.06 (q, *J* = 7.1 Hz, 2 H), 2.21 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.3, 155.1, 135.2, 129.7, 128.9 (3C), 128.7 (3C), 118.9, 61.6, 18.5, 13.9.

MS (ESI): *m*/*z* = 259.4 [M$^+$ – 2].

Anal. Calcd for $C_{14}H_{15}NO_2S$ (261.34): C, 64.34; H, 5.79; N, 5.36. Found: C, 64.33; H, 5.76; N, 5.38.

Ethyl 4,5,6,7,8,9-Hexahydrocycloocta[*b*]thiophene-2-carboxylate (3f)
Colorless gum; yield: 191 mg (85%); R_f = 0.4 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 2927, 2852, 1706, 1556, 1465, 1278, 1248, 1177, 1076, 753 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (s, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 2.8–2.71 (m, 2 H), 2. 6–2.52 (m, 2 H), 1.56 (m, 8 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 162.4, 147.1, 139.8, 135.1, 128.9, 60.7, 32.0, 30.9, 27.0, 26.9, 25.6, 25.4, 14.3.

MS (ESI): m/z = 237.9 [M^+].

Anal. Calcd for $C_{13}H_{18}O_2S$ (238.35): C, 65.51; H, 7.61. Found: C, 65.55; H, 7.63.

Ethyl 3-Amino-4,5,6,7,8,9-hexahydrocycloocta[*b*]thiophene-2-carboxylate (3g)
White solid; yield: 210 mg (88%); mp 73–75 °C; R_f = 0.3 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 3462, 3359, 2925, 2851, 1666, 1601, 1486, 1304, 1230, 1077, 770 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.39 (br s, 2 H), 4.28 (q, J = 7.0 Hz, 2 H), 2.75 (t, J = 5.8 Hz, 2 H), 2.51 (t, J = 5.9 Hz, 2 H), 1.66 (m, 8 H), 1.33 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 164.9, 152.4, 146.1, 128.4, 98.1, 59.8, 32.0, 28.5, 28.1, 26.0, 25.4, 23.6, 14.6.

MS (ESI): m/z = 254.6 [M^+ + 1].

Anal. Calcd for $C_{13}H_{19}NO_2S$ (253.36): C, 61.63; H, 7.56; N, 5.53. Found: C, 61.65; H, 7.53; N, 5.55.

Ethyl 7-Methoxy-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (3h)
Brown solid; yield: 274 mg (95%); mp 72–75 °C; R_f = 0.4 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 2980, 2937, 1702, 1607, 1576, 1451, 1422, 1286, 1248, 1260, 1073, 1035, 752 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 7.39–7.31 (m, 1 H), 6.74–6.80 (m, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 3.82 (s, 3 H), 2.75–2.98 (m, 4 H), 1.38 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): 162.6, 159.7, 143.3, 137.4, 136.0, 133.7, 129.1, 124.9, 123.9, 114.1, 112.2, 60.9, 55.3, 29.4, 23.7, 14.4.

MS (ESI): m/z = 288 [M^+].

Anal. Calcd for $C_{16}H_{16}O_3S$ (288.36): C, 66.64; H, 5.59. Found: C, 66.61; H, 5.61.

Ethyl 3-Amino-7-methoxy-4,5-dihydronaphtho[1,2-*b*]thiophene-2-carboxylate (3i)
Light yellow solid; yield: 279 mg (92%); mp 127–129 °C; R_f = 0.4 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 3467, 3359, 2978, 2935, 1733, 1663, 1606, 1578, 1479, 1300, 1251, 1163, 1069, 767 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, J = 9.1 Hz, 1 H), 6.72–6.8 (m, 2 H), 5.42 (br s, 2 H), 4.32 (q, J = 7.1 Hz, 2 H), 3.82 (s, 3 H), 2.96 (t, J = 7.7 Hz, 2 H), 2.57 (t, J = 7.7 Hz, 2 H), 1.36 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 164.9, 159.9, 151.9, 141.4, 137.4, 125.0, 124.93, 123.7, 114.0, 112.0, 98.7, 59.9, 55.3, 28.7, 20.7, 14.6.

MS (ESI): m/z = 304.9 [M^+ + 2].

Anal. Calcd for $C_{16}H_{17}NO_3S$ (303.38): C, 63.34; H, 5.65; N, 4.62. Found: C, 63.35; H, 5.68; N, 4.60.

Ethyl 3β-Acetoxyandrosta-5,16-dieno[17,16-*b*]thiophene-5′-carboxylate (3j)
Off white solid; yield: 389 mg (88%); mp 138–141 °C; R_f = 0.4 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 2941, 2854, 1733, 1702, 1407, 1244, 1155, 1031, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 5.42 (d, J = 4.8 Hz, 1 H), 4.63 (m, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 2.64 (dd, J_1 = 6.2 Hz, J_2 = 14.2 Hz, 1 H), 2.26–2.45 (m, 3 H), 2.04 (s, 3 H), 1.34 (t, J = 6.9 Hz, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.53–2.0 (m, 13 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 170.5, 162.7, 162.0, 144.1, 140.0, 133.6, 129.2, 122.0, 73.7, 60.9, 60.7, 50.1, 45.4, 38.1, 36.8 (2C), 35.3, 31.3, 30.8, 28.9, 27.7, 21.4, 20.6, 19.2, 19.1, 14.4.

MS (ESI): m/z = 442.2 [M^+].

Anal. Calcd for $C_{26}H_{34}O_4S$ (442.61): C, 70.55; H, 7.74. Found: C, 70.58; H, 7.71.

Ethyl 3-Acetoxyestra-1,3,5(10),16-tetraeno[17,16-*b*]thiophene-5′-carboxylate (3l)
White solid; yield: 382 mg (90%); mp 165–168 °C; R_f = 0.45 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 2933, 2855, 1762, 1702, 1494, 1407, 1204, 1171, 1072, 1014, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 1 H), 7.28 (d, J = 8.5 Hz, 1 H), 6.78–6.9 (m, 2 H), 4.33 (q, J = 7.1 Hz, 2 H), 2.8–3 (m, 2 H), 2.74 (dd, J_1 = 6.3 Hz, J_2 = 14.0 Hz, 1 H), 2.29 (s, 3 H), 1.61 (s, 3 H), 1.43–2.52 (m, 7 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.02 (s, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 169.9, 162.7, 162, 148.5, 144.0, 138.0, 137.6, 133.6, 129.3, 126.1, 121.6, 118.7, 60.8, 60.2, 45.8, 44.2, 37.2, 35.4, 29.3, 28.7, 27.3, 26.1, 21.1, 19.3, 14.4.

MS (LCMS): m/z = 424.9 [M^+ + 1].

Anal. Calcd for $C_{25}H_{28}O_4S$ (424.55): C, 70.73; H, 6.65. Found: C, 70.70; H, 6.68.

Ethyl Cholest-2-eno[3,2-*b*]thiophene-5′-carboxylate (3m)
White solid; yield: 444 mg (89%); mp 118–120 °C; R_f = 0.5 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 2932, 2868, 1709, 1467, 1280, 1249, 1181, 1067, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (s, 1 H), 4.31 (q, J = 7.1 Hz, 2 H), 1.34 (t, J = 7.1 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 6 H), 0.74 (s, 3 H), 0.67 (s, 3 H), 2.75–0.96 (m, 29 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 162.6, 142.5, 135.8, 134.5, 129.9, 60.7, 56.3, 56.2, 53.6, 42.4, 42.3, 39.9, 39.7, 39.5, 36.1, 35.7, 35.5 (2 C), 31.6, 28.8, 28.2, 28.0 (2 C), 24.2, 23.8, 22.8, 22.6, 21.0, 18.7, 14.3, 11.9, 11.5.

MS (ESI): m/z = 498.3 [M^+].

Anal. Calcd for $C_{32}H_{50}O_2S$ (498.80): C, 77.05; H, 10.10. Found: C, 77.01; H, 10.12.

Ethyl 4′-Aminocholest-2-eno[3,2-*b*]thiophene-5′-carboxylate (3n)
Light yellow solid; yield: 437 mg (85%); mp 83–85 °C; R_f = 0.45 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 3459, 2935, 2859, 1666, 1606, 1492, 1370, 1297, 1195, 1095, 1070, 768 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.34 (br s, 2 H), 4.25 (q, J = 7.1 Hz, 2 H), 2.56 (dd, J_1 = 4.6 Hz, J_2 = 17.6 Hz, 1 H), 2.33 (m, 3 H), 1.59 (s, 3 H), 1.32 (t, J = 7.1 Hz, 3 H), 0.96–2.08 (m, 22 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.5 Hz, 6 H), 0.76 (s, 3 H), 0.68 (s, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 164.9, 152.6, 141.6, 125.6, 97.9, 59.6, 56.3, 56.2, 53.6, 42.4, 42.2, 39.8, 39.5, 36.9, 36.1, 35.7, 35.5, 35.0, 31.5, 30.0, 28.6, 28.2, 27.9, 24.2, 23.6, 22.8, 22.5, 21.1, 18.6, 14.5, 11.9, 11.6.

MS (EI): m/z = 513.3 [M^+].

Anal. Calcd for $C_{32}H_{51}NO_2S$ (513.82): C, 74.80; H, 10.00; N, 2.73. Found: C, 74.82; H, 10.04; N, 2.70.

Ethyl 6-Oxocholesta-2,4-dieno[3,2-*b*]thiophene-5′-carboxylate (3o)
Yellow solid; yield: 357 mg (70%); mp 144–147 °C; R_f = 0.3 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2931, 2868, 1709, 1673, 1573, 1530, 1466, 1265, 1237, 1077, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 7.33 (s, 1 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 2.99 (d, *J* = 16.2 Hz, 1 H), 2.6–2.72 (m, 1 H), 1.75–2.18 (m, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 1.04–1.71 (m, 16 H), 1.25 (s, 3 H), 1.0 (s, 3 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 6 H), 0.72 (s, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 199.2, 162.1, 141.6, 138.6, 138.5, 134.4, 133.4, 124.4, 61.4, 56.5, 56.0, 49.6, 45.5, 42.4, 39.5, 39.3, 38.6, 37.8, 36.1, 35.7, 32.9, 29.7, 28.1, 24.1, 23.8, 22.9, 22.6, 21.3, 18.7, 18.4, 14.4, 11.9.

MS (LCMS): *m*/*z* = 511.6 [M^+ + 1].

Anal. Calcd for $C_{32}H_{46}O_3S$ (510.77): C, 75.25; H, 9.08. Found: C, 75.28; H, 9.03.

Diethyl Androsta-2,16-dieno[3,2-*b*:17,16-*b*′]bisthiophene-5′,5″-dicarboxylate (3p)

White solid; yield: 385 mg (75%); mp 144–147 °C; R_f = 0.5 (hexanes–EtOAc, 4:1).

IR ($CHCl_3$): 2918, 1336, 1705, 1466, 1406, 1282, 1245, 1174, 1071, 1026, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 7.44 (s, 1 H), 4.3 (m, 4 H), 2.57–2.77 (m, 3 H), 1.51–2.54 (m, 15 H), 1.34 (t, *J* = 6.4 Hz, 6 H), 1.01 (s, 3 H), 0.80 (s, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 169.3, 162.7, 162.1, 144.0, 142.3, 135.6, 134.4, 133.5, 130.1, 129.3, 61.6, 60.8, 53.6, 45.4, 42.4, 41.4, 39.4, 35.8, 35.3, 34.4, 31.2, 29.8, 28.9, 28.5, 20.8, 19.2, 14.3, 14.1, 11.5.

MS (ESI): *m*/*z* = 512.9 [M^+ + 1].

Anal. Calcd for $C_{29}H_{36}O_4S_2$ (512.72): C, 67.93, H, 7.08. Found: C, 67.90; H, 7.05.

Ethyl 4-Oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (3q)

Light brown powder; yield: 219 mg (80%); mp 147–149 °C; R_f = 0.3 (hexanes–EtOAc, 7:3).

IR (KBr): 3388, 1744, 1715, 1539, 1260, 1122, 741, 605 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 7.74 (dd, J_1 = 1.3 Hz, J_2 = 7.8 Hz, 1 H), 7.29–7.63 (m, 3 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 161.1, 156.5, 152.3, 151.8, 134.2, 132.3, 131.8, 125.3, 125.0, 123.8, 117.7, 116.4, 62.1, 14.3.

MS (EI): *m*/*z* = 274.3 [M^+].

Anal. Calcd for $C_{14}H_{10}O_4S$ (274.29): C, 61.30; H, 3.67. Found: C, 61.33; H, 3.64.

Ethyl 2-[(2-Formyl-3,4-dihydronaphthalen-1-yl)thio]acetate (4a)

Yellow oil; yield: 180 mg (65%, Table 1, entry 8); R_f = 0.75 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 2982, 1733, 1663, 1551, 1256, 1176, 1029, 769 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.65 (s, 1 H), 7.97 (m, 1 H), 7.17–7.41 (m, 3 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 3.38 (s, 2 H), 2.87 (t, *J* = 7.4 Hz, 2 H), 2.74 (t, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 192.3, 168.6, 147.4, 142.8, 139.4, 131.9, 130.7, 128.3, 127.1, 126.9, 61.6, 36.1, 27.1, 22.2, 14.1.

MS (ESI): *m*/*z* = 276 [M^+].

Anal. Calcd for $C_{15}H_{16}O_3S$ (276.35): C, 65.19; H, 5.84. Found: C, 65.17; H, 5.81.

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