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β-Nitroacrylates as Starting Materials of Thiophene-2-carboxylates Under Continuous Flow Conditions

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Abstract. We report herein a general and efficient continuous flow-based protocol for synthesizing thiophene-2-carboxylates starting from ketal-functionalized β-nitroacrilates. The protocol involves (i) a promoter-free conjugate addition of thioacetic acid to β-nitroacrilates, (ii) a base-induced elimination of nitrous acid, and (iii) a final acid-promoted domino cyclization-aromatization process to afford the title targets. Thanks to the means of the flow chemistry and the use of solid supported systems, the three steps were combined in a whole flow chemical process, by which the products were isolated in good to excellent overall yields (38-88%).

Keywords: β-Nitroacrilates; Thiophenes; Flow chemistry; Heterocycles; Solid supported systems

Introduction

β-Nitroacrilates are a versatile class of electron-poor alkenes bonding an ester and a nitro group on α- and β- position, respectively (Figure 1).

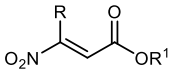
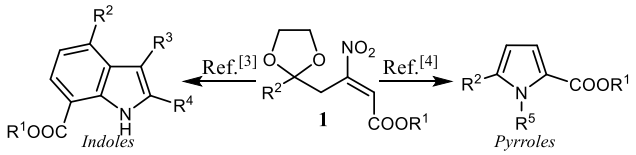


Figure 1. Generic structure of β-nitroacrylates.

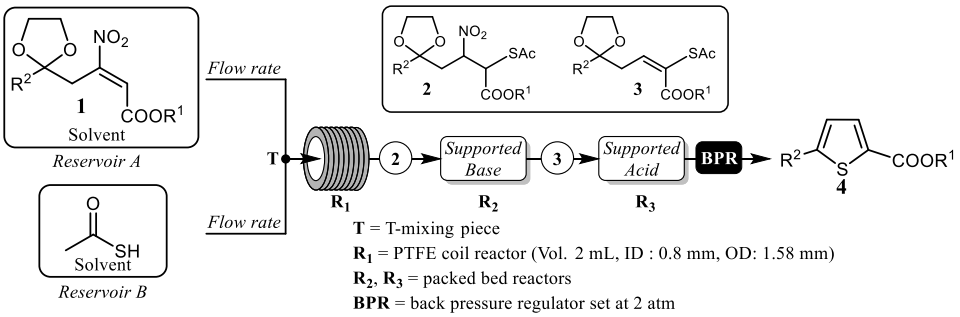
The simultaneous presence of both functionalities makes these compounds useful reactive electrophilic species and valuable building blocks of a variety of highly functionalized materials.[1] In this context, we recently discovered that ketal-functionalized β-nitroacrylates type **1** are key precursors of important heterocyclic systems, such as functionalized indoles[2] and pyrroles[3] (Scheme 1).



Scheme 1. Use of ketal-functionalized β-nitroacrilates type **1** as precursors of cyclic systems.

Following these studies, we were attracted by an important scaffold such as thiophene-2-carboxylates **4** (Scheme 2), molecular structures widely investigated for their own biological activities,[4] used as key intermediates of biologically active targets,[5] and explored for the preparation of liquid crystals.[6] Thus, as development of our research, we have now found a new profitable flow synthesis of **4** starting from β-nitroacrylates type **1**. Our protocol is based on three different steps: (i) reaction of **1** with AcSH to afford the Michael adduct **2**, (ii) elimination of nitrous acid to provide **3**, and (iii) simultaneous cleavage of the dioxolane ring and thioactetate ester to furnish, *via* an intramolecular cyclization, the 2,5-disubstituted thiophenes **4**. By the means of the flow chemistry and solid supported reagents peculiarities,[7] these transformations were joined in a single flow process to continuously produce the target thiophenes avoiding any intermediates isolation and purification, thus minimizing material and energy consumptions with evident advantages from the sustainable point of view (Scheme 2).

Moreover, this protocol offers the opportunity to overcome several important drawbacks present in published methodologies, such as low yields, limited substrates scope, harsh reaction conditions, and the use of expensive catalysts.[8]



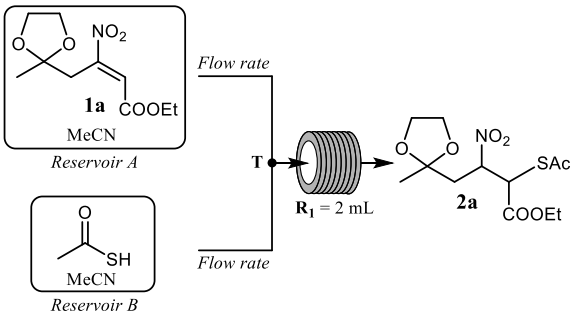
Scheme 2. Experimental setup for the flow chemical process.

Results and Discussion

With the purpose to find the best flow process conditions, we started to investigate the first step, then, based on the obtained results, we applied the optimized parameters to set in series the second and the third steps. In this context, we firstly studied the Michael addition between thioacetic acid and the β-nitroacrylate **1a** (reference substrate).

A series of preliminarily batch studies highlighted the formation of several by-products due to the instability of **1a** and **2a** under protracted acidic conditions. In fact, even testing a large variety of reaction conditions, the best trial (0.2M in MeCN, 1.1 eq. AcSH, 1h) provided **2a** only in poor yield (17%).

In order to minimize the contact between **1a** and **2a** with an excess of AcSH, and to minimize the by-products formation, we implemented the flow equipment shown in the Scheme 3. It consists of two different reservoirs, respectively containing a solution of **1a** (Reservoir A) and a solution of AcSH (Reservoir B), a T-mixing piece (**T**) and a PTFE coil reactor ($\mathbf{R_1}$). Repeating the reaction under flow conditions, **2a** was isolated in 49% of yield (Table 1, *entry a*) that, after a screening in terms of stoichiometry, concentration and residence time, was improved up to 69% of yield (Table 1, *entry i*).



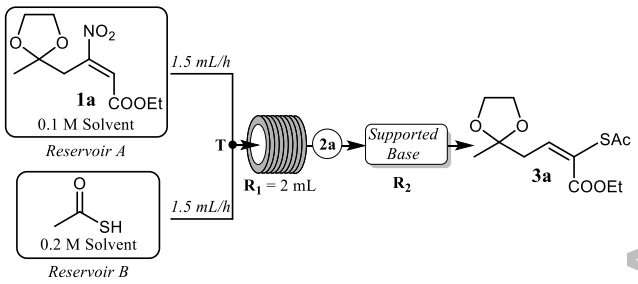
Scheme 3. Flow chemical Michael addition process.

Table 1. Optimization studies concerning the Michael addition of AcSH to **2a**.

Entry	**1a** (M)	AcSH (M)	Flow rate (mL/h/pump)	Yield (%)[1] of **2a**
a	0.4	0.44	0.5	49
b	0.2	0.22	0.5	53
c	0.1	0.11	0.5	58
d	0.05	0.055	0.5	57
e	0.1	0.11	1	56
f	0.1	0.11	1.5	59
g	0.1	0.11	2	53
h	0.1	0.15	1.5	62
i	0.1	0.2	1.5	69
k	0.1	0.25	1.5	63

[1] Yield of pure isolated product, reaction performed in MeCN.

Nevertheless, the adduct **2a** partially decomposes under column chromatography conditions. With the aim to prevent this problem and maximize the yield, we considered the possibility to execute the nitrous acid elimination step in series. Hence, we connected the coil reactor $\mathbf{R_1}$ to the reactor $\mathbf{R_2}$ packed with a solid supported base (Scheme 4).



Scheme 4. Consecutive flow chemical Michael addition and nitrous acid elimination processes.

By this equipment, we screened different bases and solvents, obtaining the best yields conducing the reactions in acetonitrile (97%) or toluene (91%) and using 2 equivalents of carbonate on polymer support (Table 2, *entries g* and *i*).

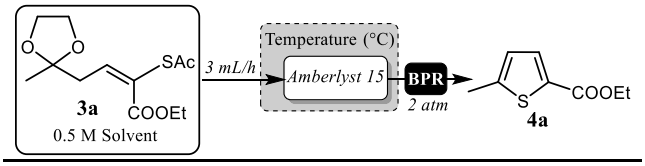
Table 2. Optimization studies about the Michael addition and nitrous acid elimination processes.

Entry	Supported base (eq.)	Solvent	Yield (%)[1] of **3a**
a	PS-TBD (1)	MeCN	41
b	PS-BEMP (1)	MeCN	52
c	PS-F (1)	MeCN	33
d	PS-DMAP (1)	MeCN	28
e	PS-Carbonate (1)	MeCN	62
f	PS-Carbonate (1.5)	MeCN	78
g	PS-Carbonate (2)	MeCN	97
h	PS-Carbonate (2)	EtOAc	75
i	PS-Carbonate (2)	Toluene	91
j	PS-Carbonate (2)	2-MeTHF	61

[1] Yield of pure isolated product.

Successively, we faced off the optimization of the third step studying the conversion of **3a** into the target **4a**. In this context, based on our experience on dioxolane ring cleavage,[3,4,9] we selected Amberlyst 15 as supported acidic species and we ran exploratory tests to set the appropriate reaction parameters such as temperature, solvents and Amberlyst 15 amount. After a series of trials, the best yield (93%) was obtained in toluene, at 100°C and using 3g/mmol of Amberlyst 15 (Table 3, *entry f*). The comparison of the results (Table 2 and Table 3) identifies toluene as the best solvent for the entire process.

Table 3. Optimization studies about the third step: conversion of **3a** into **4a** third steps.

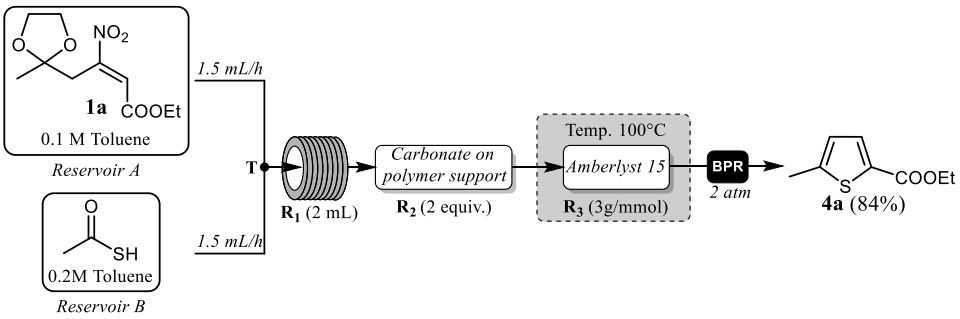


Entry	Amb. 15 (g/mmol)	Temp. (°C)	Solvent	Yield (%)[1] of **4a**
a	1	80	MeCN	26
b	1	100	MeCN	35
c	1	110	MeCN	30
d	1	100	Toluene	58
e	2	100	Toluene	77
f	3	100	Toluene	93
g	3	100	2-MeTHF	51
h	3	100	EtOAc	68

[1] Yield of pure isolated product.

Finally, in the interest of running the entire process in the one continuous flow, we set in all steps together testing the direct conversion of **1a** into **4a**. As reported in the Scheme 5 the compound **4a** was isolated in excellent overall yield (84%).

Then, we verified the generality of our approach submitting a wide range of ketal-functionalized β-nitroacrylates type **1** to the optimized reaction conditions. In all cases, thiophene-2-carboxylates **4a-k** were isolated in good to excellent overall yields (38-88%) (Figure 2).



Scheme 5. Test of the entire process under flow continuous conditions: conversion of **1a** into **4a**.

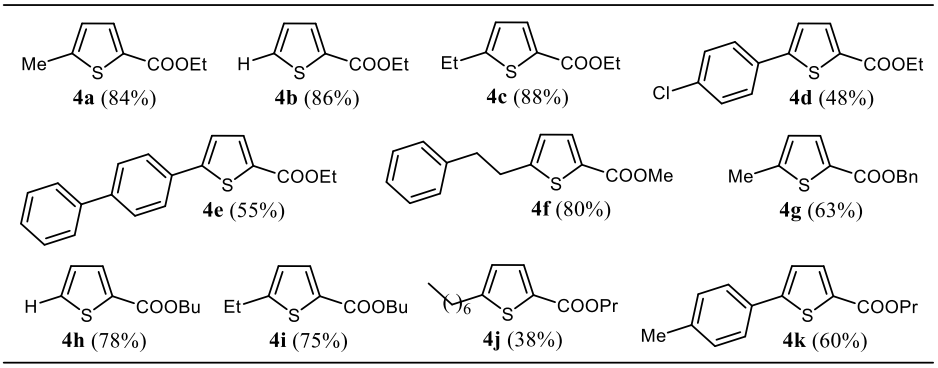


Figure 2. Synthesis of thiophene-2-carboxylates **4a-k**.

Conclusion

In conclusion, we developed a new fruitfully and general protocol for synthesizing thiophene-2-carboxylates under flow chemical conditions. Indeed, our method allows to prepare the title compounds in good to excellent overall yields, with the possibility to introduce a variety of aliphatic and aromatic substituents at the 5-position, and different esters at the 1-position. Moreover, by the means of the flow chemistry combined with the use of solid supported reagents, it was possible to avoid the isolation of any intermediates, therefore minimizing the material and energy consumptions with evident benefits from a sustainable point of view. Finally, this procedure represents a further evidence of the strategic utility of ketal-functionalized β-nitroacrylates as key and versatile precursors of heterocyclic systems.

Abbreviations

The following abbreviations are used in this manuscript:

PS-Carbonate: Carbonate on polymer support (Sigma-Aldrich code: 21850, loading: 3.5 mmol/g)
PS-DMAP: 4-(Dimethylamino)pyridine, polymer-bound (Sigma-Aldrich code: 39410, loading: 3 mmol/g)
PS-BEMP: 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, polymer-bound (Sigma-Aldrich code: 20026, loading: 2.2 mmol/g)
PS-TBD: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (Sigma-Aldrich code: 01961, loading: 3.0 mmol/g)
PS-F: Fluoride on polymer support (Sigma-Aldrich code: 47060, loading: 3.0 mmol/g)

Experimental Section

General Remarks

^{1}HNMR analyses were recorded at 400 MHz on a VarianMercury Plus 400. ^{13}CNMR analyses were recorded at 100 MHz. IR spectra were recorded with a PerkinElmer FTIR spectrometer Spectrum Two UATR. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. GS-MS analyses were obtained on a Hewlett-Packard GC/MS 6890N that works with the EI technique (70 eV). PS-Carbonate, PS-DMAP, PS-BEMP, PS-TBD and PS-F were purchased from Sigma–Aldrich and used directly without any manipulation. Amberlyst 15 was purchased from Sigma–Aldrich and purified by soaking in methanol for 24 hours, then washing with fresh methanol and THF and dried under vacuum.

General Flow Procedure for the Synthesis of Compounds 4a-k.

According to the flow equipment reported in the Scheme 5 and in the supporting information (Figure S1), 10mL of a 0.1M solution of the β-nitroacrylate **1** in toluene (Reservoir A) and 10 mL of a 0.2M thioacetic acid solution in toluene (Reservoir B) were simultaneously pumped (Syringe pumps model NE-300) with a flow rate of 1.5 mL/h/pump into the T-connector before passing through a 2 mL coil reactor (**R$_1$**), then in a packed bed reactor (**R$_2$**) containing 2 equivalents of PS-Carbonate (0.571 g, residence time ~11 min), and finally, in a further packed bed reactor (**R$_3$**) filled with Amberlyst 15 (3 g, residence time ~60 min) and heated at 100°C. The entire process is pressurized by a back pressure regulator set at 2 atm and the outflow was collected into a round bottom flask. Terminate the reaction, the solution was concentrated at reduced pressure and the crude product purified by flash column chromatography (Further chromatography techniques, such as the centrifugal partition chromatography, can potentially be associated to the flow process for directly purifying products).[10]

Ethyl 5-methylthiophene-2-carboxylate 4a. Pale yellow oil. IR (cm^{-1}, neat): 749, 815, 1089, 1256, 1464, 1540, 1708. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.35 (t, 3H, *J* = 7.3 Hz), 2.51 (s, 3H), 4.31 (q, 2H, *J* = 7.3 Hz), 6.73-6.76 (m, 1H), 7.59 (d, 1H, *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.6, 16.0, 61.1, 126.5, 131.6, 133.9, 148.0, 162.5. GC-MS (70 eV): m/z: 170 ([M$^+$], 29), 142 (19), 125 (100), 97 (16), 53 (15). Anal. Calcd. for $C_8H_{10}O_2S$ (170.23): C, 56.45; H, 5.92; S, 18.83. Found: C, 56.41; H, 5.89; S, 18.87.

Ethyl thiophene-2-carboxylate 4b. Pale yellow oil. IR (cm^{-1}, neat): 718, 750, 1091, 1258, 1420, 1526, 1703. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.37 (t, 3H, *J* = 6.8 Hz), 4.35 (q, 2H, *J* = 6.8 Hz), 7.08-7.11 (m, 1H), 7.53-7.55 (m, 1H), 7.79-7.81 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.6 61.4, 127.9, 132.4, 133.5, 134.3, 162.5. GC-MS (70 eV): m/z: 156 ([M$^+$], 19), 128 (25), 111 (100), 83 (7), 57 (5), 39 (15). Anal. Calcd. for $C_7H_8O_2S$ (156.20): C, 53.83; H, 5.16; S, 20.53. Found: C, 53.88; H, 5.19; S, 20.56.

Ethyl 5-ethylthiophene-2-carboxylate 4c. Pale yellow oil. IR (cm^{-1}, neat): 749, 1088, 1246, 1278, 1454, 1464, 1705. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.31 (t, 3H, *J* = 7.3 Hz) 1.35 (t, 3H, *J* = 6.8 Hz), 2.86 (q, 2H, *J* = 7.3 Hz), 4.31 (q, 2H, *J* = 7.3 Hz), 6.76-6.79 (m, 1H), 7.61 (d, 1H, *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.6, 15.9, 24.1, 61.1, 124.7, 131.2, 133.7, 155.6, 162.6. GC-MS (70 eV): m/z: 184 ([M$^+$], 47), 169 (37), 156 (12), 141 (48), 139 (100), 111 (12), 97 (10), 77 (9). Anal. Calcd. for $C_9H_{12}O_2S$ (184.25): C, 58.67; H, 6.56; S, 17.40. Found: C, 58.63; H, 6.52; S, 17.36.

Ethyl 5-(4-chlorophenyl)thiophene-2-carboxylate 4d. White solid, mp: 75-77. IR (cm^{-1}, neat): 749, 812, 1091, 1290, 1448, 1682. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.39 (t, 3H, *J* = 6.8 Hz), 4.36 (q, 2H, *J* = 6.8 Hz), 7.25 (d, 1H, *J* = 3.8 Hz), 7.37 (d, 2H, *J* = 8.5 Hz), 7.55 (d, 2H, *J* = 8.5 Hz), 7.74 (d, 1H, *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.6, 61.5, 124.1, 127.6, 129.5, 132.2, 133.2, 134.5, 134.8, 149.8, 162.4. GC-MS (70 eV): m/z: 266 ([M$^+$], 81), 237 (48), 220 (100), 193 (22), 149 (51), 114 (10), 79 (8). Anal. Calcd. for $C_{13}H_{11}ClO_2S$ (266.74): C, 58.54; H, 4.16; S, 12.02. Found: C, 58.58; H, 4.12; S, 11.99.

Ethyl 5-([1,1'-biphenyl]-4-yl)thiophene-2-carboxylate 4e. White solid, mp: 136-138°C. IR (cm^{-1}, neat): 650, 727, 904, 1098, 1268, 1702. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.40 (t, 3H, *J* = 7.3 Hz), 4.38 (q, 2H, *J* = 7.3 Hz), 7.33 (d, 1H, *J* = 3.8 Hz), 7.35- 7.40 (m, 1H), 7.43-7.49 (m, 2H), 7.60-7.66 (m, 4H), 7.70-7.74 (m, 2H), 7.78 (d, 1H, *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.6, 61.4, 123.8, 126.8, 127.2, 127.9, 128.0, 129.1, 132.6, 132.7, 134.5, 140.4, 141.8, 150.9, 162.5. GC-MS (70 eV): m/z: 308 ([M$^+$], 100), 280 (46), 263 (47), 236 (17), 191 (48), 131 (13), 95 (12).

Anal. Calcd. for $C_{19}H_{16}O_2S$ (308.39): C, 74.00; H, 5.23; S, 10.40. Found: C, 74.04; H, 5.20; S, 10.37.

Methyl 5-phenethylthiophene-2-carboxylate 4f. White solid, mp: 50-52°C. IR (cm^{-1}, neat): 740, 824, 1091, 1254, 1461, 1703, 3009, 3033. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 2.97-3.03 (m, 2H), 3.12-3.18 (m, 2H), 3.86 (s, 3H), 6.75 (d, 1H, *J* = 3.8 Hz), 7.15-7.33 (m, 5H), 7.62 (d, 1H, *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 32.5, 37.8, 52.2, 125.8, 126.6, 128.6, 128.7, 131.1, 133.9, 140.6, 152.7, 163.0. GC-MS (70 eV): m/z: 246 ([M^+], 31), 155 (100), 126 (10), 91 (47), 65 (48). Anal. Calcd. for $C_{14}H_{14}O_2S$ (246.32): C, 68.27; H, 5.73; S, 13.02. Found: C, 68.32; H, 5.77; S, 12.98.

Benzyl 5-methylthiophene-2-carboxylate 4g. Pale yellow oil. IR (cm^{-1}, neat): 744, 814, 1035, 1076, 1268, 1371, 1451, 1691. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 2.52 (s, 3H), 5.32 (s, 2H), 6.76 (d, 1H, *J* = 3.8 Hz), 7.30-7.46 (m, 5H), 7.65 (d, 1H, *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 16.0, 66.7, 126.6, 128.3, 128.4, 128.8, 131.1, 134.4, 136.2, 148.5, 162.3. GC-MS (70 eV): m/z: 232 ([M^+], 45), 187 (11), 125 (100), 91 (48). Anal. Calcd. for $C_{13}H_{12}O_2S$ (232.30): C, 67.22; H, 5.21; S, 13.80. Found: C, 67.17; H, 5.18; S, 13.76.

Butyl thiophene-2-carboxylate 4h. Pale yellow oil. IR (cm^{-1}, neat): 750, 1092, 1257, 1419, 1526, 1705. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.97 (t, 3H, *J* = 7.3 Hz), 1.40-1.41 (m, 2H), 1.65-1.77 (m, 2H), 4.30 (t, 2H, *J* = 6.8 Hz), 7.08-7.11 (m, 1H), 7.53-7.55 (m, 1H), 7.78-7.80 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.0, 19.4, 31.0, 65.2, 127.9, 132.4, 133.5, 134.3, 162.6. GC-MS (70 eV): m/z: 184 ([M^+], 9), 128 (60), 111 (100), 83 (8), 56 (8), 39 (19). Anal. Calcd. for $C_9H_{12}O_2S$ (184.25): C, 58.67; H, 6.56; S, 17.40. Found: C, 58.62; H, 6.60; S, 17.37.

Butyl 5-ethylthiophene-2-carboxylate 4i. Pale yellow oil. IR (cm^{-1}, neat): 750, 1089, 1253, 1278, 1449, 1526, 1705. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.96 (t, 3H, *J* = 7.3 Hz), 1.32 (t, 3H, *J* = 7.3 Hz), 1.39-1.50 (m, 2H), 1.67-1.75 (m, 2H), 2.86 (q, 2H, J = 7.3 Hz), 4.26 (t, 2H, *J* = 6.8 Hz), 6.77-6.79 (m, 1H), 7.63 (d, 1H , *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.0, 15.9, 19.4, 24.1, 31.0, 65.0, 124.7, 131.2, 133.7, 155.6, 162.7. GC-MS (70 eV): m/z: 212 ([M^+], 20), 156 (78), 141 (100), 139 (90), 124 (7), 111 (14). Anal. Calcd. for $C_{11}H_{16}O_2S$ (212.31): C, 62.23; H, 7.60; S, 15.10. Found: C, 62.27; H, 7.57; S, 15.13.

Propyl 5-heptylthiophene-2-carboxylate 4j. Pale yellow oil. IR (cm^{-1}, neat): 733, 748, 1086, 1258, 1281, 1461, 1708. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.88 (t, 3H, *J* = 7.3 Hz), 1.00 (t, 3H, *J* = 7.3 Hz), 1.21-1.41 (m, 8H), 1.62-1.81 (m, 4H), 2.82 (t, 2H, *J* = 7.7 Hz), 4.22 (t, 2H, *J* = 6.8 Hz), 6.77 (d, 1H, *J* = 3.8 Hz), 7.62 (d, 1H, *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 10.7, 14.3, 22.4, 22.9, 29.2, 30.7, 31.7, 32.0, 66.7, 125.3, 131.2, 133.7, 154.2, 162.7. GC-MS (70 eV): m/z: 268 ([M^+], 45), 209 (64), 183 (96), 141 (100), 97 (51), 43 (25). Anal. Calcd. for $C_{15}H_{24}O_2S$ (268.41): C, 67.12; H, 9.01; S, 11.94. Found: C, 67.17; H, 9.05; S, 11.91.

Propyl 5-(p-tolyl)thiophene-2-carboxylate 4k. White solid, mp: 54-56°C. IR (cm^{-1}, neat): 747, 806, 1086, 1234, 1263, 1344, 1447, 1539, 1701. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.03 (t, 3H, *J* = 7.3 Hz), 1.72-1.85 (m, 2H), 2.38 (s, 3H), 4.26 (t, 2H, *J* = 6.8 Hz) 7.21 (d, 2H, 8.1 Hz), 7.25 (d, 1H, J = 3.8 Hz), 7.53 (d, 2H, J = 8.1 Hz), 7.74 (d, 1H, *J* = 3.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 10.7, 21.5, 22.4, 66.9, 123.3, 126.3, 130.0, 131.0, 132.2, 134.4, 139.1, 151.6, 162.6. GC-MS (70 eV): m/z: 260 ([M^+], 71), 218 (100), 201 (67), 173 (18), 129 (40). Anal. Calcd. for $C_{15}H_{16}O_2S$ (260.35): C, 69.20; H, 6.19; S, 12.31. Found: C, 69.25; H, 6.22; S, 12.34.

Acknowledgements

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FULL PAPER

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