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The study of Friedel–Crafts alkylation reaction of thiophenes with glyoxylate imine catalyzed by Fe(III): an easy access to α-aminoesters

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ABSTRACT

A Friedel–Crafts alkylation reaction of thiophenes with glyoxylate imine was developed to give α-aminoesters. In the presence of $FeCl_3 \cdot 6H_2O$ as the catalyst, various α-aminoesters were prepared with moderate to high yields (up to 95%) except for some special substrates.

1. Introduction

The well-known Friedel–Crafts alkylation reaction is one of the most fundamental and popular carbon–carbon bond-forming reaction in organic synthesis.[1] As one type of the Friedel–Crafts alkylation reaction, the addition of electron-rich aromatic compounds to imines can be a very facile synthetic method to produce nitrogen-containing compounds.[2] However, the reaction of aromatic compounds as nucleophiles with imines has been far less studied than ketones, aldehydes, and esters etc., which contain an active α hydrogen.[3] And thus, the Friedel–Crafts alkylation reaction of aromatic compounds with imines needs to be further investigated. Recently, there have been some reports about the Friedel–Crafts alkylation reaction of aromatic compounds with imines, and most of these studies employed the active aromatic compounds, such as indoles[2] or aromatic amines.[2a]

Sulfur-containing heterocycles have diverse applications in the areas of materials science,[4] agrochemicals,[5] and pharmaceuticals[6] due to their unique chemical and biological properties. These widely used drugs include the famous penicillin[6a,b] and cefalotin sodium[6c,d] as antibiotic, prasugrel[6e] and clopidogrel[6f] as antiplatelet drugs, raloxifene hydrochloride as a second generation drug for osteoporosis in postmenopausal women,[6g,h] aminopeptidase N (APN) as an efficient anticancer drug,[6i] eprosartan as antihypertensive drugs[6j,k] etc. These applications severely capture our interest on the sulfur-containing heterocycles. There have been several reports involving the reaction of thiophenes with imines, but they separately studied only one thiophene as a substrate, and no one of them specially focused on the Friedel–Crafts alkylation reaction of thiophenes.[7] In view of the great utility of sulfur-containing compounds and the inconspicuous achievement of the Friedel–Crafts alkylation reaction of thiophenes, the exploration of the Friedel–Crafts alkylation reaction about thiophenes is still highly desirable.

To the best knowledge of us, there has not been a special report on the Friedel–Crafts alkylation of thiophenes with imines. This may be due to the lower activity of thiophene ring than active aromatic compounds, such as indoles and aromatic amines. Herein, we would like to report our results on the Friedel–Crafts alkylation of thiophenes with imine. Expected products with good yields for the majority of the substrates were obtained.

2. Results and discussion

We initiated the study from the reaction of 2-ethylthiophene (**1a**) with imines prepared from aromatic aldehyde, such as benzaldehyde, *p*-nitrobenzaldehyde, *p*-methoxybenzaldhyde, 2,4-dichlorobenzaldehyde with anisidine, but after our best efforts, no target compound was obtained. To overcome this problem, we envisioned that since 2-ethylthiophene (**1a**) is not active enough, it is necessary to use imines that are much reactive than those aromatic imines. On the basis of this fact, we chose glyoxylate imine (**2**) as the

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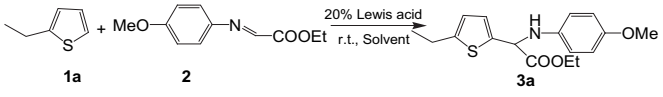
electrophile, which was prepared by the reaction of ethyl glyoxylate with anisidine under ultrasound, and obtained the target product. Therefore, the reaction of thiophenes with glyoxylate imine (**2**) can provide an easy access to α-aminoester, which can be a precursor for the amino acid. During this preliminary exploration, we found that the prepared glyoxylate imine (**2**) is so active that it is very easy to deteriorate. And thus, we stored it in toluene with the concentration of 1 mol/L at 0 °C.

At the beginning of the selected reaction system, we investigated the reaction of 2-ethylthiophene (**1a**) with the imine (**2**) by using the moderately acidic $SnCl_2$ as catalyst in CH_2Cl_2. To our delight, after the completion of the reaction for 48 h, we obtained the target compound, which was a α-aminoester (**3a**). Encouraged by this result, we examined the reaction of 2-ethylthiophene (**1a**) with imine (**2**) as the model reaction. Several Lewis acids and solvents were screened, and the results are summarized in Table 1. Of these Lewis acids used, $FeCl_3·6H_2O$ was revealed to be the most promising catalyst, 20 mol % of which afforded the desired Friedel–Crafts product in 56% yield in CH_2Cl_2 (entry 4). When we changed the Lewis acid to $SnCl_2$, $Mg(ClO_4)_2$, and CuBr, the yields were much lower even in a much longer reaction time (entries 1–3). The lower catalytic activity of $SnCl_2$, $Mg(ClO_4)_2$, and CuBr is attributed to their relatively weak Lewis acidity, which is essential for the Friedel–Crafts reaction. Then, we changed the Lewis acid to Ni salt with the similar nature of Fe salt, but unexpectedly, no target product (**3a**) was found in 48 h (entry 5). This may be attributed to that CH_3COO^- with a strong coordination effect prevents Ni(II) coordinating with the substrate, resulting in that Ni(II) did not participate in the reaction. Considering the influence of Lewis acidity, we used $BF_3·Et_2O$ and $AlCl_3$ with a stronger acidity, finding that the reactions quickly finished in 6 h (entries 6–7), but the yields were much lower and many by-products were detected by TLC. Subsequently, we added some 4 Å molecular sieves to the Fe (III)-catalyzed reaction, but the yield had a slightly decrease in the same reaction time (entry 8).

Table 1
Optimization of the Friedel–Crafts alkylation reaction of **1a** with **2**[a]



Entry	Solvent	Lewis acid	Time [h]	Yield[b] [%]
1	CH_2Cl_2	$SnCl_2$	48	16
2	CH_2Cl_2	$Mg(ClO_4)_2$	48	<10
3	CH_2Cl_2	CuBr	48	<10
4	CH_2Cl_2	$FeCl_3·6H_2O$	15	56
5	CH_2Cl_2	$(CH_3COO)_2Ni$	48	Trace
6	CH_2Cl_2	$BF_3·Et_2O$	6	31
7	CH_2Cl_2	$AlCl_3$	6	28
8	$CHCl_3$	$FeCl_3·6H_2O$	24	50
9[c]	CH_2Cl_2	$FeCl_3·6H_2O$	15	50
10	THF	$FeCl_3·6H_2O$	24	31
11	Toluene	$FeCl_3·6H_2O$	30	49
12	EtOH	$FeCl_3·6H_2O$	48	Trace
13[d]	Ionic liquid	$FeCl_3·6H_2O$	30	Trace
14	CH_3NO_2	$FeCl_3·6H_2O$	15	82
15[e]	CH_3NO_2	$FeCl_3·6H_2O$	24	50

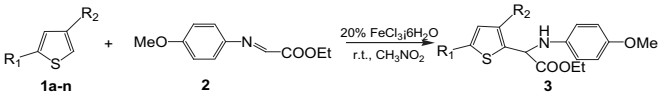
[a] All reactions were performed with Lewis acid (0.02 mmol), 2-ethylthiophene **1a** (0.2 mmol), and imine gloxylate **2** (0.1 mmol) in 0.5 mL of solvent at room temperature detected by TLC unless otherwise stated.
[b] Isolated yield **3a** after flash chromatography.
[c] 4 Å Molecular sieves (25 mg) were added.
[d] The ionic liquid was $[EtPy]^+Br^-$.
[e] The mol ratio of **1a** and **2** was 1:2.

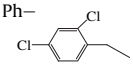
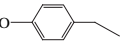
With $FeCl_3·6H_2O$ as the selected catalyst, we screened the effect of solvents to identify the best reaction conditions (Table 1, entries 4 and 10–14). Among the various organic solvents tested, CH_3NO_2 was much superior to other solvents (up to 82%). This is because CH_3NO_2 can improve the acidity of Lewis acid.[2a,8] When the reaction was carried out in THF and toluene, the yields were not so high as in CH_3NO_2 in much longer reaction times (entries 10, 11, and 14). Moreover, when the reaction was carried out in some more polar solvents, such as EtOH and ionic liquid, the target α-aminoester was not obtained (entries 12 and 13). Finally, we examined the mole ratio of 2-ethylthiophene (**1a**) to the glyoxylate imine (**2**). When the ratio was changed to be 1:2, the yield decreased to 50%.

With the established optimal reaction condition, we then studied the substrate scope of thiophenes, and the results are summarized in Table 2. With different properties of thiophenes (**1a**–**n**),[9] each thiophene performed different reactivity, leading to various results in the yield. On the whole, the majority of thiophenes reacted smoothly with the glyoxylate imine (**2**), producing the isolated corresponding α-aminoester. With an electron-donating group (MeO–), 2-methoxythiophene (**1c**) is too active, and the reaction finished very quickly, but we failed in isolating the target α-aminoester from numerous by-products (entry 3). On the contrary, 3-bromothiophene (**1n**) with an electron-withdrawing group (–Br) did not have enough nucleophilic ability, so the reaction of **1n** did not give the corresponding α-aminoester when the reaction time was even prolonged to 144 h (entry 14). Although thiophene (**1i**) without any substituent could react with amine (**2**) to give the corresponding α-aminoester (**3i**), the relatively low nucleophilic ability resulted in a yield less than 10%. In addition to the electric effect, the steric effect of substituent also plays a very important role for the yield. Reactions of thiophenes (**1e**–**h**, **m**) with bulky substituents only gave low to moderate yields even in a very prolonged reaction time, while reactions of thiophenes (**1a**,**b**, **d**, **j**–**l**) with small substituents could finish in a relatively short time, giving high yields. Additionally, we found that for 3-substituted thiophenes, their nucleophilic reaction with the imine (**2**) cannot proceed at 5-positions. The reason is that the charge density at 5-position is less than 2-position.

Enlightened by previous proposed mechanism about the reaction of indole with ethyl glyoxylate,[10] we envisioned the catalytic cycle of

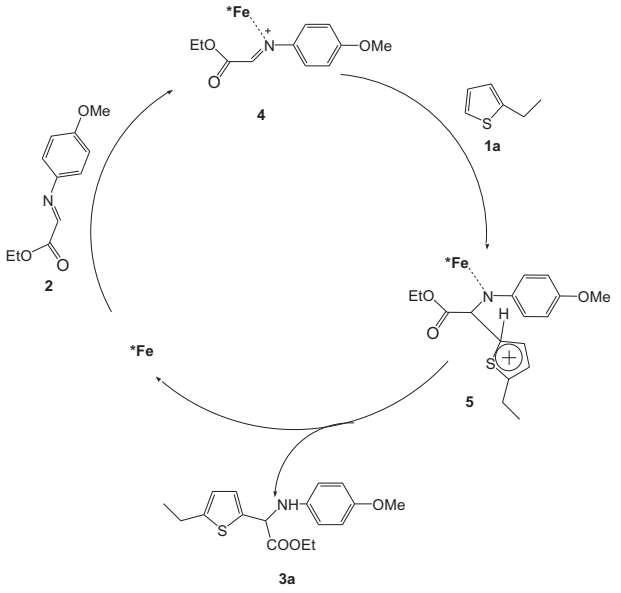
Table 2
Substrate scope of the Friedel–Crafts reaction of thiophenes **1a**–**n** with glyoxylate imine **2** catalyzed by Fe(III)[a]



Entry	R_1–	R_2–	Time [h]	Yield[b] [%]
1	Et–	H–	15	**3a**; 82
2	Me–	H–	20	**3b**; 95
3	MeO–	H–	5	**3c**; —
4	Ph–	H–	24	**3d**; 93
5		H–	48	**3e**; 20
6		H–	24	**3f**; 58
7		H–	24	**3g**; 56
8		H–	24	**3h**; <10
9	H–	H–	120	**3i**; <10
10	H–	MeO–	7	**3j**; 95
11	H–	EtO–	4	**3k**; 87
12	H–	Me–	24	**3l**; 75
13	H–	$C_{10}H_{21}$–	48	**3m**; 30
14	H–	Br–	144	**3n**; —

[a] All reactions were performed with $FeCl_3·6H_2O$ (0.02 mmol), thiophene **1** (0.2 mmol), and imine gloxylate **2** (0.1 mmol) in 0.5 mL of CH_3NO_2 at room temperature detected by TLC.
[b] Isolated yield **3** after flash chromatography.

the Friedel–Crafts reaction of 2-ethylthiophene (**1a**) with imine (**2**) catalyzed by Fe(III) as shown in Scheme 1. We found that the catalyst $FeCl_3 \cdot 6H_2O$ was very soluble in CH_3NO_2, so we labeled the catalyst as *Fe for short. At the first step, imine (**2**) combines with *Fe through the coordination effect to give an organic ion (**4**), strengthening the electrophilic abiltity of C=N, which is then more easily attacked by 2-ethylthiophene (**1a**) to produce a transition state (**5**). Consequently, *Fe leaves from the transition state to combine with imine (**2**) again, giving out the target α-aminoester (**3a**).



Scheme 1. Proposed catalytic cycle.

3. Summary

In summary, we developed here the Friedel–Crafts alkylation reaction of thiophenes with imine using $FeCl_3 \cdot 6H_2O$ as the catalyst in CH_3NO_2. For this investigation, we chose more active glyoxylate imine instead of aromatic amine to realize the Friedel–Crafts reaction of wide thiophenes with glyoxylate imine. The method was proved to be efficient for the majority of thiophenes to give target α-aminoesters, which are precursors for amino acids. Furthermore, some reactions allow the desired α-aminoesters to be isolated in good yield (up to 95%). Further investigations into an asymmetric version of the developed reaction are in progress.

4. Experimental

4.1. General information

All solvents before use were dried and degassed by standard methods. All reactions were monitored by TLC with silica gel-coated plates. IR spectra were recorded on an Excalibur 3100 (Varian) spectrophotometer using KBr optics. NMR spectra were recorded with a Bruker spectrometer at 400 MHz using TMS as an internal standard. Coupling constants (*J*) are reported in Hertz and refer to apparent peak multiplications. Mass spectra were recorded on a Bruker Microflex mass spectrometer. Thiophenes **1a**–**d**, **1i**–**n** are commercial available, and thiophenes **1e**–**h** were prepared according to literature.[9]

4.2. General procedure for synthesis of α-aminoesters

In a closed round-bottom flask with 0.5 mL of CH_3NO_2, $FeCl_3 \cdot 6H_2O$ (0.02 mmol, 0.2 equiv), thiophene **1** (0.2 mmol, 2 equiv), and imine gloxylate **2** (0.1 mmol) in toluene (1 mol/L) were added. The mixture was stirred at room temperature until the imine gloxylate disappeared (by TLC). After removal of CH_3NO_2 under vacuum, the mixture was filtrated through a short pad of basic aluminum oxide eluting with petroleum ether–ethyl acetate=5:1 to remove the catalyst. After the removal of petroleum ether and ethyl acetate under vacuum, the target product **3** was isolated by a flash column chromatography using basic aluminum oxide as adsorbent and petroleum ether–ethyl acetate=15:1 as eluant.

4.3. Analytical data for compounds 3a–n

*4.3.1. Ethyl (4-methoxyphenylamino)(5-ethylthiophen-2-yl)acetate (**3a**).* Following the general procedure to yield the title compound as a brown oil (82%); ^{1}H NMR (400 MHz, $CDCl_3$): 6.93 (d, *J*=3.5 Hz, 1H), 6.77 (d, *J*=8.9 Hz, 2H), 6.66–6.63 (m, 3H), 5.20 (s, 1H), 4.59 (s, 1H), 4.31–4.17 (m, 2H), 3.73 (s, 3H), 2.80 (q, *J*=7.5 Hz, 2H), 1.31–1.26 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): 171.4, 152.9, 147.7. 140.2, 138.3, 125.3, 123.2, 115.2, 114.9, 62.0, 58.1, 55.7, 23.6, 15.8, 14.2; IR (KBr, cm^{-1}): 3358, 3062, 2955, 2924, 2853, 1730, 1512, 1459, 1372, 1233, 1019, 807, 756; HRMS (EI): *m*/*z* calculated for $C_{17}H_{21}NO_3S$: 319.1242, found: 319.1218.

*4.3.2. Ethyl (4-methoxyphenylamino)(5-methylthiophen-2-yl)acetate (**3b**).* Following the general procedure to yield the title compound as a brown oil (95%); ^{1}H NMR (400 MHz, $CDCl_3$): 6.90 (d, *J*=3.4 Hz, 1H), 6.76 (d, *J*=8.9 Hz, 2H), 6.63–6.61 (m, 3H), 5.16 (s, 1H), 4.58 (s, 1H), 4.26–4.18 (m, 2H), 3.73 (s, 3H), 2.43 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 171.4, 153.0, 140.2, 140.1, 138.9, 125.6, 125.2, 115.3, 114.9, 62.1, 58.1, 55.8, 15.5, 14.2; IR (KBr, cm^{-1}): 3385, 3063, 2956, 2924, 2838, 1736, 1604, 1513, 1466, 1300, 1237, 1188, 1033, 817, 761.

*4.3.3. Ethyl (4-methoxyphenylamino)(5-phenylthiophen-2-yl)acetate (**3d**).* Following the general procedure to yield the title compound as a brown oil (93%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.56 (d, *J*=7.4 Hz, 2H), 7.35 (t, *J*=7.6 Hz, 2H), 7.28–7.25 (m, 1H), 7.18 (d, *J*=3.7 Hz, 1H), 7.10 (d, *J*=3.7 Hz, 1H), 6.77 (d, *J*=8.9 Hz, 2H), 6.66 (d, *J*=8.9 Hz, 2H), 5.24 (d, *J*=5.5 Hz, 1H), 4.68 (d, *J*=5.3 Hz, 1H), 4.33–4.20 (m, 2H), 3.73 (s, 3H), 1.29 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 171.1, 153.1, 144.4, 141.1, 140.1, 134.3, 129.0, 127.7, 126.6, 125.8, 123.0, 115.4, 115.0, 62.3, 58.3, 55.8, 14.2; IR (KBr, cm^{-1}): 3379, 3058, 3024, 2953, 2916, 2847, 1728, 1599, 1512, 1451, 1300, 1242, 1185, 1029, 818, 753, 694; HRMS (EI): *m*/*z* calculated for $C_{21}H_{21}NO_3S$: 367.1242, found: 367.1086.

*4.3.4. Ethyl (4-methoxyphenylamino)(5-(2,4-dichlorobenzyl)thiophen-2-yl)acetate (**3e**).* Following the general procedure to yield the title compound as a brown oil (20%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (d, *J*=1.9 Hz, 1H), 7.17 (d, *J*=2.0 Hz, 1H), 7.15 (s, 1H), 6.93 (d, *J*=3.4 Hz, 1H), 6.75 (d, *J*=8.9 Hz, 2H), 6.66 (d, *J*=3.5 Hz, 1H), 6.61 (d, *J*=8.9 Hz, 2H), 5.16 (s, 1H), 4.54 (s, 1H), 4.27–4.18 (m, 2H), 4.15 (s, 2H), 3.73 (s, 3H), 1.25 (t, *J*=7.1 Hz, 3H); IR (KBr, cm^{-1}): 3441, 3114, 2953, 2923, 2853, 1735, 1512, 1463, 1261, 1025, 740, 670, 649, 578.

*4.3.5. Ethyl (4-methoxyphenylamino)(5-benzylthiophen-2-yl)acetate (**3f**).* Following the general procedure to yield the title compound as a brown oil (58%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.32–7.28 (m, 2H), 7.24–7.22 (m, 3H), 6.92 (d, *J*=3.5 Hz, 1H), 6.75 (d, *J*=8.9 Hz, 2H), 6.63 (d, *J*=3.6 Hz, 1H), 6.61 (d, *J*=8.9 Hz, 2H), 5.16 (s, 1H), 4.54 (s, 1H), 4.27–4.17 (m, 2H), 4.08 (s, 2H), 3.73 (s, 3H), 1.25 (t, *J*=7.1 Hz, 3H); IR (KBr, cm^{-1}): 3361, 3061, 3029, 2955, 2923, 2853, 1730, 1511, 1459, 1293, 1235, 1179, 1018, 815, 693.

*4.3.6. Ethyl (4-methoxyphenylamino)(5-(4-methoxybenzyl)thiophen-2-yl)acetate (**3g**).* Following the general procedure to yield the

title compound as a brown oil (56%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (d, J=8.7 Hz, 2H), 6.91 (d, J=3.5 Hz, 1H), 6.84 (d, J=8.7 Hz, 2H), 6.75 (d, J=8.9 Hz, 2H), 6.62–6.59 (m, 3H), 5.15 (s, 1H), 4.51 (s, 1H), 4.28–4.15 (m, 2H), 4.01 (s, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 1.25 (t, J=7.1 Hz, 3H); IR (KBr, cm^{-1}): 3395, 3115, 2952, 2923, 2852, 1733, 1613, 1512, 1458, 1241, 1179, 1025, 816, 732.

*4.3.7. Ethyl (4-methoxyphenylamino)(5-(1-phenylpropyl)thiophen-2-yl)acetate (**3h**).* Following the general procedure to yield the title compound as a brown oil (<10%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.31–7.27 (m, 2H), 7.26–7.17 (m, 3H), 6.89 (d, J=3.4 Hz, 1H), 6.75 (d, J=8.9 Hz, 2H), 6.66–6.63 (m, 1H), 6.61 (d, J=8.9 Hz, 2H), 5.14 (d, J=5.3 Hz, 1H), 4.49 (d, J=6.9 Hz, 1H), 4.29–4.11 (m, 2H), 3.92 (t, J=7.7 Hz, 1H), 3.73 (s, 3H), 2.13–1.96 (m, 2H), 1.23 (t, J=7.1 Hz, 3H), 0.88 (t, J=7.3 Hz, 3H); IR (KBr, cm^{-1}): 3385, 3062, 3025, 2953, 2924, 2854, 1735, 1512, 1458, 1241, 1183, 910, 819, 734.

*4.3.8. Ethyl (4-methoxyphenylamino)(thiophen-2-yl)acetate (**3i**).* Following the general procedure to yield the title compound as a brown oil (<10%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.24 (dd, J=5.1, 1.1 Hz, 1H), 7.13 (d, J=3.5 Hz, 1H), 6.98 (dd, J=5.0, 3.6 Hz, 1H), 6.76 (d, J=8.9 Hz, 2H), 6.62 (d, J=8.9 Hz, 2H), 5.26 (s, 1H), 4.64 (s, 1H), 4.29–4.18 (m, 2H), 3.73 (s, 3H), 1.26 (t, J=7.1 Hz, 3H); IR (KBr, cm^{-1}): 3361, 3111, 3054, 2924, 2853, 1738, 1512, 1457, 1373, 1251, 1156, 852, 740, 703.

*4.3.9. Ethyl (4-methoxyphenylamino)(3-methoxythiophen-2-yl)acetate (**3j**).* Following the general procedure to yield the title compound as a brown oil (95%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.13 (d, J=5.5 Hz, 1H), 6.82 (d, J=5.5 Hz, 1H), 6.74 (d, J=8.9 Hz, 2H), 6.64 (d, J=8.9 Hz, 2H), 5.37 (s, 1H), 4.54 (s, 1H), 4.30–4.12 (m, 2H), 3.90 (s, 3H), 3.72 (s, 3H), 1.23 (t, J=7.1 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 171.7, 155.7, 153.0, 140.2, 123.7, 118.0, 116.5, 115.4, 114.9, 61.9, 59.2, 55.8, 54.2, 14.2; IR (KBr, cm^{-1}): 3388, 3106, 2925, 2851, 1729, 1552, 1512, 1460, 1382, 1236, 1190, 1025, 911, 818, 731; HRMS (EI): m/z calculated for $C_{16}H_{19}NO_4S$: 321.1035, found: 321.1013.

*4.3.10. Ethyl (4-methoxyphenylamino)(3-ethoxythiophen-2-yl)acetate (**3k**).* Following the general procedure to yield the title compound as a brown oil (87%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.11 (d, J=5.5 Hz, 1H), 6.78 (d, J=5.5 Hz, 1H), 6.74 (d, J=9.0 Hz, 2H), 6.65 (d, J=9.0 Hz, 2H), 5.38 (s, 1H), 4.55 (s, 1H), 4.28–4.14 (m, 2H), 4.12 (q, J=7.0 Hz, 2H), 3.72 (s, 3H), 1.41 (t, J=7.0 Hz, 3H), 1.23 (t, J=7.1 Hz, 3H); IR (KBr, cm^{-1}): 3383, 3116, 3052, 2980, 2921, 2849, 1728, 1550, 1513, 1451, 1379, 1233, 1188, 909, 817, 733.

*4.3.11. Ethyl (4-methoxyphenylamino)(3-methylthiophen-2-yl)acetate (**3l**).* Following the general procedure to yield the title compound as a brown oil (75%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (d, J=5.1 Hz, 1H), 6.82 (d, J=5.1 Hz, 1H), 6.74 (d, J=8.9 Hz, 2H), 6.56 (d, J=8.9 Hz, 2H), 5.22 (s, 1H), 4.67 (s, 1H), 4.30–4.12 (m, 2H), 3.72 (s, 3H), 2.36 (s, 3H), 1.24 (t, J=7.2 Hz, 3H); IR (KBr, cm^{-1}): 3386, 3104, 3060, 2953, 2923, 2850, 1728, 1612, 1511, 1450, 1371, 1233, 1177, 1018, 819, 708.

*4.3.12. Ethyl (4-methoxyphenylamino)(3-decylthiophen-2-yl)acetate (**3m**).* Following the general procedure to yield the title compound as a brown oil (30%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.15 (d, J=5.2 Hz, 1H), 6.86 (d, J=5.2 Hz, 1H), 6.74 (d, J=8.8 Hz, 2H), 6.57 (d, J=8.9 Hz, 2H), 5.25 (s, 1H), 4.58 (s, 1H), 4.29–4.17 (m, 2H), 3.72 (s, 3H), 2.78–2.63 (m, 2H), 1.69–1.59 (m, 2H), 1.30–1.20 (m, 17H), 0.88 (t, J=6.8 Hz, 3H); IR (KBr, cm^{-1}): 3410, 3108, 3057, 2924, 2855, 1735, 1620, 1513, 1461, 1287, 1240, 1187, 1031, 816, 731.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.039. These data include MOL files and InChIKeys of the most important compounds described in this article.

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