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Development and Application of Pyridinium 1,4-Zwitterionic Thiolates: Synthesis of Polysubstituted Thiophenes

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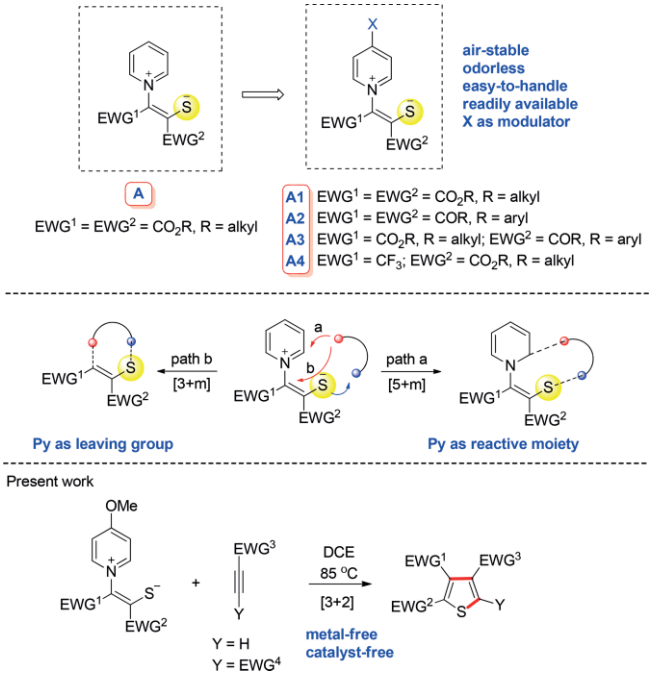
Abstract: Pyridinium 1,4-zwitterionic thiolates as a class of sulfur-containing synthons were applied to a [3+2] cascade cyclization reaction with activated alkynes, affording a library of polysubstituted thiophenes with excellent regioselectivities, especially those bearing various fluorine-containing groups. The freshly disclosed pyridinium 1,4-zwitterionic thiolates decorated with acyl or trifluoromethyl groups exhibited powerful potential in the synthesis of polysubstituted thiophenes. Of particular note is that pyridinium **A4** could introduce sulfur and CF_3 groups to target products simultaneously.

Introduction

Organosulfur compounds occupy a significant place in organic chemistry because they serve diverse functions in many aspects of human life in an array of existing forms.[1] Among them, thiophenes, one class of sulfur-containing five-membered heterocycles, widely spread in pharmaceuticals, bioactive molecules,[2] and functional materials.[3] Furthermore, they are often used as vital organic synthetic intermediates in organic chemistry and material chemistry.[4] Thus, a great number of methods have been harnessed to construct this unique heterocycle.[5] However, there are limited approaches to the synthesis of polysubstituted thiophenes and many of them involve metal catalysts, malodorous starting materials, and/or harsh reaction conditions. In addition, metal pollution in the products is always a conundrum, especially for pharmaceutical and material chemistry. Moreover, incorporating multifarious fluorine-containing groups (e.g., SCF_3, CF_3) into thiophenes with the same protocol is scare and fascinating.[6,10,11] Thus, the development of versatile and general to access polysubstituted, thiophenes and fluorine-containing ones in particular under metal-free and catalyst-free conditions is highly desired.

Recently, we carried out a program to comprehensively explore and understand the properties and reactivities of one kind of novel pyridinium 1,4-zwitterionic thiolates **A** (Scheme 1), which could be readily prepared from a three-component reaction of dialkyl acetylene dicarboxylates, elemental sulfur, and pyridine.[7] The solid organosulfur compounds are air-stable, odorless, easy- to- handle, and readily available. Alizadeh had proposed these thiolates were the key intermediates in the synthesis of tetraalkyl 2,3,4,5-thiophenetetracarboxylate,[12] but this kind of pyridinium 1,4-zwitterionic thiolates have not yet been recognized as useful and versatile synthons ever since their emergence, to the best of our knowledge. In this context, intrigued by their unique structures, we envisaged that the reactive intermediates could be used to prepare sulfur-containing



Scheme 1. Reaction modes of pyridinium 1,4-zwitterionic thiolates and this work.

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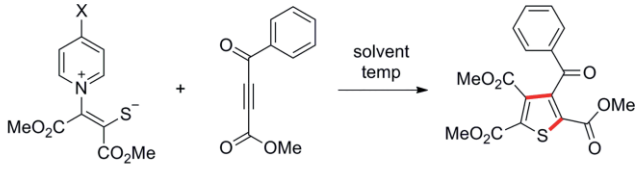
heterocycles via two reaction modes: [5+m, path a], with pyridine as a reactive moiety, and [3+m, path b], with pyridine as a leaving group (Scheme 1). Preliminary results indicated that this kind of pyridinium 1,4-zwitterionic thiolates as three-atom components could react with 1,2-diaza-1,3-dienes derived from α-halo hydrazones in situ to afford 2,5-dihydro-1,4,5-thiadiazepines via path b in a cascade fashion.[8] To exploit more interesting reaction modes of these thiolates and develop new analogs of **A**, we successfully prepared pyridinium 1,4-zwitterionic thiolates **A1**-**A4** decorated with alkoxyl carbonyl, acyl or trifluoromethyl groups and applied them to a [3+2] cascade cyclization reaction with activated alkynes, delivering a library of polysubstituted, especially various fluorine-containing thiophenes (Scheme 1). Meanwhile, we found that the X group at the 4-position of pyridine could be used as a modulator to tune the reaction speed.

Results and Discussion

We began our study using **1a** and **2a** as the model substrates to acquire the optimal reaction conditions. When **1a** and **2a** were simply mixed and stirred in DCM in air at room temperature and without any additives, a spontaneous cascade cyclization reaction occurred, but it proceeded very sluggishly. Subsequently, when the reaction temperature was elevated to 45 °C, tetrasubstituted thiophene **3** was obtained in 76 % yield with excellent regioselectivity after two days (Table 1, entry 1). The regioselectivity was established by analogy with **27** (vide infra).[9] When the solvent was switched to DCE and accordingly the temperature was elevated to 85 °C, the reaction was accelerated remarkably, offering a maintained yield (entry 2). Next, we studied the reaction behaviors of pyridiniums with distinct X groups at the 4-position of pyridine moiety (entries 3–5). Pyridinium **1b** bearing a *N*,*N*-dimethylamino group offered **3** in only a low yield of 29 %, while pyridinium **1c** containing a methyl group gave a moderate yield of 60 %. To our delight, pyridinium **1d** bearing a methoxyl group exhibited the best reactivity and furnished the highest yield of 81 % within only 1 h. Then, we adjusted the ratio of reactants, but no better results were obtained. In addition, we also examined a series of common solvents including ethyl acetate, acetone, toluene, and so on (entries 8–14). All of them could support the reaction, but only moderate yields were delivered. Water as a green solvent could not be compatible with this cyclization reaction and only a trace amount of **3** was detected, probably owing to the very poor solubility of **1d** in water. Thus, the optimal reaction conditions (**1d**:**2a** = 1.5:1, DCE, 85 °C, entry 5) were determined.

With the optimal reaction conditions in hand, we turned our attention to examining the generality and scope of this cascade cyclization reaction (Scheme 2). For pyridinium 1,4-zwitterionic thiolates **1d** and **1e**, an array of asymmetric internal alkynes were first investigated. For methyl 4-oxo-4-phenylbut-2-ynoate, substituents on the phenyl group had little influence on the efficiency of the cyclization reaction (**3**–**8**) as strong electron-donating and electron-withdrawing groups induced slightly lower yields (**7** and **8**). Heteroaryl-substituted (e.g., 2-thienyl and 2-furyl) alkynes were also well-tolerated, providing the corresponding thiophenes (**9** and **10**) in good yields. Steric hindrance impacted on the cyclization efficiency. For example, *tert*-butyl ester substrate delivered thiophene **11** in only 73 % yield. *N*-methyl-4-oxo-*N*,4-diphenylbut-2-ynamide was also compatible with this cascade cyclization reaction, affording **12** and **13** in 88 % and 95 % yields, respectively. Pyridiniums decorated with ethyl esters performed better than those with methyl esters (e.g., **3** vs. **4** and **12** vs. **13**). The diethoxyacetal substrate reacted as well and furnished **14** in a yield of 80 %. For 1,4-diketone alkynes, the diaryl ketone gave a better performance than dialkyl ketone (**15** vs. **16**). As for 1,3-diyne substrate, the cyclization product **17** was gained in a moderate yield of 59 %, wherein only one alkynyl group got involved in the cyclization reaction while another one remained intact. These results indicated that the EWG[4] of the reaction partner **2** should be a suitable functional group, while thienyl group was not the right choice. Then, 1,4-diester alkynes were examined, only moderate yields of thiophenes (**18** and **19**) were obtained. To further develop the chemistry of pyridinium 1,4-zwitterionic thiolates, we successfully prepared two new pyridinium 1,4-zwitterionic thiolates (**1f** and **1g**), which had not been described in the literature previously. It is worthy to note that the formation of pyridinium **1g** features excellent regioselectivity. The reactions of pyridinium **1f** with 4-oxo-4-phenylbut-2-ynoate and 1,4-diketone alkyne finished the thiophenes **20** and **21** in 68 % and 55 % yields, respectively. It should be mentioned that for the synthesis of **15** from pyridinium **1f**, only 40 % yield could be afforded compared with the route from pyridinium **1e**. Pyridinium **1g** was also applicable to this transformation and it could react with *N*-methyl-4-oxo-*N*,4-diphenylbut-2-ynamide to afford

Table 1. Optimization of the reaction conditions.[a]



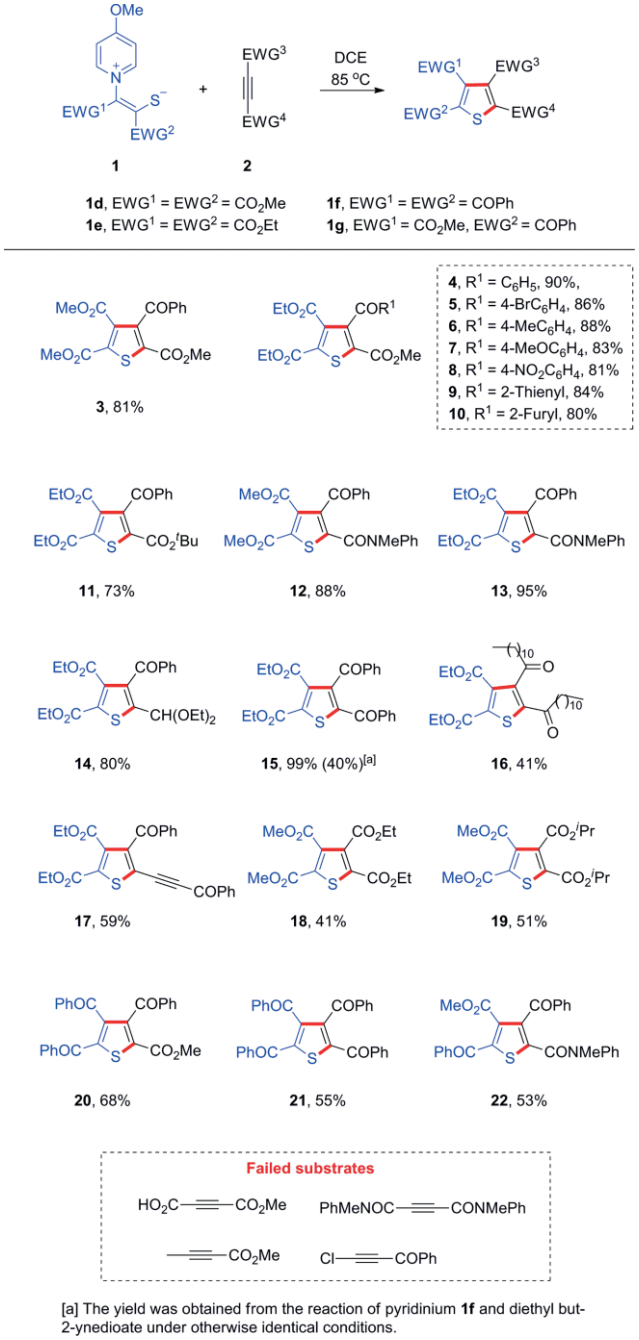
1a, X = H **1c**, X = Me
1b, X = NMe_2 **1d**, X = OMe

2a **3**

Entry	1	1/2a	Solvent	Time [h]	Yield [%]
1[b]	**1a**	1.5:1	DCM	50	76
2	**1a**	1.5:1	DCE	11.5	76
3	**1b**	1.5:1	DCE	1	29
4	**1c**	1.5:1	DCE	1.5	60
5	***1d***	***1.5:1***	***DCE***	***1***	***81***
6	**1d**	1.2:1	DCE	2.5	75
7	**1d**	1.8:1	DCE	1	74
8	**1d**	1.5:1	EtOAc	2	71
9	**1d**	1.5:1	$(CH_3)_2CO$	2	68
10	**1d**	1.5:1	THF	2	70
11	**1d**	1.5:1	PhMe	2	71
12	**1d**	1.5:1	DMF	2	45
13	**1d**	1.5:1	CH_3CN	2	51
14	**1d**	1.5:1	MeOH	2	22

[a] Reaction conditions: **1**, **2a** (0.3 mmol), solvent (3 mL), 85 °C, in air. Isolated yield. [b] 45 °C was adopted instead.

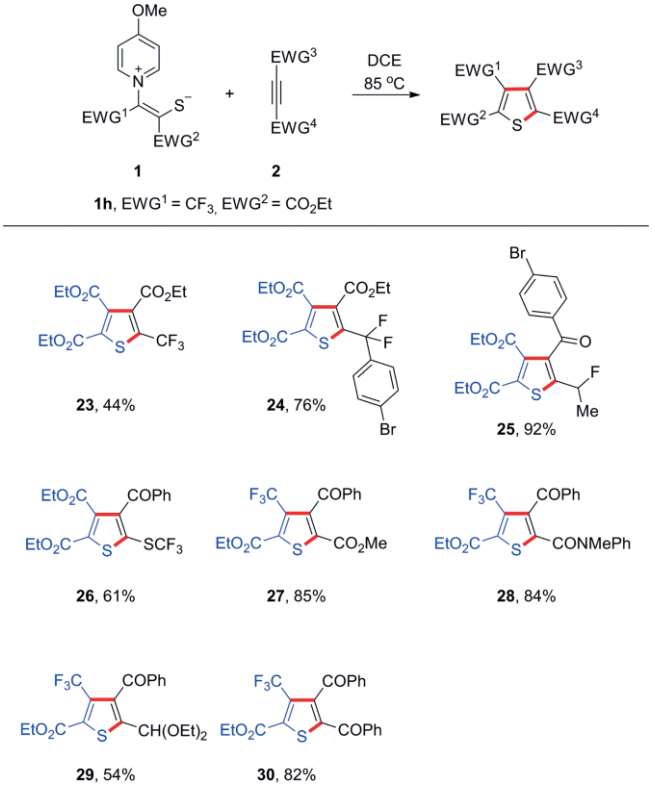
thiophene **22** in a yield of 53 %. The regioselectivities for the formation pyridinium **1g** and thiophenes (**3–14**, **17**, **20** and **22**) were established by analogy with **27** (vide infra).[9] Despite the above success, some failed substrates should be mentioned. 4-Methoxy-4-oxobut-2-ynoic acid, N^1,N^4-dimethyl-N^1,N^4-diphenylbut-2-ynediamide, and methyl but-2-ynoate did not react with pyridinium **1d**. The results gained from methyl but-2-ynoate and **17** indicated that the EWG[4] of the reaction partner **2** should be a suitable electron-withdrawing group, while aryl or alkyl groups were not the right choices. Moreover, 3-chloro-1-phenylprop-2-yn-1-one gave only a trace amount of the desired thiophene along with other unidentified side-products.



[a] The yield was obtained from the reaction of pyridinium **1f** and diethyl but-2-ynedioate under otherwise identical conditions.

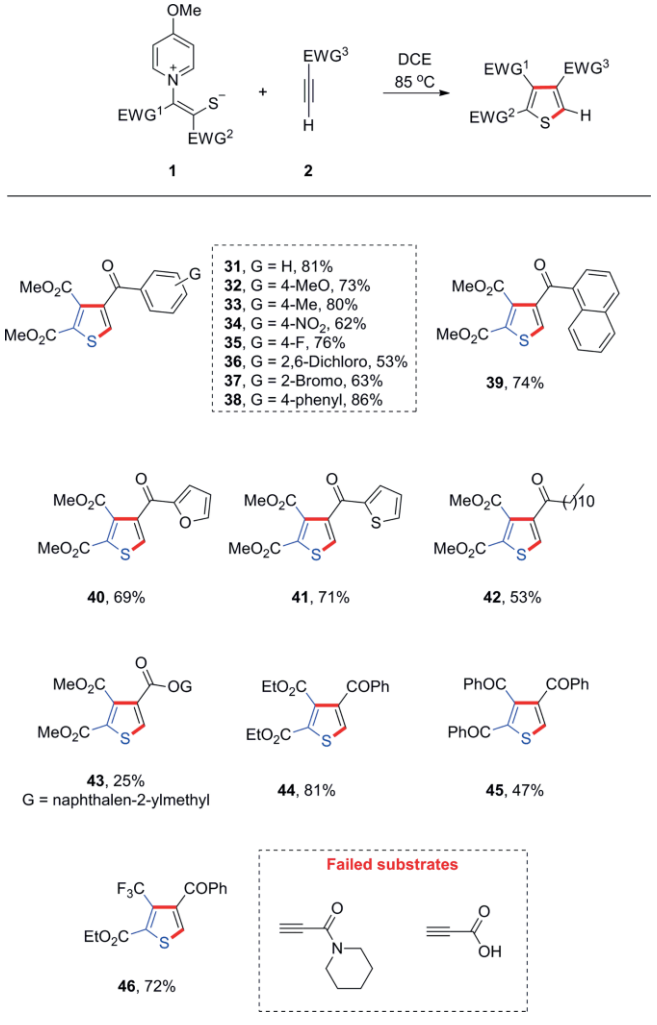
Scheme 2. [3+2] cascade cyclization reaction of internal alkynes. Reaction conditions: **1** (1.5 equiv.), **2** (0.3 mmol), DCE (3 mL), 85 °C, in air. Isolated yield.

As we know that incorporating of fluorine-containing groups into bioactive molecules has been developed as an important tool to alter their lipophilicity, bioavailability, and metabolic ability.[10] On the other hand, fluorine-bearing thiophenes were usually synthesized from preconstructed thiophenes via fluorinated reactions with the aid of metal catalysts.[11] Thus far, there have been no unified approaches that could access multifarious fluorine-containing thiophenes under metal-free and catalyst-free conditions, to the best of our knowledge. Thus, we examined the reaction between ethyl 4,4,4-trifluorobut-2-ynoate and pyridinium **1e**. Delightfully, a moderate yield of triethyl 5-(trifluoromethyl)thiophene-2,3,4-tricarboxylate (**23**) was successfully obtained with a CF_3 group installed at the 5-position (Scheme 3). Likewise, thiophenes bearing CF_2 (**24**), CF (**25**) or SCF_3 (**26**) groups were also obtained from the corresponding alkynes in 61 % to 92 % yields. To our satisfaction, ethyl 4,4,4-trifluorobut-2-ynoate could also be transformed into pyridinium **1h** using Bazgir's method,[7] which was a CF_3-containing organosulfur compound and of great potential to incorporate sulfur and CF_3 group into organic molecules simultaneously. With **1h** in hand, we investigated its reactions with various internal alkynes comprising ester, amide, acetal, or ketone moieties. The cyclization reactions of them proceeded smoothly, affording thiophenes (**27**–**30**) with a CF_3 group installing at the different position compared with **23**. The regioselectivity of **27** was confirmed by X-ray diffraction analysis and that of other thiophenes were established by analogy with **27**.[9]



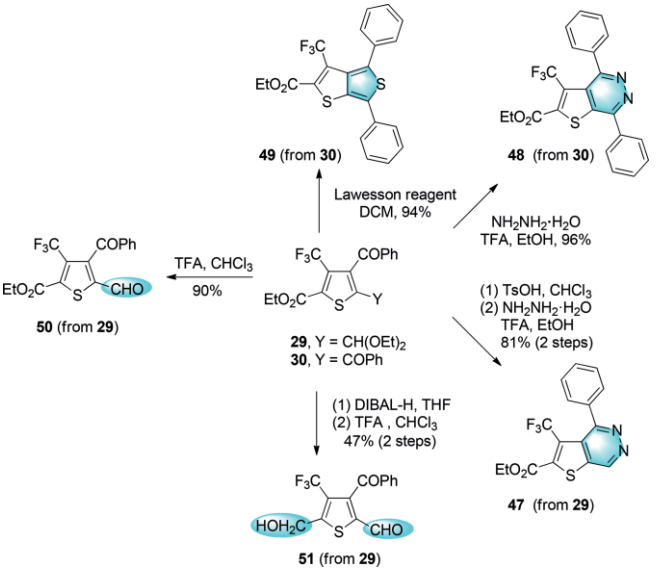
Scheme 3. [3+2] cascade cyclization reaction of internal alkynes. Reaction conditions: **1** (1.5 equiv.), **2** (0.3 mmol), DCE (3 mL), 85 °C, in air. Isolated yield.

With the success in the synthesis of tetrasubstituted thiophenes (**3**–**30**), we wondered if this facile protocol could be extended to accessing trisubstituted thiophenes using terminal alkynes as the reactants. Gratifyingly, when 1-phenylprop-2-yn-1-one was adopted as the substrate, trisubstituted thiophene **31** was obtained in 81 % yield and the structure of **31** was unambiguously assigned by X-ray structural analysis (Scheme 4).[9] Then, the electrophilic and steric effects of the substituents on the benzoyl groups (**32**–**38**) were investigated. Strong electron-donating and electron-withdrawing substituents (e.g., **32** and **34**) resulted in slightly attenuated yields and bulky substituents (**36** and **37**) sharply cut down the yields. The fused aryl (e.g., 1-naphthyl) and heteroaryl (e.g., 2-furyl and 2-thienyl) group-substituted terminal alkynes were also well-tolerated and gave high yields of the desired thiophenes (**39**–**41**). Terminal alkyne with alkylacyl group furnished **42** only in a moderate yield of 53 %. Naphthalen-2-ylmethyl propiolate exhibited lower reactivity compared with acyl substrates and an inferior yield of 25 % (**43**) could be obtained with prolonged time. The diester pyridiniums (**1d** and **1e**) performed better than diketone substrate **1f** and gave higher yields (**31** vs. **45** and **44** vs. **45**). In addition, trisubstituted thiophene **46** containing a CF_3 group was obtained as well in 72 % yield. Propiolic acid and its amide derivatives (e.g., 1-(piperidin-1-yl)prop-2-yn-1-one) failed to react with pyridinium **1d** as no reactions were detected.



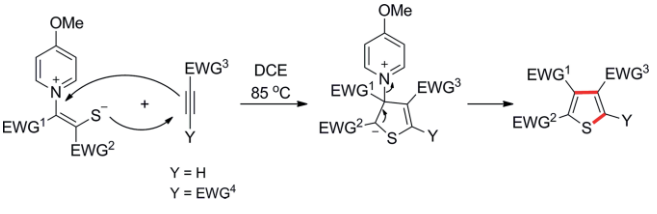
Scheme 4. [3+2] cascade cyclization reaction of terminal alkynes. Reaction conditions: **1** (1.5 equiv.), **2** (0.3 mmol), DCE (3 mL), 85 °C, in air. Isolated yield.

To further demonstrate the utility of this synthetic protocol, a series of derivatization reactions were conducted (Scheme 5). The condensation reaction of **29** and **30** with hydrazine hydrate afforded **47** and **48** bearing a thieno[2,3-*d*]pyridazine fused system. The sulfurization of **30** with Lawesson reagent afforded thieno[3,4-b]thiophene **49** in 94 % yield. Deprotection of the acetal group of **29** under acidic conditions could afford a new tetrasubstituted thiophene **50** with an aldehyde function. In addition, curiously the ester group of **29** could be selectively reduced to hydroxylmethyl group with DIBAL-H in the presence of ketone function, probably owing to the bulky steric hindrance. After hydrolysis, tetrasubstituted thiophene **51** decorated with a hydroxylmethyl and an aldehyde motif was obtained in 47 % total yield for two steps.



Scheme 5. Further transformations of thiophenes decorated with CF_3.

Based on the previous reports,[12] we proposed a possible mechanism for the [3+2] cascade cyclization reaction (Scheme 6). The cascade process is initiated by an *S*-Michael addition of thiolates to the more electron-deficient end of activated alkynes followed by a *C*-Michael addition, the first step of which dominates the regioselectivities of final products. Then a retro-Michael addition results in extrusion of 4-MeO-Py from the system affording the desired thiophenes.



Scheme 6. Proposed mechanism for [3+2] cascade cyclization reaction.

Conclusions

In summary, pyridinium 1,4-zwitterionic thiolates (**A1**–**A4**) have been developed to react with a series of activated alkynes, delivering a library of polysubstituted thiophenes, especially those bearing precious fluorine-containing groups. The freshly disclosed pyridiniums **A2**–**A4** could be powerful and potential synthons to incorporate sulfur atom into organic molecules in the future. Of particular note is that pyridinium **A4** could introduce sulfur and trifluoromethyl group to target products simultaneously. The other performances and reaction modes of pyridinium 1,4-zwitterionic thiolates will be described in due course.

Experimental Section

General Information: All isolated compounds were characterized on Varian 300, Bruker 400 and JEOL 400 MHz spectrometers in the $CDCl_3$, $(CD_3)_2CO$, or $(CD_3)_2SO$. Chemical shifts are reported as δ values relative to internal chloroform (δ = 7.26 for ^1H NMR and 77.00 for ^{13}C NMR), acetone (δ = 2.05 for ^1H NMR and 29.84 for ^{13}C NMR), and dimethyl sulfoxide (δ = 2.50 for ^1H NMR and 39.52 for ^{13}C NMR). ^9F NMR chemical shifts were determined as δ values relative to external standard $PhCF_3$ at –63.00. High-resolution mass spectra (HRMS) were obtained on a 4G mass spectrometer by using electrospray ionization (ESI) analyzed by quadrupole time-of-flight (QTof). All melting points were measured with the samples after column chromatography and uncorrected. Column chromatography was performed on silica gel. Anhydrous THF, PhMe were distilled from sodium benzophenone ketyl under Ar. All other solvents and reagents were used as obtained from commercial sources without further purification.

General Procedure for the Preparation of Alkynes: Methyl 4-oxo-4-phenylbut-2-ynoate (**S1**, i.e., **2a**), methyl 4-oxo-4-(*p*-tolyl)but-2-ynoate (**S3**), methyl 4-(4-methoxyphenyl)-4-oxobut-2-ynoate (**S4**), methyl 4-oxo-4-(thiophen-2-yl)but-2-ynoate (**S6**), methyl 4-(furan-2-yl)-4-oxobut-2-ynoate (**S7**), *tert*-butyl 4-oxo-4-phenylbut-2-ynoate (**S8**), and *N*-methyl-4-oxo-*N*,4-diphenylbut-2-ynamide (**S9**) were prepared according to the literature.[13] 4-(4-Bromophenyl)-4-oxobut-2-ynoate (**S2**) and methyl 4-(4-nitrophenyl)-4-oxobut-2-ynoate (**S5**) were prepared according to the literature.[14] 4,4-Diethoxy-1-phenylbut-2-yn-1-one (**S10**) was prepared according to the literature.[15] 4-diphenylbut-2-yne-1,4-dione (**S11**) and hexacos-13-yne-12,15-dione (**S12**) were prepared according to the literature.[16] 1,6-Diphenylhexa-2,4-diyne-1,6-dione (**S13**) was prepared according to the literature.[17] Diisopropyl but-2-ynedioate (**S14**) was prepared according to the literature.[18] Ethyl 4-(4-bromophenyl)-4,4-difluorobut-2-ynoate (**S15**) was prepared according to the literature.[19] 1-(4-Bromophenyl)-4-fluoropent-2-yn-1-one (**S16**) was prepared according to the literature.[20] 1-Phenyl-3-((trifluoromethyl)thio)prop-2-yn-1-one (**S17**) was prepared according to the literature.[21] All the terminal alkynes were prepared according to the literature[22] besides 1-naphthalen-2-ylmethyl propiolate (**S18**) and 1-(piperidin-1-yl)prop-2-yn-1-one (**S19**). 1-Naphthalen-2-ylmethyl propiolate (**S18**) was prepared according to the literature.[23] 1-(Piperidin-1-yl)prop-2-yn-1-one (**S19**) was prepared according to the literature.[24]

General Procedure for the Preparation of Pyridinium 1,4-Zwitterionic Thiolates: Pyridinium 1,4-zwitterionic thiolates (**1a**–**h**) were prepared according to the literature.[7]

General Experimental Procedure for Thiophenes 3–46: To a solution of alkyne (0.3 mmol, 1.0 equiv.) in DCE (3 mL) was added pyridinium 1,4-zwitterionic thiolate (0.45 mmol, 1.5 equiv.), then the reaction mixture was stirred at 85 °C. After completion as monitored by TLC, the mixture was concentrated and the residue was directly subjected to silica gel column chromatography to afford the desired thiophene.

Procedures for the Synthesis of Thiophene Derivatives (47–51)

For the Synthesis of 47: To a solution of **29** (26 mg, 0.060 mmol, 1.0 equiv.) in $CHCl_3$ (1 mL) was added TsOH (10 mg, 0.060 mmol, 1.0 equiv.), then the reaction mixture was stirred at room temperature. After completion as monitored by TLC, the solvent was removed and the residue was redissolved in EtOH (1 mL). To this solution were added $NH_2NH_2{\cdot}H_2O$ (80 %, 0.5 mL) and TFA (0.3 equiv.), then the reaction mixture was heated at 80 °C. After completion as monitored by TLC, the mixture was concentrated and the residue was directly subjected to silica gel column chromatography (PE/EtOAc = 8:1) to afford the desired product **47** (17 mg, 81 % yield for 2 steps).

For the Synthesis of 48: To a solution of **30** (26 mg, 0.060 mmol, 1.0 equiv.) in EtOH (1 mL) were added $NH_2NH_2{\cdot}H_2O$ (80 %, 0.4 mL) and TFA (cat.), then the reaction mixture was heated at 80 °C. After completion as monitored by TLC, the mixture was concentrated and the residue was directly subjected to silica gel column chromatography (PE/EtOAc = 8:1) to afford the desired product **48** (25 mg, 96 % yield).

For the Synthesis of 49: To a solution of **30** (34 mg, 0.080 mmol, 1.0 equiv.) in DCM (4 mL) was added Lawesson reagent (48 mg, 0.12 mmol, 1.5 equiv.), then the reaction mixture was heated at 45 °C. After completion as monitored by TLC, the mixture was concentrated and the residue was directly subjected to silica gel column chromatography (PE/EtOAc = 10:1) to afford the desired product **49** (32 mg, 94 % yield).

For the Synthesis of 50: To a solution of **29** (70 mg, 0.16 mmol, 1.0 equiv.) in $CHCl_3$ (1 mL) was added TFA (0.3 equiv.), then the reaction mixture was stirred at room temperature. After completion as monitored by TLC, the solvent was removed and the residue was directly subjected to silica gel column chromatography (PE/EtOAc = 15:1) to afford the desired product **50** (52 mg, 90 % yield).

For the Synthesis of 51: To a solution of **29** (46 mg, 0.11 mmol, 1.0 equiv.) in THF (10 mL) at –78 °C was added DIBAL-H (1.65 mL, 1 M in hexane, 1.65 mmol, 15 equiv.), then the reaction mixture was stirred at the same temperature. After completion as monitored by TLC, the mixture was quenched with saturated aqueous potassium sodium tartrate solution. Then, the mixture was extracted with DCM. The combined organic phases were concentrated and the residue was redissolved in $CHCl_3$ (5 mL). To this solution was added TFA (cat.), then the reaction mixture was stirred at room temperature. After completion as monitored by TLC, the solvent was removed and the residue was directly subjected to silica gel column chromatography (PE/EtOAc = 5:1) to afford the desired product **51** (16 mg, 47 % yield for 2 steps).

Characterization Data of Products: Trimethyl 4-Benzoylthiophene-2,3,5-tricarboxylate. Compound **3** (88 mg, Y = 81 %, R_f = 0.2 (PE/EA = 6:1)) was isolated as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 3.95 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.8, 162.3, 160.4, 160.2, 145.4 137.9, 136.6, 136.4, 133.8, 133.7, 129.0, 128.6, 53.3, 52.9, 52.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{17}H_{15}O_7S$ 363.0533, found 363.0547.

2,3-Diethyl 5-Methyl 4-Benzoylthiophene-2,3,5-tricarboxylate: Compound **4** (105 mg, Y = 90 %, R_f = 0.4 (PE/EA = 6:1)) was isolated

as a light yellow solid; m.p. 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.80 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.69 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.8, 161.7, 160.3, 160.0, 145.4, 138.6, 136.5, 133.6, 133.4, 129.0, 128.5, 62.6, 62.0, 52.8, 13.9, 13.4, (1C missing); HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{19}H_{19}O_7S$ 391.0846, found 391.0859.

2,3-Diethyl 5-Methyl 4-(4-Bromobenzoyl)thiophene-2,3,5-tricarboxylate: Compound **5** (121 mg, Y = 86 %, R_f = 0.4 (PE/EA = 5:1))was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.71 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.9, 161.5, 160.2, 159.9, 145.0, 138.9, 136.2, 135.5, 133.3, 131.9, 130.4, 128.9, 62.6, 62.1, 52.9, 13.9, 13.5; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{19}H_{18}BrO_7S$ 468.9951, found 468.9970.

2,3-Diethyl 5-Methyl 4-(4-Methylbenzoyl)thiophene-2,3,5-tricarboxylate: Compound **6** (106 mg, Y = 88 %, R_f = 0.3 (PE/EA = 5:1)) was isolated as a white solid; m.p. 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.69 (s, 3H), 2.40 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.3, 161.7, 160.3, 160.1, 145.7, 144.6, 138.4, 136.6, 134.2, 133.3, 129.2 (2C), 62.5, 62.0, 52.7, 21.7, 13.9, 13.4; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{20}H_{21}O_7S$ 405.1003, found 405.1014.

2,3-Diethyl 5-Methyl 4-(4-Methoxybenzoyl)thiophene-2,3,5-tricarboxylate: Compound **7** (105 mg, Y = 83 %, R_f = 0.25 (PE/EA = 3:1)) was isolated as a yellow solid; m.p. 85.2–86.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 1.38 (d, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 189.2, 164.0, 161.8, 160.3, 160.0, 145.7, 138.1, 136.6, 133.2, 131.4, 129.7, 113.8, 62.5, 61.9, 55.4, 52.7, 13.9, 13.4; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{20}H_{21}O_8S$ 421.0952, found 421.0965.

2,3-Diethyl 5-Methyl 4-(4-Nitrobenzoyl)thiophene-2,3,5-tricarboxylate: Compound **8** (106 mg, Y = 81 %, R_f = 0.25 (PE/EA = 4:1)) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 4.43 (q, J = 7.1 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.5, 161.4, 160.1, 159.9, 150.4, 144.6, 141.1, 139.7, 136.0, 133.3, 129.8, 123.8, 62.8, 62.3, 53.0, 13.9, 13.5; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{19}H_{18}NO_9S$ 436.0697, found 436.0711.

2,3-Diethyl 5-Methyl 4-(Thiophene-2-carbonyl)thiophene-2,3,5-tricarboxylate: Compound **9** (100 mg, Y = 84 %, R_f = 0.2 (PE/EA = 4:1)) was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.74 (dd, J = 4.9, 1.1 Hz, 1H), 7.39 (dd, J = 3.8, 1.2 Hz, 1H), 7.10 (dd, J = 4.9, 3.9 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.4, 161.7, 160.2, 159.9, 144.4, 143.7, 138.2, 136.5, 135.1, 134.6, 133.8, 128.1, 62.6, 62.1, 52.9, 13.9, 13.4; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{17}H_{17}O_7S_2$ 397.0410, found 397.0424.

2,3-Diethyl 5-Methyl 4-(Furan-2-carbonyl)thiophene-2,3,5-tricarboxylate: Compound **10** (91 mg, Y = 80 %, R_f = 0.3 (PE/EA = 3:1)) was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.62 (d, J = 1.2 Hz, 1H), 7.13 (d, J = 3.5 Hz, 1H), 6.57 (dd, J = 3.6, 1.7 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.5, 161.8, 160.3, 159.9, 152.5, 147.3, 143.4, 137.8, 136.9, 134.6, 119.3, 112.6, 62.5, 62.1, 52.9, 13.9, 13.5; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{17}H_{17}O_8S$ 381.0639, found 381.0649.

5-(*tert*-Butyl) 2,3-Diethyl 4-Benzoylthiophene-2,3,5-tricarboxylate: Compound **11** (95 mg, Y = 73 %, R_f = 0.5 (PE/EA = 4:1)) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ = 7.72–7.70 (m, 2H), 7.56–7.51 (m, 1H), 7.43–7.40 (m, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.98 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ = 190.9, 162.6, 160.7, 159.9, 144.7, 138.1 (2C), 137.8, 137.5, 134.6, 130.1, 129.5, 84.9, 63.2, 62.5, 27.7, 14.3, 13.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{22}H_{24}O_7SNa$ 455.1135, found 455.1150.

Dimethyl 4-Benzoyl-5-(methyl(phenyl)carbamoyl)thiophene-2,3-dicarboxylate: Compound **12** (116 mg, Y = 88 %, R_f = 0.1 (PE/EA = 6:1)) was isolated as a pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.34–7.21 (m, 3H), 7.18–7.05 (m, 2H), 3.81 (s, 3H), 3.44 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 189.9, 162.8, 160.8, 160.2, 142.4, 142.2, 142.1, 136.4, 136.3, 133.8, 133.2, 129.6, 129.0, 128.2, 128.1, 127.0, 52.8, 52.4, 38.1; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{23}H_{20}NO_6S$ 438.1006, found 438.1018.

Diethyl 4-Benzoyl-5-(methyl(phenyl)carbamoyl)thiophene-2,3-dicarboxylate: Compound **13** (133 mg, Y = 95 %, R_f = 0.4 (PE/EA = 2:1)) was isolated as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.72–7.63 (m, 2H), 7.58–7.53 (m, 1H), 7.45–7.39 (m, 2H), 7.32–7.23 (m, 3H), 4.28 (q, J = 7.1 Hz, 2H), 3.89 (q, J = 7.0 Hz, 2H), 3.29 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.1, 162.4, 160.9, 160.0, 142.4, 142.3, 141.8, 136.5, 136.1, 134.5, 133.2, 129.6, 129.1, 128.2, 128.0, 127.1, 62.1, 61.7, 38.2, 13.8, 13.2; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{25}H_{24}NO_6S$ 466.1319, found 466.1331.

Diethyl 4-Benzoyl-5-(diethoxymethyl)thiophene-2,3-dicarboxylate: Compound **14** (104 mg, Y = 80 %, R_f = 0.5 (PE/EA = 5:1)) was isolated as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.82–7.76 (m, 2H), 7.62–7.54 (m, 1H), 7.47–7.42 (m, 2H), 5.68 (s, 1H), 4.35 (d, J = 7.1 Hz, 2H), 4.00 (q, J = 7.2 Hz, 2H), 3.62–3.53 (m, 2H), 3.50–3.39 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.11–1.03 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.2, 162.9, 160.5, 149.1, 137.8, 137.5, 137.1, 133.4, 132.4, 129.1, 128.4, 96.8, 62.1, 61.8, 61.7, 14.6, 14.0, 13.4; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{22}H_{26}O_7SNa$ 457.1291, found 457.1309.

Diethyl 4,5-Dibenzoylthiophene-2,3-dicarboxylate: Compound **15** (130 mg, Y = 99 %, R_f = 0.4 (PE/EA = 5:1)) was isolated as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56–7.45 (m, 6H), 7.34–7.26 (m, 4H), 4.42 (q, J = 7.1 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.2, 186.9, 162.6, 159.8, 144.2, 143.5, 138.5, 137.0, 136.8, 136.1, 133.4, 133.3, 128.9, 128.7, 128.4, 128.3, 62.4, 62.1, 13.9, 13.5; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{24}H_{21}O_6S$ 437.1053, found 437.1067.

Diethyl 4,5-Didodecanoylthiophene-2,3-dicarboxylate: Compound **16** (73 mg, Y = 41 %, R_f = 0.7 (PE/EA = 4:1)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.41–4.36 (m, 2H), 4.36–4.30 (m, 2H), 2.81 (t, J = 7.3 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 1.79–1.70 (m, 4H), 1.40–1.26 (m, 38H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.4, 192.1, 162.5, 160.1, 146.8, 140.0, 136.6 (2C), 62.6, 62.3, 43.4, 41.1, 31.9 (2C), 29.6 (3C), 29.5, 29.4 (2C), 29.3 (2C), 29.0 (2C), 24.2, 23.3, 22.7, 14.1, 14.0, 13.8, (4C missing); HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{34}H_{57}O_6S$ 593.3870, found 593.3894.

Diethyl 4-Benzoyl-5-(3-oxo-3-phenylprop-1-yn-1-yl)thiophene-2,3-dicarboxylate: Compound **17** (81 mg, Y = 59 %, R_f = 0.4 (PE/EA = 5:1)) was isolated as a brown red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95–7.93 (m, 2H), 7.88–7.86 (m, 2H), 7.61–7.55 (m, 2H), 7.51 (t,

J = 7.6 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 4.50 (q, *J* = 7.2 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 6.4 Hz, 3H), 1.39 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 186.8, 176.7, 162.8, 159.6, 149.2, 142.0, 136.3 (2C), 135.1, 134.2, 134.1, 129.9, 129.5, 128.7, 128.5, 121.2, 92.9, 82.3, 62.8, 62.7, 14.0, (1C missing); HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{26}H_{21}O_6S$ 461.1053, found 461.1067.

2,3-Diethyl 4,5-Dimethyl Thiophene-2,3,4,5-tetracarboxylate: Compound **18** (42 mg, Y = 41 %, R_f = 0.2 (PE/EA = 4:1)) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.41–4.34 (m, 4H), 3.92 (s, 6H), 1.39–1.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.9, 162.3, 160.4, 159.8, 137.0, 136.9, 136.6, 135.6, 62.5, 62.3, 53.1, 53.0, 14.0, 13.9; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{14}H_{17}O_8S$ 345.0639, found 345.0651.

2,3-Diisopropyl 4,5-Dimethyl Thiophene-2,3,4,5-tetracarboxylate: Compound **19** (57 mg, Y = 51 %, R_f = 0.4 (PE/EA = 5:1)) was isolated as a neon yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.27–5.19 (m, 2H), 3.91 (s, 6H), 1.36 (d, *J* = 6.3 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.9, 161.8, 160.3, 159.3, 137.2, 136.8 (2C), 135.4, 70.7, 70.2, 53.1, 52.9, 21.6, 21.5; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{21}O_8S$ 373.0952, found 373.0967.

Methyl 3,4,5-Tribenzoylthiophene-2-carboxylate: Compound **20** (93 mg, Y = 68 %, R_f = 0.3 (PE/EA = 6:1)) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 7.2 Hz, 2H), 7.59–7.50 (m, 3H), 7.48–7.34 (m, 6H), 7.31–7.24 (m, 2H), 7.18 (t, *J* = 7.7 Hz, 2H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.1, 190.2, 187.0, 160.4, 146.6, 145.6, 144.0, 137.2, 136.9, 136.7, 134.3, 133.6, 133.4, 133.2, 129.0, 128.9, 128.8, 128.4, 128.2, 52.8, (1C missing); HRMS (ESI) *m/z*: $[M + H]^+$ *calcd.* for $C_{27}H_{19}O_5S$ 455.0948, found 455.0963.

Thiophene-2,3,4,5-tetrayltetrakis(phenylmethanone): Compound **21** (82 mg, Y = 55 %, R_f = 0.2 (PE/EA = 5:1)) was isolated as a wine red oil. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ = 7.81 (d, *J* = 7.3 Hz 4H), 7.73 (d, *J* = 7.3 Hz, 4H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.52–7.47 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 4H), 7.32 (t, *J* = 7.8 Hz, 4H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 191.2, 187.7, 146.4, 145.0, 138.3, 138.1, 134.5, 134.2, 130.0, 129.7, 129.5, 129.2; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{32}H_{21}O_4S$ 501.1155, found 501.1174.

Methyl 2,4-Dibenzoyl-5-(methyl(phenyl)carbamoyl)thiophene-3-carboxylate: Compound **22** (77 mg, Y = 53 %, R_f = 0.1 (PE/EA = 4:1)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 7.3 Hz, 2H), 7.69 (d, *J* = 7.3 Hz, 2H), 7.59–7.52 (m, 2H), 7.47–7.39 (m, 4H), 7.37–7.30 (m, 3H), 7.27–7.24 (m, 2H), 3.34 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.5, 188.1, 161.3, 160.6, 147.2, 144.7, 142.4, 137.7, 137.0, 136.7, 133.8, 133.1, 131.8, 129.9, 129.0, 128.7, 128.6, 128.4, 127.9, 51.8, 38.5, (1C missing); HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{28}H_{22}NO_5S$ 484.1213, found 484.1229.

Triethyl 5-(Trifluoromethyl)thiophene-2,3,4-tricarboxylate: Compound **23** (49 mg, Y = 44 %, R_f = 0.55 (PE/EA = 6:1)) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.40–4.27 (m, 6H), 1.34–1.27 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.3, 159.6, 159.3, 140.9, 138.6 (q, *J* = 39.1 Hz), 132.1, 132.0 (q, *J* = 2.5 Hz), 120.6 (q, *J* = 270.2 Hz), 62.6, 62.4, 62.3, 14.0, 13.9, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –55.3; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{14}H_{16}F_3O_6S$ 369.0614, found 369.0626.

Triethyl 5-((4-Bromophenyl)difluoromethyl)thiophene-2,3,4-tricarboxylate: Compound **24** (115 mg, Y = 76 %, R_f = 0.4 (PE/EA = 5:1)) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 4.45–4.34 (m, 4H), 4.09 (q, *J* = 7.1 Hz, 2H), 1.43–1.34 (m, 6H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 160.0, 159.6, 146.9 (t, *J* = 33.0 Hz), 140.7, 134.7 (t, *J* = 27.1 Hz), 131.6, 131.4, 130.8 (t, *J* = 3.8 Hz), 127.5 (t, *J* = 5.0 Hz), 125.1, 117.8 (t, *J* = 240.8 Hz), 62.3, 62.2, 61.7, 14.0, 13.8, 13.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –76.9; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{20}H_{20}BrF_2O_6S$ 505.0127, found 505.0146.

Diethyl 4-(4-Bromobenzoyl)-5-(1-fluoroethyl)thiophene-2,3-dicarboxylate: Compound **25** (126 mg, Y = 92 %, R_f = 0.5 (PE/EA = 5:1)) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69–7.56 (m, 4H), 5.90 (dq, *J* = 46.4, 6.4 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.96–3.92 (m, 2H), 1.70 (dd, *J* = 23.6, 6.4 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.8, 162.7, 160.1, 152.2 (d, *J* = 21.7 Hz), 137.2, 136.5 (d, *J* = 4.7 Hz), 135.8, 132.3 (d, *J* = 2.1 Hz), 131.9, 130.7, 129.0, 85.5 (d, *J* = 167.8 Hz), 62.2, 62.0, 23.6 (d, *J* = 24.7 Hz), 14.0, 13.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –157.6; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{19}H_{19}BrFO_5S$ 457.0115, found 457.0134.

Diethyl 4-Benzoyl-5-((trifluoromethyl)thio)thiophene-2,3-dicarboxylate: Compound **26** (79 mg, Y = 61 %, R_f = 0.6 (PE/EA = 5:1)) was isolated as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77–7.75 (m, 2H), 7.64–7.60 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.4, 161.9, 159.4, 148.7, 139.5, 137.3, 136.4, 134.0, 129.5, 128.7, 127.7 (q, *J* = 310.1 Hz), 126.8 (q, *J* = 2.5 Hz), 62.6, 62.2, 14.0, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –42.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{18}H_{16}F_3O_5S_2$ 433.0386, found 433.0399.

5-Ethyl 2-Methyl 3-Benzoyl-4-(trifluoromethyl)thiophene-2,5-dicarboxylate: Compound **27** (99 mg, Y = 85 %, R_f = 0.45 (PE/EA = 5:1)) was isolated as a white solid; m.p. 120.6–122.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 7.3 Hz, 2H), 7.63–7.58 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 4.44 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.1, 159.9, 158.9, 145.0 (q, *J* = 2.3 Hz), 139.7 (q, *J* = 2.7 Hz), 136.2, 134.0, 133.6, 131.8 (q, *J* = 36.6 Hz), 128.9, 128.8, 120.2 (q, *J* = 272.0 Hz), 63.0, 53.0, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –55.0; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{17}H_{14}F_3O_5S$ 387.0509, found 387.0527.

Ethyl 4-Benzoyl-5-(methyl(phenyl)carbamoyl)-3-(trifluoromethyl)thiophene-2-carboxylate: Compound **28** (116 mg, Y = 84 %, R_f = 0.2 (PE/EA = 5:1)) was isolated as a yellow solid; m.p. 139.6–140.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80–7.77 (m, 2H), 7.58–7.56 (m, 1H), 7.49–7.43 (m, 2H), 7.42–7.38 (m, 3H), 7.29–7.23 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.31 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.0, 160.3, 159.3, 144.5, 142.4, 138.4, 137.4 (q, *J* = 3.0 Hz), 136.9, 133.4, 130.3 (q, *J* = 36.4 Hz), 130.1, 128.9, 128.5, 127.9, 127.3, 120.4 (q, *J* = 272.0 Hz), 62.6, 38.7, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –54.4; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{23}H_{19}F_3NO_4S$ 462.0981, found 462.0999.

Ethyl 4-Benzoyl-5-(diethoxymethyl)-3-(trifluoromethyl)thiophene-2-carboxylate: Compound **29** (70 mg, Y = 54 %, R_f = 0.5 (PE/EA = 5:1)) was isolated as a brown yellow oil. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ = 7.86–7.84 (m, 2H), 7.71–7.67 (m, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 5.62 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.58–3.43 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ = 191.2, 160.0, 148.2, 138.4 (q, *J* = 2.3 Hz), 137.8, 135.5 (q, *J* = 3.0 Hz), 134.8, 131.8 (q, *J* = 35.7 Hz), 130.0, 129.7, 121.9 (q, *J* = 270.9 Hz), 97.6, 63.1, 62.8, 14.9, 14.3; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ = –54.7; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd. for $C_{20}H_{21}F_3O_5SNa$ 453.0954, found 453.0966.

Ethyl 4,5-Dibenzoyl-3-(trifluoromethyl)thiophene-2-carboxylate: Compound **30** (107 mg, Y = 82 %, R_f = 0.45 (PE/EA = 5:1)) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75–7.72 (m, 4H), 7.60–7.53 (m, 2H), 7.44–7.39 (m, 4H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.4, 186.0, 159.1, 145.0 (q, *J* = 2.2 Hz), 141.0, 139.3 (q, *J* = 2.8 Hz), 136.6, 136.5,

133.7 (2C), 132.1 (q, J = 36.5 Hz), 129.2, 128.8, 128.6, 121.0 (q, J = 272.1 Hz), 63.1, 13.8, (1C missing); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –54.7; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{22}H_{16}F_3O_4S$ 433.0716, found 433.0729.

Dimethyl 4-Benzoylthiophene-2,3-dicarboxylate: Compound **31** (74 mg, Y = 81 %, R_f = 0.3 (PE/EA = 5:1)) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 (s, 1H), 7.84–7.77 (m, 2H), 7.64–7.57 (m, 1H), 7.52–7.45 (m, 2H), 3.93 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 188.3, 165.0, 160.5, 139.8, 139.7, 137.7, 137.0, 133.0, 132.3, 129.3, 128.5, 53.0, 52.8; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd. for $C_{15}H_{12}O_5SNa$ 327.0298, found 327.0308.

Dimethyl 4-(4-Methoxybenzoyl)thiophene-2,3-dicarboxylate: Compound **32** (73 mg, Y = 73 %, R_f = 0.4 (PE/EA = 2:1)) was isolated as a white solid; m.p. 127.6–128.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (s, 1H), 7.82 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.0, 165.0, 163.6, 160.6, 140.3, 139.8, 136.5, 132.2, 131.8, 129.6, 113.8, 55.4, 52.9, 52.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{15}O_6S$ 335.0584, found 335.0596.

Dimethyl 4-(4-Methylbenzoyl)thiophene-2,3-dicarboxylate: Compound **33** (77 mg, Y = 80 %, R_f = 0.2 (PE/EA = 5:1)) was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.90 (s, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 188.0, 165.0, 160.6, 144.0, 140.1, 139.8, 137.2, 134.4, 132.2, 129.6, 129.2, 53.0, 52.8, 21.6; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{15}O_5S$ 319.0635, found 319.0647.

Dimethyl 4-(4-Nitrobenzoyl)thiophene-2,3-dicarboxylate: Compound **34** (65 mg, Y = 62 %, R_f = 0.5 (PE/EA = 2:1)) was isolated as a yellow solid; m.p. 154.5–155.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.35 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 7.5 Hz, 2H), 7.96 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 186.6, 164.6, 160.3, 150.1, 142.0, 139.4, 138.8, 138.4, 133.0, 130.2, 123.7, 53.1, 53.0; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd. for $C_{15}H_{11}NO_7SNa$ 372.0148, found 372.0158.

Dimethyl 4-(4-Fluorobenzoyl)thiophene-2,3-dicarboxylate: Compound **35** (74 mg, Y = 76 %, R_f = 0.15 (PE/EA = 5:1)) was isolated as a brown yellow solid; m.p. 105.2–106.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.88–7.84 (m, 2H), 7.18 (t, J = 8.6 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 186.9, 165.6 (d, J = 253.7 Hz), 164.9, 160.5, 139.7, 139.6, 137.2, 133.3 (d, J = 3.0 Hz), 132.6, 132.1 (d, J = 9.2 Hz), 115.8 (d, J = 21.8 Hz), 53.0, 52.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –104.7; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd. for $C_{15}H_{11}FO_5SNa$ 345.0203, found 345.0214.

Dimethyl 4-(2,6-Dichlorobenzoyl)thiophene-2,3-dicarboxylate: Compound **36** (60 mg, Y = 53 %, R_f = 0.1 (PE/EA = 4:1)) was isolated as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.80 (s, 1H), 7.39–7.35 (m, 3H), 3.99 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 184.5, 164.8, 160.4, 140.0, 139.0, 138.5, 136.7, 132.6, 132.0, 131.3, 128.2, 53.2, 52.9; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{11}Cl_2O_5S$ 372.9699, found 372.9715.

Diethyl 4-(2-Bromobenzoyl)thiophene-2,3-dicarboxylate: Compound **37** (73 mg, Y = 63 %, R_f = 0.4 (PE/EA = 2:1) was isolated as a yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.42–7.36 (m, 3H), 3.97 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 187.8, 165.0, 160.5, 140.2, 139.5, 139.4, 138.8, 133.4, 131.9, 129.1, 127.3, 119.5, 53.2, 52.9, (1C missing); HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{12}BrO_5S$ 382.9583, found 382.9598.

Dimethyl 4-([1,1′-Biphenyl]-4-carbonyl)thiophene-2,3-dicarboxylate: Compound **38** (98 mg, Y = 86 %, R_f = 0.2 (PE/EA = 4:1)) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.65–7.63 (m, 2H), 7.51–7.46 (m, 2H), 7.44–7.42 (m, 1H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.9, 165.0, 160.5, 145.7, 139.9, 139.7, 139.5, 137.4, 135.6, 132.3, 130.0, 128.9, 128.3, 127.1 (2C), 53.0, 52.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{21}H_{17}O_5S$ 381.0791, found 381.0804.

Dimethyl 4-(1-Naphthoyl)thiophene-2,3-dicarboxylate: Compound **39** (78 mg, Y = 74 %, R_f = 0.2 (PE/EA = 5:1)) was isolated as an orange red solid; m.p. 130.2–131.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13–8.10 (m, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.82–7.79 (m, 1H), 7.68 (s, 1H), 7.57 (dd, J = 7.1, 1.3 Hz, 1H), 7.45–7.43 (m, 2H), 7.40 (t, J = 8.3, 1H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.6, 165.2, 160.6, 141.5, 139.5, 139.2, 135.0, 133.6, 132.2 (2C), 130.4, 128.3, 128.1, 127.6, 126.7, 125.3, 124.1, 53.1, 52.9; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{19}H_{15}O_5S$ 355.0635, found 355.0648.

Dimethyl 4-(Furan-2-carbonyl)thiophene-2,3-dicarboxylate: Compound **40** (61 mg, Y = 69 %, R_f = 0.4 (PE/EA = 2:1)) was isolated as a yellow solid; m.p. 104.5–105.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59 (s, 1H), 7.69 (dd, J = 1.7, 0.8 Hz, 1H), 7.37 (dd, J = 3.7, 0.8 Hz, 1H), 6.62 (dd, J = 3.7, 1.7 Hz, 1H), 4.00 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.4, 165.3, 160.6, 152.2, 146.9, 140.1, 138.2, 137.8, 131.5, 120.0, 112.7, 53.0, 52.8; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{10}O_6SNa$ 317.0090, found 317.0103.

Dimethyl 4-(Thiophene-2-carbonyl)thiophene-2,3-dicarboxylate: Compound **41** (66 mg, Y = 71 %, R_f = 0.4 (PE/EA = 5:1)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (s, 1H), 7.68–7.64 (m, 2H), 7.09 (dd, J = 5.2, 4.0 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.6, 164.8, 160.5, 142.5, 139.7, 139.5, 136.0, 134.7, 134.2, 132.4, 128.1, 53.0, 52.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{13}H_{11}O_5S_2$ 311.0042, found 311.0052.

Dimethyl 4-Dodecanoylthiophene-2,3-dicarboxylate: Compound **42** (61 mg, Y = 53 %, R_f = 0.4 (PE/EA = 5:1)) was isolated as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13 (s, 1H), 4.00 (s, 3H), 3.89 (s, 3H), 2.84 (t, J = 7.4 Hz, 2H), 1.71–1.67 (m, 2H), 1.40–1.15 (m, 16H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.2, 165.1, 160.2, 140.4, 138.8, 136.2, 132.1, 62.0, 61.9, 39.3, 31.8, 29.5, 29.3 (2C), 29.2, 29.1, 23.8, 22.6, 14.0, 13.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{20}H_{31}O_5S$ 383.1887, found 383.1901.

2,3-Dimethyl 4-(Naphthalen-2-ylmethyl) Thiophene-2,3,4-tricarboxylate: Compound **43** (29 mg, Y = 25 %, R_f = 0.25 (PE/EA = 5:1)) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (s, 1H), 7.88–7.84 (m, 4H), 7.52–7.47 (m, 3H), 5.44 (s, 2H), 3.88 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.2, 160.6 (2C), 139.5, 138.2, 133.2, 133.1, 132.4, 131.8, 131.6, 128.5, 128.0, 127.7 (2C), 126.4 (2C), 126.0, 67.5, 53.0, 52.8; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd. for $C_{20}H_{16}O_6SNa$ 407.0560, found 407.0573.

Diethyl 4-Benzoylthiophene-2,3-dicarboxylate: Compound **44** (81 mg, Y = 81 %, R_f = 0.45 (PE/EA = 4:1)) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (s, 1H), 7.81 (d, J = 6.8 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 4.42–4.35 (m, 4H), 1.37 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.4, 164.5, 160.2, 139.9, 139.7, 137.5, 137.2, 132.9, 129.3, 128.5, 62.1, 62.0, 14.0, 13.8, (1C missing); HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{17}H_{17}O_5S$ 333.0791, found 333.0804.

Thiophene-2,3,4-triyltris(phenylmethanone): Compound **45** (56 mg, Y = 47 %, R_f = 0.15 (PE/EA = 5:1)) was isolated as a brown red oil. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ = 8.45 (s, 1H), 7.90–7.86 (m, 2H), 7.80–7.72 (m, 4H), 7.69–7.63 (m, 1H), 7.63–7.58 (m, 1H), 7.55–7.49 (m, 3H), 7.47–7.42 (m, 2H), 7.40–7.36 (m, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ = 192.0, 189.5, 187.9, 147.5, 142.8, 141.9, 138.7, 138.6, 138.1, 134.0 (2C), 133.7, 130.4, 129.9, 129.6, 129.5,

129.4, 129.2, (1C missing); HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{25}H_{17}O_3S$ 397.0893, found 397.0910.

Ethyl 4-Benzoyl-3-(trifluoromethyl)thiophene-2-carboxylate: Compound **46** (71 mg, Y = 72 %, R_f = 0.5 (PE/EA = 4:1)) was isolated as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.84–7.79 (m, 2H), 7.65–7.59 (m, 2H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.1, 159.7, 141.3 (q, *J* = 2.2 Hz), 136.8 (q, *J* = 3.0 Hz), 136.5, 134.0, 131.6 (q, *J* = 36.5 Hz), 131.0, 129.8, 128.7, 120.8 (q, *J* = 271.4 Hz), 62.6, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –55.6; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{18}F_3O_3S$ 329.0454, found 329.0467.

Ethyl 4-Phenyl-3-(trifluoromethyl)thieno[2,3-*d*]pyridazine-2-carboxylate: Compound **47** (17 mg, Y = 81 % for 2 steps, R_f = 0.2 (PE/EA = 2:1)) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.69 (s, 1H), 7.66–7.57 (m, 2H), 7.57–7.47 (m, 3H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.5, 157.9, 144.2, 143.3 (q, *J* = 3.6 Hz), 139.0, 137.9 (q, *J* = 2.9 Hz), 130.7, 129.5, 128.8, 128.2, 126.4 (q, *J* = 37.2 Hz), 120.2 (q, *J* = 271.6 Hz), 63.8, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –52.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{12}F_3N_2O_2S$ 353.0566, found 353.0583.

Ethyl 4,7-Diphenyl-3-(trifluoromethyl)thieno[2,3-*d*]pyridazine-2-carboxylate: Compound **48** (25 mg, Y = 96 %, R_f = 0.4 (PE/EA = 4:1)) was isolated as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.10–8.06 (m, 2H), 7.69–7.65 (m, 2H), 7.64–7.60 (m, 3H), 7.56–7.51 (m, 3H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.6, 156.3, 154.0, 143.7 (q, *J* = 3.8 Hz), 138.2, 138.0 (q, *J* = 2.0 Hz), 135.4, 131.7, 130.8, 129.4, 129.3, 129.0, 128.5, 128.2, 126.9 (q, *J* = 37.2 Hz), 120.1 (q, *J* = 271.6 Hz), 63.7, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –52.5; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{22}H_{16}F_3N_2O_2S$ 429.0879, found 429.0891.

Ethyl 4,6-Diphenyl-3-(trifluoromethyl)thieno[3,4-b]thiophene-2-carboxylate: Compound **49** (32 mg, Y = 94 %, R_f = 0.75 (PE/EA = 4:1)) was isolated as a yellow solid; m.p. 113–114 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.66–7.64 (m, 2H), 7.50–7.41 (m, 7H), 7.34 (t, *J* = 7.5 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.5, 142.0 (q, *J* = 4.0 Hz), 137.9, 135.6, 133.4, 132.4, 129.9, 129.6, 129.3, 128.6, 128.1, 127.8, 125.8, 122.0 (q, *J* = 37.2 Hz), 121.0 (q, *J* = 270.8 Hz), 62.8, 13.9, (1C missing); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –54.7; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{22}H_{16}F_3O_2S_2$ 433.0538, found 433.0553.

Ethyl 4-Benzoyl-5-formyl-3-(trifluoromethyl)thiophene-2-carboxylate: Compound **50** (52 mg, Y = 90 %, R_f = 0.45 (PE/EA = 4:1)) was isolated as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.68 (s, 1H), 7.82–7.80 (m, 2H), 7.70–7.66 (m, 1H), 7.54–7.50 (m, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.3, 181.2, 158.9, 146.2 (q, *J* = 2.3 Hz), 143.0, 141.7 (q, *J* = 2.9 Hz), 136.3, 134.9, 132.1 (q, *J* = 36.6 Hz), 129.6, 129.1, 120.2 (q, *J* = 272.0 Hz), 63.3, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –54.9; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd. for $C_{16}H_{11}F_3O_4SNa$ 379.0222, found 379.0239.

3-Benzoyl-5-(hydroxymethyl)-4-(trifluoromethyl)thiophene-2-carbaldehyde: **51** (16 mg, Y = 47 % for 2 steps, R_f = 0.1 (PE/EA = 4:1)) was isolated as a faint yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.57 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 5.09 (s, 2H), 3.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.7, 181.1, 159.8 (q, *J* = 3.0 Hz), 146.0 (q, *J* = 2.3 Hz), 139.2, 136.5, 134.9, 129.8, 129.0, 124.5 (q, *J* = 35.5 Hz), 121.9 (q, *J* = 271.2 Hz), 59.4 (q, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = –55.5; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{14}H_{10}F_3O_3S$ 315.0297, found 315.0311.

Characterization Data of Substrates S2–3, S5, S7–9, S12, S20, and S21: Methyl 4-(4-Bromophenyl)-4-oxobut-2 ynoate. Compound **S2** (R_f = 0.55 (PE/EA = 6:1)) was isolated as a white solid; m.p. 39.5–40.4 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=174.8,152.3,134.2,132.2,130.9,130.7,80.3,79.4,53.4;HRMS(ESI)*m/z*: $[M + H]^+$ calcd. for $C_{11}H_8BrO_3$ 266.9651, found 266.9664.

Methyl 4-Oxo-4-(*p*-tolyl)but-2-ynoate: Compound **S3** (R_f = 0.5 (PE/EA = 6:1)) was isolated as a white solid; m.p. 46.0–47.5 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 3.89 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.4, 152.6, 146.5, 133.2, 129.7, 129.5, 80.1, 79.6, 53.3, 21.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{12}H_{11}O_3$ 203.0703, found 203.0711.

Methyl 4-(4-Nitrophenyl)-4-oxobut-2-ynoate: Compound **S5** (R_f = 0.5 (PE/EA = 6:1)) was isolated as a white solid; m.p. 68.8–69.6 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.34 (d, *J* = 8.9 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.3, 152.2, 151.4, 139.4, 130.7, 124.1, 81.6, 78.9, 53.7; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{11}H_8NO_5$ 234.0397, found 234.0401.

Methyl 4-(Furan-2-yl)-4-oxobut-2-ynoate: Compound **S7** (R_f = 0.4 (PE/EA = 6:1)) was isolated as an orange red oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.76 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.47 (dd, *J* = 3.9, 0.9 Hz, 1H), 6.66 (dd, *J* = 3.7, 1.7 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.0, 152.3, 152.0, 149.2, 122.8, 113.1, 78.9, 78.4, 53.3; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_9H_7O_4$ 179.0339, found 179.0346.

***tert*-Butyl 4-Oxo-4-phenylbut-2-ynoate**: Compound **S8** (R_f = 0.6 (PE/EA = 6:1)) was isolated as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.14–8.07 (m, 2H), 7.71–7.61 (m, 1H), 7.56–7.45 (m, 2H), 1.56 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.3, 151.0, 135.5, 134.9, 129.6, 128.7, 85.3, 81.7, 77.8, 27.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{14}H_{15}O_3$ 231.1016, found 231.1024.

***N*-Methyl-4-oxo-*N*,4-diphenylbut-2-ynamide**: Compound **S9** (R_f = 0.15 (PE/EA = 6:1)) was isolated as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71–7.67 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.51–7.34 (m, 7H), 3.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.2, 152.0, 141.8, 135.6, 134.6, 129.6, 129.4, 128.6, 128.5, 127.2, 84.9, 82.1, 36.6; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{17}H_{14}NO_2$ 246.1019, found 246.1030.

Hexacos-13-yne-12,15-dione: Compound **S12** (R_f = 0.7 (PE/EA = 30:1)) was isolated as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ = 2.57 (t, *J* = 7.4 Hz, 4H), 1.73–1.54 (m, 4H), 1.33–1.12 (m, 32H), 0.82 (t, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 186.2, 84.1, 45.1, 31.8, 29.5 (2C), 29.3, 29.2 (2C), 28.8, 23.4, 22.6, 14.0; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{26}H_{47}O_2$ 391.3571, found 391.3563.

1-(2,6-Dichlorophenyl)prop-2-yn-1-one: Compound **S20** (R_f = 0.5 (PE/EA = 6:1)) was isolated as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.36–7.31 (m, 3H), 3.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.2, 137.2, 131.4, 131.2, 128.3, 82.9, 81.0; HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_9H_5Cl_2O$ 198.9712, found 198.9720.

Tetradec-1-yn-3-one: Compound **S21** (R_f = 0.7 (PE/EA = 6:1)) was isolated as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ = 3.21 (s, 1H), 2.58 (t, *J* = 7.4 Hz, 2H), 1.73–1.59 (m, 2H), 1.36–1.19 (m, 16H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 187.3, 81.3, 78.2, 45.3, 31.8, 29.5, 29.3, 29.2 (2C), 28.8, 23.6, 22.6, 14.0, (1C missing); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd. for $C_{14}H_{24}ONa$ 231.1719, found 231.1728.

Characterization Data of Pyridinium 1,4-Zwitterionic Thiolates 1b, 1d–h: 3-(4-(Dimethylamino)pyridin-1-ium-1-yl)-1,4-dimethoxy-1,4-dioxobut-2-ene-2-thiolate. Compound **1b** was isolated as a yellow solid, m.p. > 200 °C. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ = 7.95

(d, J = 7.2 Hz, 2H), 6.96 (d, J = 7.6 Hz, 2H), 3.66 (s, 3H), 3.51 (s, 3H), 3.20 (s, 6H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ = 177.9, 169.6, 161.5, 155.9, 145.6, 122.7, 107.2, 51.8, 51.3, 39.9; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{13}H_{17}N_2O_4S$ 297.0904, found 297.0900.

1,4-Dimethoxy-3-(4-methoxypyridin-1-ium-1-yl)-1,4-dioxobut-2-ene-2-thiolate: Compound **1d** was isolated as a yellow solid, m.p. 161–162 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ = 8.62 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 4.12 (s, 3H), 3.70 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ = 178.1, 170.8, 169.3, 160.7, 150.0, 123.6, 113.1, 58.1, 52.0, 51.5; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{12}H_{14}NO_5S$ 284.0587, found 284.0584.

1,4-Diethoxy-3-(4-methoxypyridin-1-ium-1-yl)-1,4-dioxobut-2-ene-2-thiolate: Compound **1e** was isolated as a yellow solid, m.p. 144–145 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ = 8.62 (d, J = 6.8 Hz, 2H), 7.56 (d, J = 7.2 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 4.12 (s, 3H), 4.03 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ = 177.9, 170.6, 168.7, 160.3, 150.1, 123.8, 113.0, 60.6, 60.0, 58.1, 14.3, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{14}H_{18}NO_5S$ 312.0900, found 312.0897.

3-(4-Methoxypyridin-1-ium-1-yl)-1,4-dioxo-1,4-diphenylbut-2-ene-2-thiolate: Compound **1f** was isolated as a yellow solid, m.p. 175–176 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ = 8.92 (d, J = 7.2 Hz, 2H), 7.98–7.86 (m, 2H), 7.59–7.50 (m, 3H), 7.44 (t, J = 7.2 Hz, 2H), 7.31–7.25 (m, 1H), 7.25–7.20 (m, 2H), 7.20–7.12 (m, 2H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ = 191.2, 191.1, 181.6, 170.6, 150.2, 139.1, 135.8, 135.4, 132.0, 130.1, 129.1, 128.0, 128.0, 127.2, 112.9, 58.1; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{22}H_{18}NO_3S$ 376.1002, found 376.1000.

4-Methoxy-3-(4-methoxypyridin-1-ium-1-yl)-1,4-dioxo-1-phenylbut-2-ene-2-thiolate: Compound **1g** is a yellow solid, m.p. 169–170 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ = 8.83 (d, J = 3.6 Hz, 2H), 8.00–7.92 (m, 2H), 7.66–7.60 (m, 2H), 7.58–7.52 (m, 1H), 7.50–7.44 (m, 2H), 4.14 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ = 191.0, 185.9, 170.7, 160.8, 150.1, 135.6, 132.2, 129.2, 128.2, 123.9, 113.0, 58.1, 51.10; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{17}H_{16}NO_4S$ 330.0795, found 330.0791.

1-Ethoxy-4,4,4-trifluoro-3-(4-methoxypyridin-1-ium-1-yl)-1-oxobut-2-ene-2-thiolate: Compound **1h** was isolated as a yellow solid, m.p. 121–122 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ = 8.70 (d, J = 7.2 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H), 4.20–4.10 (m, 5H), 1.22 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ = 171.8, 168.6, 167.5, 150.8, 122.6 (q, J = 267.3 Hz), 116.8 (q, J = 35.8 Hz), 114.1, 60.9, 58.4, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{12}H_{13}F_3NO_3S$ 308.0563, found 308.0560.

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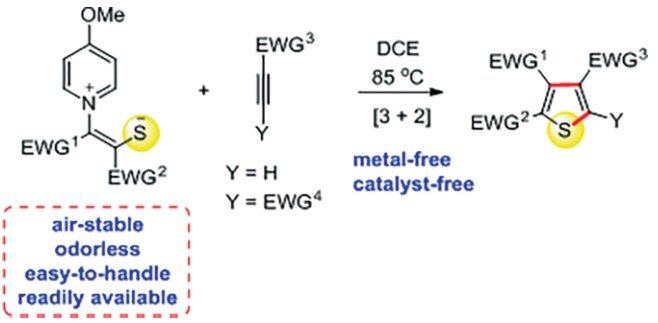

Pyridinium 1,4-zwitterionic thiolates as a class of sulfur-containing synthons were applied to a [3+2] cascade cyclization reaction with activated alkynes, affording a library of polysubstituted thiophenes with excellent regioselectivities, especially those bearing multifarious fluorine-containing groups.

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