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Three-Component Cascade Annulation of β-Ketothioamides Promoted by CF_3CH_2OH: A Regioselective Synthesis of Tetrasubstituted Thiophenes

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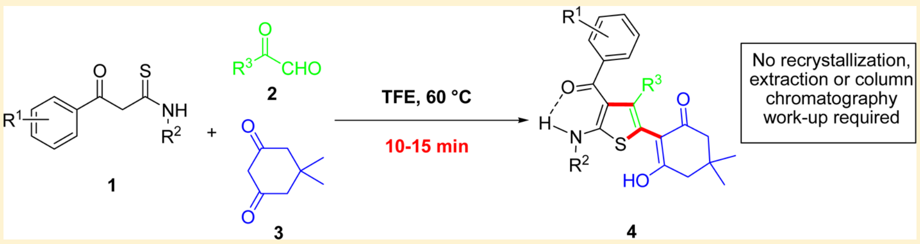
Supporting Information



ABSTRACT: A rapid and highly efficient method for the regioselective synthesis of thiophene derivatives has been developed by annulation of β-ketothioamides with arylglyoxals and 5,5-dimethyl-1,3-cyclohexanedione in CF_3CH_2OH within 15 min. The present synthesis has several desirable features, such as high regioselectivity, a concise one-pot protocol, short reaction time, and easy purification. This methodology provides an alternative approach for easy access to tetrasubstituted thiophenes via a one-pot cascade reaction without other additives.

INTRODUCTION

The thiophene core is an important privileged heterocyclic scaffold in numerous biologically active pharmacophores and natural products.[1] Some examples of them include therapeutically active substances such as allosteric agonists and modulators of the adenosine A1 receptor 2A3BTs[2] and PD81,723[3] (Figure 1). They can also be used as potent PI3K inhibitors[4] and checkpoint kinase inhibitors.[5] In addition, thiophene derivatives also have broad applications as functional materials in electrically conducting organic materials,[6] semiconductors,[7] organic light-emitting diodes (OLEDs),[8] and organic field-effect transistors (OFETs).[9]

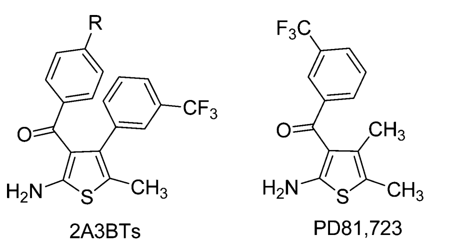


Figure 1. Biologically active thiophene-containing products.

The conventional synthetic methods for the thiophene scaffold include the Gewald,[10] Paal–Knorr,[11] and Fiesselmann[12] syntheses. Recently, a variety of protocols have been reported by a number of organic, pharmaceutical, and materials chemists.[13] Although the reported approaches are useful tools for the synthesis of thiophene derivatives, most of them suffer from significant limitations such as the utilization of elemental sulfur, harsh reaction conditions, expensive catalysts, long reaction times, and multistep syntheses or difficult purification. Therefore, the exploration of more general, efficient, rapid, and viable routes is very desirable.

A rapidly increasing recognition of the rich and fascinating chemistry of *N,S*-keteneacetals in organic synthesis has been brought out in the past decades.[14] β-Ketothioamides (KTAs) as α-oxoketene *N,S*-acetal precursors have been shown to exhibit intriguing multinucleophilic reactivities (four active centers) that determine the chemical properties of KTAs, and they have proven to be important building blocks in the construction of heterocyclic systems.[15] Because of the presence of these active centers, the reactions of KTAs with dielectrophilic reagents may proceed by four different modes[16−19] (Scheme 1), depending on the nature of the dielectrophile and the reaction conditions.

In recent years, extensive work in this area has been done on the reactivities of the nucleophilic sites (N and C atoms) of KTAs with dielectrophilic groups. However, the three-component reaction by means of mode D to form highly substituted thiophenes has not been disclosed to date.

Multicomponent reactions (MCRs)[20] involving domino processes are an important strategy that allows the generation of high levels of diversity, giving rise to complex structures by the simultaneous formation of two or more bonds from simple substrates, and provides unmatched opportunities for the

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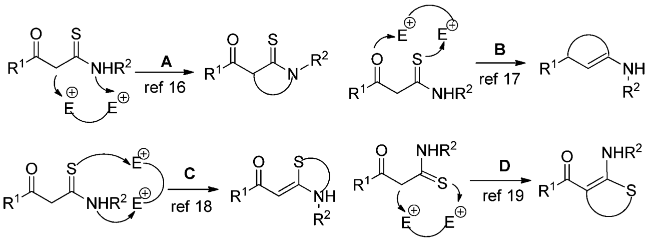
Scheme 1. Four Reaction Modes of KTAs with Dielectrophilic Reagents



expeditious increase in complexity of synthetic outcomes. Because of their unique properties, including high hydrogen-bond donor ability, low nucleophilicity, high ionizing power, and the ability to solvate water, fluorinated alcohols such as hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) have attracted much attention in modern organic synthesis.[21] In addition, the development of new environmentally benign MCRs has been recognized as one of the most important topics of green chemistry. In continuation of our research interests regarding the development of MCRs,[22] herein we report a rapid and efficient synthesis of highly substituted thiophenes by a three-component cascade reaction of KTAs, arylglyoxals, and 5,5-dimethyl-1,3-cyclohexanedione in CF_3CH_2OH without other additives.

■ RESULTS AND DISCUSSION

The reactions of *β*-ketothioamides (**1**) with arylglyoxals (**2**) and 5,5-dimethyl-1,3-cyclohexanedione (**3a**) might occur in two directions, as shown in Scheme 2. The intermediate [C] could probably undergo *S*-cyclization or *N*-cyclization, leading to the formation of thiophenes (**4**) or pyrroles (**4′**), respectively. When the above reaction mixtures were heated in EtOH, only one product isomer was obtained. However, the common characterization involving IR, ^{1}H and ^{13}C NMR, and HRMS analyses could not sufficiently identify the structure of the product as **4** or **4′**. Fortunately, we obtained a single crystal of the product **4c**, and the X-ray diffraction analysis of **4c** revealed that the obtained product was a thiophene derivative, which demonstrated that the three-component reactions showed high regioselectivity.

Encouraged by this result, we focused on exploring the optimal reaction conditions for the synthesis of thiophene compounds **4**. 3-Oxo-*N*,3-diphenylpropanethioamide (**1a**), phenylglyoxal (**2a**), and 5,5-dimethyl-1,3-cyclohexanedione (**3a**) were selected as the test substrates. The various attempts are summarized in Table 1. Initially, the above three-component reaction was carried out in EtOH without any catalysts, and the target compound **4a** was obtained in only a trace amount even after 10 h at room temperature, while in refluxing EtOH only a 40% yield of **4a** was obtained (Table 1, entries 1 and 2).

Next, different organic bases such as Et_3N and DABCO were employed as the catalyst, but no reactions occurred (Table 1, entries 3 and 4). Next, an inorganic base, NaOH, was used as the catalyst. Unfortunately, the reaction system became a complex mixture and did not give the desired product **4a** (Table 1, entry 5). Then an organic acid, AcOH, was examined as the catalyst for this reaction. Delightedly, the reaction gave the product **4a** in 60% yield after 3 h in refluxing EtOH (Table 1, entry 6). Thus, other acids such as HCOOH and HCl were also tested as the catalyst. However, their catalytic efficiency was inferior to that of AcOH (Table 1, entries 7 and 8). To our surprise, when 5.0 equiv of AcOH was employed without other solvent or catalyst at 80 °C, the reaction afforded **4a** in a yield of 74% within 12 min (Table 1, entry 9). Consequently, the reaction was carried out in AcOH at 80 °C. Excitingly, the yield of **4a** was improved to 81% within 8 min (Table 1, entry 10). These results made us consider that the hydrogen-bonding effect of AcOH as a protic solvent may be the key factor in promoting the reaction rather than its action as an acidic catalyst. Thus, two polar aprotic solvents such as CH_2Cl_2 and CH_3CN were used. As expected, they did not afford satisfactory results (Table 1, entries 11 and 12). Therefore, we decided to use various polar protic solvents to evaluate the hypothesis. The use of less polar CF_3COOH as the solvent did not give a satisfactory result (Table 1, entry 13). Next, the model reaction was performed in refluxing CH_3OH, but the corresponding product was obtained in only 58% yield, even when the reaction time was prolonged (Table 1, entry 14). The use of H_2O as the

Scheme 2. Regioselectivity of the Reaction

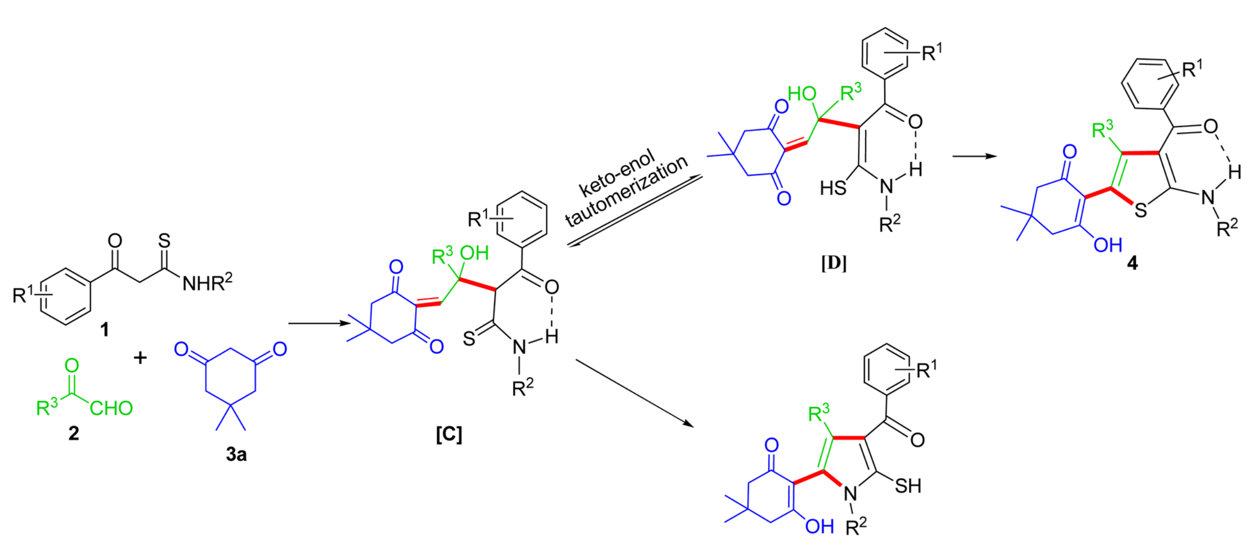
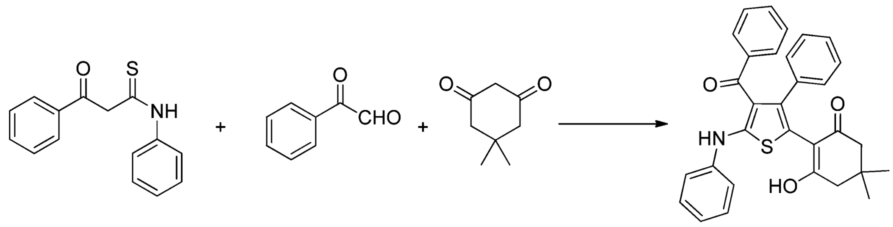


Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a 4a

Entry	Catalyst (equiv)	Solvent	T (°C)	t (min)	Yield (%)[b]
1	—	EtOH	r.t.	10 h	trace
2	—	EtOH	reflux	10 h	40
3	Et_3N (1.0)	EtOH	reflux	3 h	NR[c]
4	DABCO (1.0)	EtOH	reflux	3 h	NR[c]
5	NaOH (1.0)	EtOH	reflux	3 h	complex mixture
6	AcOH (1.0)	EtOH	reflux	3 h	60
7	HCOOH (1.0)	EtOH	reflux	3 h	36
8	HCl (1.0)	EtOH	reflux	3 h	23
9	AcOH (5.0)	—	80 °C	12 min	74
10	—	AcOH	80 °C	8 min	81
11	—	CH_2Cl_2	reflux	15 min	45
12	—	CH_3CN	reflux	10 min	47
13	—	CF_3COOH	reflux	5 min	52
14	—	CH_3OH	reflux	12 min	58
15	—	H_2O	reflux	30 min	NR[c]
16	—	TFE	reflux	15 min	89
17	—	HFIP	reflux	12 min	63
18	—	**TFE**	**60 °C**	**15 min**	**94**
19	—	TFE	40 °C	45 min	78

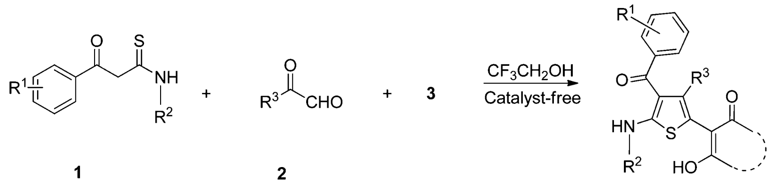
[a]Reaction conditions: The mixture of **1a** (0.5 mmol), **2a** (0.6 mmol), **3a** (0.5 mmol), and solvent (2 mL) was stirred in a 25 mL flask. [b]Isolated yields of the product after washing with EtOH/H_2O (1:1). [c]No reaction.

solvent shut down the reaction because of its poor ability to dissolve the substrates (Table 1, entry 15). To our delight, the use of boiling CF_3CH_2OH (TFE) as the solvent gave an excellent yield of 89% (Table 1, entry 16). However, the more polar $(CF_3)_2CHOH$ (HFIP) gave a lower yield of 63% (Table 1, entry 17). Obviously, screening of the solvents revealed that TFE turned out to be an appropriate solvent, as it not only resulted in a shorter reaction time but also provided a higher yield than the other examined solvents. Next, different reaction temperatures were investigated, and the results showed 60 °C to be suitable (Table 1, entries 18 and 19). Consequently, the best reaction conditions were achieved by employing **1a**, **2a**, and **3a** in TFE at 60 °C without other additives, and the precipitate needed only to be washed with EtOH/H_2O (1:1) to provide the pure product **4a** in an excellent yield of 94%.

With the optimal conditions in hand, we commenced exploring the substrate scope. The results are summarized in Table 2. As can be seen, a wide range of β-aroylthioacetanilides and arylglyoxals were well-tolerated, and in all cases the reactions proceeded smoothly to afford the corresponding thiophenes in moderate to good yields. β-Aroylthioacetanilides **1b−i** with either monosubstituted electron-donating or electron-withdrawing groups (R^1) on the aroyl group showed similar reactivities and reacted efficiently to yield the desired products (Table 2, entries 2−9). Even extremely electron-rich β-aroylthioacetanilides such as **1j** reacted smoothly, but the product **4j** was formed in relatively low yield (Table 2, entry 10). When disubstituted and trisubstituted β-aroylthioacetanilides **1k−n** were used, the reactions gave moderate yields (Table 2, entries 11−14). However, β-aroylthioamides **1o−s** bearing either electron-donating or electron-withdrawing substituents (R^2) on the *N*-aryl group afforded lower yields than those on the aroyl (R^1) group, which should be related to electronic effects (Table 2, entries 15−19). In addition, β-aroylthioamides bearing an electron-donating or an electron-withdrawing group at the *para* position on the aroyl and *N*-aryl groups, such as **1t** and **1u**, were also applied to the protocol successfully, but the corresponding products were obtained in lower yields than the corresponding β-aroylthioamides bearing only a single substituent at the *para* position on the aroyl or *N*-aryl group (Table 2, entries 20 and 21). *N*-Benzyl-3-oxo-3-phenylpropanethioamide (**1v**) was also employed and afforded the desired product **4v** (Table 2, entry 22).

To further broaden the scope of this three-component reaction, we also focused on employing arylglyoxals bearing various substituents (R^3) in this protocol. To our delight, arylglyoxal derivatives containing *m*-chloro, *p*-chloro, and *p*-methoxy substituents gave the corresponding thiophene derivatives in good yields (Table 2, entries 23−25). However, when an arylglyoxal with an *o*-chloro group was employed, the reaction system became a complex mixture and did not give the desired product, which might be due to steric hindrance (Table 2, entry 26). Unfortunately, when the aliphatic pyruvaldehyde was used, this reaction did not occur (Table 2, entry 27), and employing *N*-unsubstituted 3-oxo-3-phenylpropanethioamide resulted in a mixture without the desired product (Table 2, entry 28).

Table 2. Substrate Scope for the Synthesis of Thiophenes[a]



1 2 4

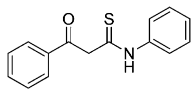
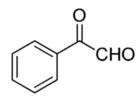
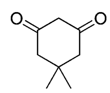
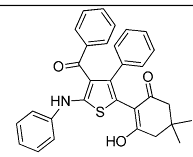
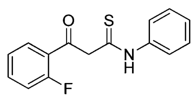
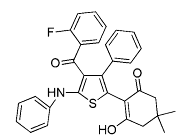
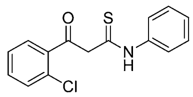
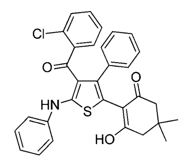
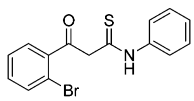
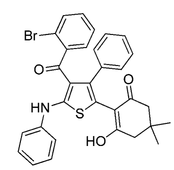
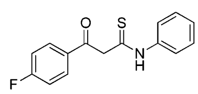
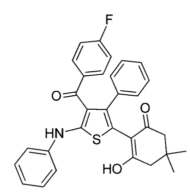
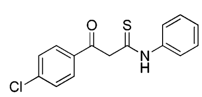
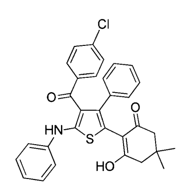
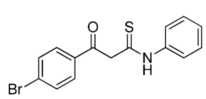
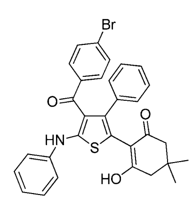
Entry	1	2	3	4	Time (min)	Yield (%)[b]
1	 1a	 2a	 3a	 4a	15	94
2	 1b	2a	3a	 4b	10	89
3	 1c	2a	3a	 4c	10	92
4	 1d	2a	3a	 4d	15	93
5	 1e	2a	3a	 4e	12	92
6	 1f	2a	3a	 4f	12	90
7	 1g	2a	3a	 4g	10	92

Table 2. continued

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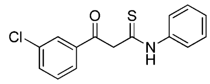
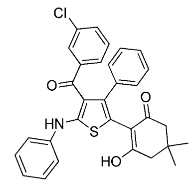
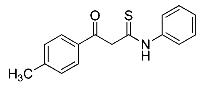
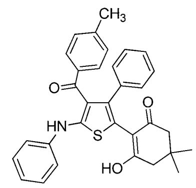
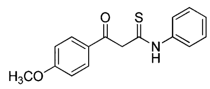
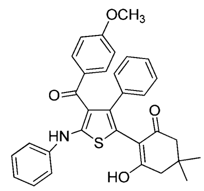
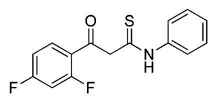
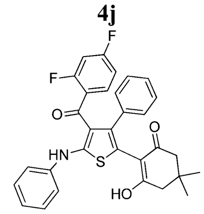
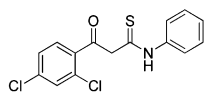
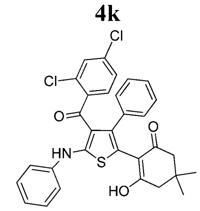
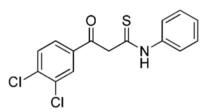
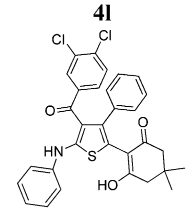
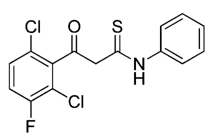
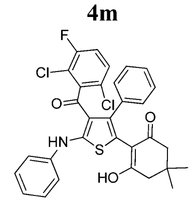
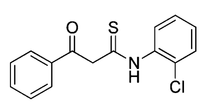
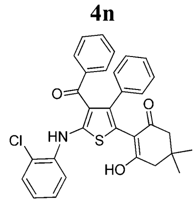
8	 **1h**	**2a**	**3a**	 **4h**	12	89
9	 **1i**	**2a**	**3a**	 **4i**	15	88
10	 **1j**	**2a**	**3a**	 **4j**	12	85
11	 **1k**	**2a**	**3a**	 **4k**	10	79
12	 **1l**	**2a**	**3a**	 **4l**	12	81
13	 **1m**	**2a**	**3a**	 **4m**	10	84
14	 **1n**	**2a**	**3a**	 **4n**	15	73
15	 **1o**	**2a**	**3a**	 **4o**	12	72

Table 2. continued

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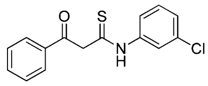
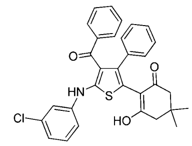
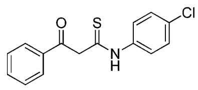
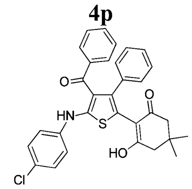
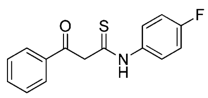
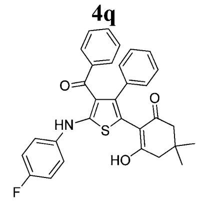
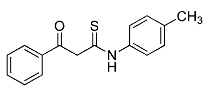
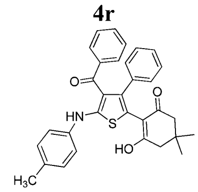
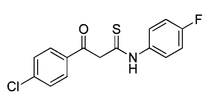
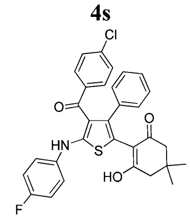
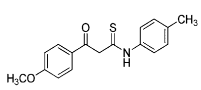
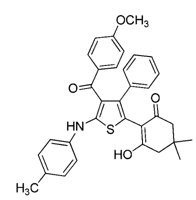
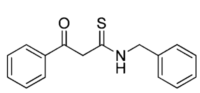
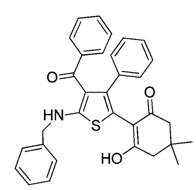
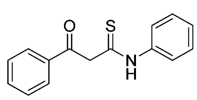
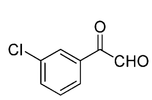
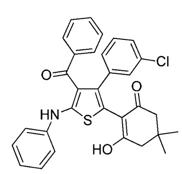
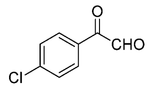
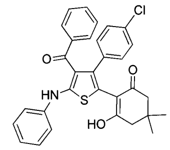
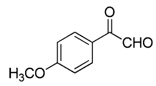
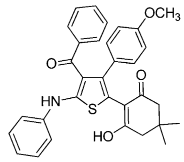
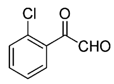
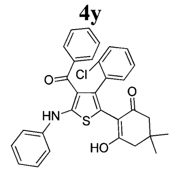
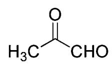
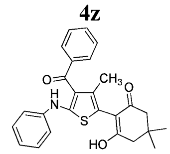
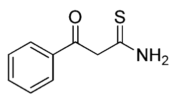
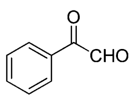
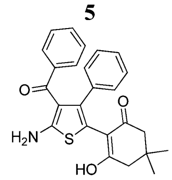
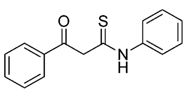
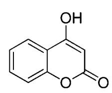
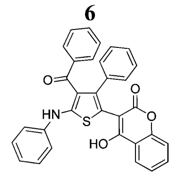
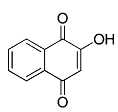
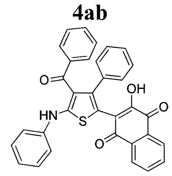
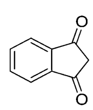
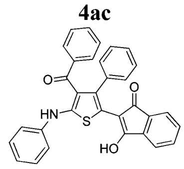
16	 **1p**	**2a**	**3a**	 **4p**	12	68
17	 **1q**	**2a**	**3a**	 **4q**	14	70
18	 **1r**	**2a**	**3a**	 **4r**	12	73
19	 **1s**	**2a**	**3a**	 **4s**	12	58
20	 **1t**	**2a**	**3a**	 **4t**	12	69
21	 **1u**	**2a**	**3a**	 **4u**	12	52
22	 **1v**	**2a**	**3a**	 **4v**	10	63
23	 **1a**	 **2b**	**3a**	 **4w**	10	89

Table 2. continued

Entry	1	2	3	4	Time (min)	Yield (%)[b]
24	**1a**	 **2c**	**3a**	 **4x**	10	90
25	**1a**	 **2d**	**3a**	 **4y**	12	87
26	**1a**	 **2e**	**3a**	 **4z**	30	0
27	**1a**	 **2f**	**3a**	 **5**	30	0
28	 **1w**	 **2a**	**3a**	 **6**	30	0
29	 **1a**	**2a**	 **3b**	 **4ab**	14	74
30	**1a**	**2a**	 **3c**	 **4ac**	30	0
31	**1a**	**2a**	 **3d**	 **4ad**	30	0

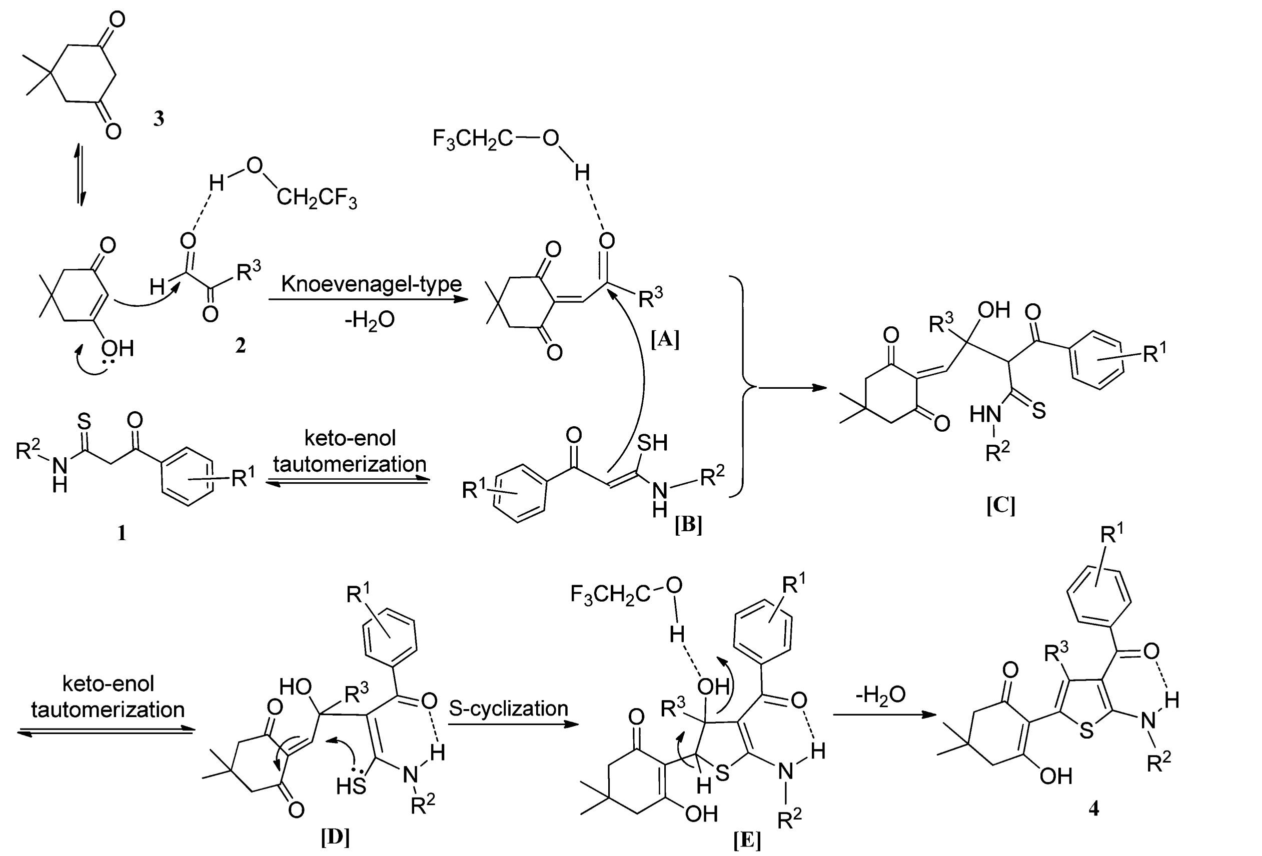
[a]Reaction conditions: compounds **1** (0.5 mmol), **2** (0.6 mmol), and **3** (0.5 mmol) in 2.0 mL of CF_3CH_2OH at 60 °C. [b]Isolated yields of the products after washing with $EtOH/H_2O$ (1:1).

Efforts were also made to expand the scope of the method to substrates **3**. 5,5-Dimethyl-1,3-cyclohexanedione (**3a**) was successfully replaced with 4-hydroxycoumarin (**3b**) in this reaction, leading to the formation of **4ab** in 74% yield within 14 min (Table 2, entry 29). Unfortunately, the attempts to replace **3a** with 2-hydroxynaphthalene-1,4-dione (**3c**) or 2*H*-indene-1,3-dione (**3d**) failed because the substrate **1a** could not react with the Knoevenagel product derived from **2a** and **3c** or **3d** (Table 2, entries 30 and 31).

It is noteworthy that all of the precipitated products needed only to be washed with $EtOH/H_2O$ (1:1) to afford the pure compounds. This ease of purification makes this methodology facile, practical, and rapid to execute.

The structures of all of the new thiophenes were identified by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra and unequivocally confirmed by X-ray diffraction analysis of a single crystal of **4c** (Figure S1 in the Supporting Information).

Scheme 3. Plausible Mechanism for the Formation of Products 4



On the basis of the above experimental results together with the related reports,[23] a plausible reaction scenario for this one-pot three-component heteroannulation is outlined in Scheme 3. In this process, TFE plays a significant role in increasing the electrophilicity of the electrophiles. The Knoevenagel-type reaction of arylglyoxals **2** with 5,5-dimethyl-1,3-cyclohexanedione **3a** results in the formation of adducts [**A**]. The *β*-aroylthioacetanilides **1** undergo a rapid keto–enol tautomerization to give intermediates [**B**]. Intermediates [**B**] then react with adducts [**A**] to generate intermediates [**C**], which undergo intramolecular *S*-cyclization to give compounds **4** with elimination of H_2O. From the crystallographic data for compound **4c**, a strong intramolecular O···H–N hydrogen bond was observed, which restricted the free rotation of NH, favoring the formation of thiophenes **4**.

■ CONCLUSION

We have successfully developed a straightforward, cheap, and environmentally friendly one-pot three-component reaction to synthesize novel highly substituted thiophene derivatives in CF_3CH_2OH within 15 min by using KTAs, arylglyoxals, and 5,5-dimethyl-1,3-cyclohexanedione. The procedure can be considered as an ideal means for the synthesis of thiophenes because of the following features: (1) the rapid production of thiophenes by the three-component process, which minimizes the generation of waste; (2) no need for the use of any acid, base, transition-metal catalyst, or other additives; (3) easy workup method without extensive purification procedures such as recrystallization, column chromatography, and extraction; (4) high atom economy and an ecologically benign process in which only two molecules of water are lost. These advantages make this process suitable for broad application for the synthesis of thiophenes. Further investigations to expand the scope of KTAs as versatile building blocks are in progress and will be reported in due course.

■ EXPERIMENTAL SECTION

General Procedure for the Synthesis of Products 4 (Exemplified by 4a). A mixture of 3-oxo-*N*,3-diphenylpropanethioamide (**1a**) (0.5 mmol, 0.128 g), phenylglyoxal (**2a**) (0.6 mmol, 0.080 g), and 5,5-dimethyl-1,3-cyclohexanedione (**3a**) (0.5 mmol, 0.070 g) was stirred for 15 min in TFE (2 mL) at 60 °C. After completion of the reaction as indicated by TLC (petroleum ether/EtOAc, 2:1 v/v), the mixture was cooled to room temperature, and the solid product was filtered, washed with EtOH/H_2O (1:1), and subsequently dried to give the pure product **4a**.

*2-(4-Benzoyl-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4a**).* Isolated yield 232 mg (94%); yellow solid; mp 239–241 °C. IR (KBr, cm^{-1}) ν: 3445, 1622, 1599, 1586, 1540, 1252, 741, 698. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.40 (s, 1H), 7.39–7.44 (m, 4H), 7.29 (s, 1H), 7.13–7.16 (m, 1H), 7.07–7.10 (t, J = 7.37 Hz, 1H), 6.90–6.97 (m, 8H), 5.92 (s, 1H), 2.33 (s, 2H), 2.19 (s, 2H), 0.98 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 197.3, 193.2, 172.3, 163.5, 141.4, 140.3, 139.8, 135.2, 130.3, 129.6, 129.4, 128.7, 127.7, 127.2, 127.1, 124.2, 120.0, 116.7, 109.4, 108.7, 50.8, 41.5, 31.6, 28.2. HRMS (ESI–TOF, $[M + H]^+$): calcd for $C_{31}H_{28}NO_3S$, 494.1790; found, 494.1790.

*2-(4-(2-Fluorobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5-methylcyclohex-2-enone (**4b**).* Isolated yield 227 mg (89%); yellow solid; mp 234–236 °C. IR (KBr, cm^{-1}) ν: 3446, 1626, 1597, 1585, 1545, 1403, 751, 703. ^1H NMR ($CDCl_3$, 500 MHz) δ: 11.98 (s, 1H), 7.41–7.43 (m, 4H), 6.97–7.16 (m, 3H), 6.88 (s, 5H), 6.76–6.77 (m, 1H), 6.51–6.54 (m, 1H), 6.25 (s, 1H), 2.20 (s, 4H), 0.87 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 197.0, 188.3, 172.6, 164.9, 158.3 ($^1J_{C-F}$ = 248.9 Hz), 141.7, 140.0, 134.6, 131.2 ($^3J_{C-F}$ = 8.0

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Hz), 129.6, 129.4, 129.2, 129.1, 127.3, 127.1, 124.6, 123.3, 120.4, 117.0, 115.2 ($^2J_{C-F}$ = 21.6 Hz), 109.3, 108.4, 50.5, 41.5, 31.5, 28.2. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SF$, 512.1696; found, 512.1686.

*2-(4-(2-Chlorobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4c**).* Isolated yield 237 mg (90%); yellow solid; mp 234−236 °C. IR (KBr, cm^{-1}) ν: 3445, 1624, 1597, 1542, 1492, 851, 754, 701. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 12.09 (s, 1H), 7.40−7.46 (m, 4H), 7.16−7.19 (m, 1H), 6.89−6.97 (m, 8H), 6.79−6.82 (m, 1H), 6.13 (s, 1H), 2.20 (s, 2H), 2.14 (s, 2H), 0.84 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.1, 190.3, 172.8, 165.4, 141.8, 140.1, 139.7, 134.9, 130.8, 129.9, 129.7, 129.3, 129.2, 127.4, 127.2, 125.9, 124.8, 120.5, 116.6, 109.5, 108.5, 50.6, 41.6, 31.6, 28.1. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3ClS$, 528.1400; found, 528.1418.

*2-(4-(2-Bromobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4d**).* Isolated yield 260 mg (91%); yellow solid; mp 247−249 °C. IR (KBr, cm^{-1}) ν: 3441, 1626, 1598, 1586, 1545, 1492, 1245, 851, 791, 754, 701. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 12.06 (s, 1H), 7.40−7.46 (m, 4H), 7.16−7.19 (m, 2H), 6.82−6.91 (m, 8H), 6.23 (s, 1H), 2.19 (s, 2H), 2.15 (s, 2H), 0.84 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.1, 190.9, 172.8, 165.4, 141.6, 141.3, 140.0, 134.8, 132.4, 129.8, 129.6, 129.3, 127.3, 127.0, 126.3, 124.7, 120.4, 119.9, 116.2, 109.5, 108.4, 50.5, 41.5, 31.5, 28.0. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SBr$, 572.0895; found, 572.0889.

*2-(4-(4-Fluorobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4e**).* Isolated yield 235 mg (92%); yellow solid; mp 251−253 °C. IR (KBr, cm^{-1}) ν: 3432, 1600, 1582, 1540, 1253, 847, 784, 751, 700. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.33 (s, 1H), 7.39−7.43 (m, 4H), 7.29−7.30 (m, 2H), 7.14−7.16 (m, 1H), 6.88−7.00 (m, 5H), 6.61−6.64 (t, J = 8.33 Hz, 2H), 5.95 (s, 1H), 2.33 (s, 2H), 2.19 (s, 2H), 0.98 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.3, 191.6, 172.4, 163.8 ($^1J_{C-F}$ = 251.4 Hz), 163.6, 141.1, 140.2, 135.9, 135.1, 131.0 ($^3J_{C-F}$ = 8.5 Hz), 129.6, 129.4, 127.8, 127.2, 124.1, 120.0, 116.5, 114.2 ($^2J_{C-F}$ = 21.9 Hz), 109.6, 108.5, 50.7, 41.5, 31.5, 28.3. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3FS$, 512.1696; found, 512.1690.

*2-(4-(4-Chlorobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4f**).* Isolated yield 237 mg (90%); yellow solid; mp 241−242 °C. IR (KBr, cm^{-1}) ν: 3442, 1596, 1542, 1491, 1450, 1251, 856, 838, 777, 754, 728, 701. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.43 (s, 1H), 7.39−7.44 (m, 4H), 7.15−7.20 (m, 3H), 6.99−7.02 (m, 1H), 6.87−6.96 (m, 6H), 5.92 (s, 1H), 2.33 (s, 2H), 2.19 (s, 2H), 0.98 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.3, 191.6, 172.3, 164.1, 141.1, 140.1, 138.1, 136.3, 129.9, 129.6, 129.4, 127.8, 127.4, 127.2, 124.4, 120.1, 116.4, 109.5, 108.5, 50.7, 41.5, 31.6, 28.2. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3ClS$, 528.1400; found, 528.1408.

*2-(4-(4-Bromobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4g**).* Isolated yield 263 mg (92%); yellow solid; mp 237−239 °C. IR (KBr, cm^{-1}) ν: 3447, 1623, 1596, 1581, 1542, 1250, 855, 755, 701. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.44 (s, 1H), 7.40 (s, 4H), 6.99−7.14 (m, 6H), 6.92 (s, 2H), 6.84 (s, 2H), 6.28 (s, 1H), 2.29 (s, 2H), 2.18 (s, 2H), 0.95 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.5, 191.7, 172.6, 164.1, 141.1, 140.0, 138.5, 135.0, 130.3, 130.1, 129.6, 129.4, 127.8, 127.2, 124.8, 124.4, 120.0, 116.4, 109.6, 108.4, 50.6, 41.5, 31.6. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SBr$, 572.0895; found, 572.0886.

*2-(4-(3-Chlorobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4h**).* Isolated yield 235 mg (89%); yellow solid; mp 236−238 °C. IR (KBr, cm^{-1}) ν: 3440, 1620, 1596, 1583, 1544, 1251, 837, 777, 754, 702. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.41 (s, 1H), 7.41 (s, 4H), 7.16−7.18 (m, 3H), 6.86−6.99 (m, 7H), 6.01 (s, 1H), 2.31 (s, 2H), 2.18 (s, 2H), 0.97 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.4, 191.6, 172.4, 164.0, 141.1, 140.1, 138.1, 136.3, 135.1, 130.0, 129.6, 129.4, 127.8, 127.4, 127.2, 124.4, 120.1, 116.4, 109.6, 108.5, 50.7, 41.5, 31.6, 28.3. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}ClNO_3S$, 528.1400; found, 528.1390.

*3-Hydroxy-5,5-dimethyl-2-(4-(4-methylbenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)cyclohex-2-enone (**4i**).* Isolated yield 223 mg (88%); yellow solid; mp 225−227 °C. IR (KBr, cm^{-1}) ν: 3442, 1625, 1599, 1582, 1543, 1255, 778, 754, 701. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.24 (s, 1H), 7.36−7.42 (m, 4H), 7.17−7.19 (d, J = 7.55 Hz, 2H), 7.10−7.13 (t, J = 6.70 Hz, 1H), 6.89−6.91 (m, 5H), 6.72−6.74 (d, J = 7.50 Hz, 2H), 5.96 (s, 1H), 2.32 (s, 2H), 2.15 (s, 5H), 0.98 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.4, 193.1, 172.3, 162.8, 141.4, 140.8, 136.9, 135.3, 129.5, 129.4, 128.9, 127.8, 127.6, 126.8, 123.9, 119.7 117.0, 109.3, 108.6, 50.7, 41.5, 31.5, 28.0, 21.3. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{32}H_{30}NO_3S$, 508.1946; found, 508.1952.

*3-Hydroxy-2-(4-(4-methoxybenzoyl)-3-phenyl-5-(phenylamino)-thiophen-2-yl)-5,5-dimethylcyclohex-2-enone (**4j**).* Isolated yield 222 mg (85%); yellow solid; mp 232−233 °C. IR (KBr, cm^{-1}) ν: 3442, 1624, 1600, 1581, 1541, 1251, 840, 784, 755, 702. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.02 (s, 1H), 7.35−7.40 (m, 4H), 7.29−7.30 (d, J = 8.60 Hz, 2H), 7.08−7.11 (m, 1H), 6.92−6.94 (m, 5H), 6.44−6.45 (d, J = 8.60 Hz, 2H), 6.02 (s, 1H), 3.67 (s, 3H), 2.34 (s, 2H), 2.19 (s, 2H), 0.99 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.6, 192.1, 172.5, 162.2, 161.5, 141.3, 140.3, 135.2, 132.1, 129.5, 129.4, 127.7, 127.1, 123.4, 119.5, 117.1, 112.5, 109.3, 108.6, 55.2, 50.7, 41.5, 31.6. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{32}H_{30}NO_4S$, 524.1896; found, 524.1886.

*2-(4-(2,4-Difluorobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4k**).* Isolated yield 209 mg (79%); yellow solid; mp 237−238 °C. IR (KBr, cm^{-1}) ν: 3440, 1599, 1572, 1547, 1499, 1258, 849, 756, 703. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.90 (s, 1H), 7.41−7.43 (m, 4H), 7.17 (m, 1H), 6.88−7.07 (m, 6H), 6.49 (m, 1H), 6.24−6.26 (m, 1H), 6.15 (s, 1H), 2.22 (s, 2H), 2.17 (s, 2H), 0.88 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.0, 187.0, 172.6, 165.1, 140.7 ($^1J_{C-F}$ = 198.2 Hz), 134.6, 130.7, 129.6, 128.3 ($^1J_{C-F}$ = 257.5 Hz), 127.5, 125.6, 124.8, 120.4, 116.9, 110.6 ($^2J_{C-F}$ = 20.7 Hz), 109.5, 108.4, 103.7, 103.5, 103.3, 50.6, 41.5, 31.5, 28.0. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{26}NO_3SF_2$, 530.1601; found, 530.1612.

*2-(4-(2,4-Dichlorobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4l**).* Isolated yield 227 mg (81%); yellow solid; mp 233−235 °C. IR (KBr, cm^{-1}) ν: 3443, 1626, 1584, 1537, 1450, 1260, 857, 782, 733, 701. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 12.05 (s, 1H), 7.40−7.46 (m, 4H), 7.17−7.20 (t, J = 6.75 Hz, 1H), 6.98−7.14 (m, 1H), 6.83−6.94 (m, 6H), 6.76−6.78 (m, 1H), 6.17 (s, 1H), 2.19 (s, 4H), 0.84 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 196.8, 189.0, 172.7, 165.6, 141.4, 139.9, 138.2, 135.0, 134.8, 131.7, 129.9, 129.6, 129.1, 127.5, 127.1, 126.1, 124.9, 120.5, 116.6, 108.4, 50.6, 41.6, 31.5, 28.0. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{26}NO_3SCl_2$, 562.1010; found, 562.1021.

*2-(4-(3,4-Dichlorobenzoyl)-3-phenyl-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4m**).* Isolated yield 236 mg (84%); yellow solid; mp 213−214 °C. IR (KBr, cm^{-1}) ν: 3446, 1624, 1597, 1577, 1545, 754, 702. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.48 (s, 1H), 7.36−7.42 (m, 4H), 7.23 (s, 1H), 7.16−7.18 (m, 1H), 7.10−7.12 (d, J = 8.05 Hz, 1H), 7.03−7.04 (d, J = 8.15 Hz, 1H), 6.98−6.99 (m, 3H), 6.88 (s, 2H), 6.12 (s, 1H), 2.29 (s, 2H), 2.18 (s, 2H), 0.96 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.3, 189.9, 172.5, 164.8, 140.9, 139.9, 139.4, 135.0, 134.2, 131.3, 130.7, 129.7, 129.4, 129.1, 127.9, 127.4, 127.3, 124.7, 120.3, 116.1, 109.8, 108.3, 50.6, 41.5, 31.5. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{26}NO_3SCl_2$, 562.1010; found, 562.1015.

*2-(4-(2,6-Dichloro-3-fluorobenzoyl)-3-phenyl-5-(phenylamino)-thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4n**).* Isolated yield 211 mg (73%); yellow solid; mp 274−276 °C. IR (KBr, cm^{-1}) ν: 3445, 1616, 1597, 1580, 1539, 1450, 840, 811, 754, 701. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 12.20 (s, 1H), 7.43−7.47 (m, 4H), 7.20 (m, 1H), 6.83−7.02 (m, 6H), 6.65−6.66 (m, 1H), 6.25 (s, 1H), 2.13 (s, 4H), 0.74 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 196.5, 185.2, 172.9, 166.3, 156.4 ($^1J_{C-F}$ = 250.1 Hz), 141.3, 140.0, 139.7, 134.2, 129.6, 128.5 ($^3J_{C-F}$ = 7.3 Hz), 127.7, 127.2, 127.0, 125.1, 120.7, 119.5, 119.3, 116.5 ($^2J_{C-F}$ = 22.9 Hz), 109.8, 108.2, 50.4, 41.5, 31.4, 27.8.

HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{25}NO_3SCl_2F$, 580.0916; found, 580.0924.

*2-(4-Benzoyl-5-((2-chlorophenyl)amino)-3-phenylthiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4o**).* Isolated yield 190 mg (72%); yellow solid; mp 245−247 °C. IR (KBr, cm^{-1}) ν: 3447, 1622, 1591, 1540, 1490, 1255, 766, 742, 698. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.45 (s, 1H), 7.80−7.82 (d, J = 7.85 Hz, 1H), 7.45−7.47 (d, J = 7.60 Hz, 1H), 7.27−7.33 (m, 3H), 6.90−7.09 (m, 9H), 6.12 (s, 1H), 2.33 (s, 2H), 2.18 (s, 2H), 0.98 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.5, 193.4, 172.7, 160.4, 141.3, 139.3, 137.3, 135.0, 130.7, 130.1, 129.4, 128.9, 127.7, 127.6, 127.2, 127.1, 124.1, 123.7, 118.5, 117.8, 110.6, 108.3, 50.7, 41.6, 31.6, 28.2. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SCl$, 528.1400; found, 528.1409.

*2-(4-Benzoyl-5-((3-chlorophenyl)amino)-3-phenylthiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4p**).* Isolated yield 161 mg (68%); yellow solid; mp 213−215 °C. IR (KBr, cm^{-1}) ν: 3439, 1595, 1541, 1482, 1251, 858, 776, 738, 696. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.27 (s, 1H), 7.40 (s, 1H), 7.27−7.30 (m, 4H), 7.06−7.09 (m, 2H), 6.89−6.95 (m, 7H), 6.29 (s, 1H), 2.32 (s, 2H), 2.20 (s, 2H), 0.97 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.5, 193.5, 172.7, 161.7, 141.4, 139.3, 135.3, 135.0, 130.6, 130.5, 129.4, 128.8, 127.7, 127.2, 127.1, 123.7, 119.2, 117.6, 117.4, 110.4, 108.4, 50.7, 41.6, 31.6, 28.3. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SCl$, 528.1400; found, 528.1406.

*2-(4-Benzoyl-5-((4-chlorophenyl)amino)-3-phenylthiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4q**).* Isolated yield 184 mg (70%); yellow solid; mp 218−220 °C. IR (KBr, cm^{-1}) ν: 3439, 1616, 1596, 1569, 1533, 1491, 1252, 822, 767, 697. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.32 (s, 1H), 7.34 (s, 4H), 7.25 (s, 1H), 7.07−7.10 (m, 1H), 6.88−6.96 (m, 8H), 6.10 (s, 1H), 2.32 (s, 2H), 2.19 (s, 2H), 0.98 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.6, 193.4, 172.6, 162.6, 141.4, 139.4, 138.8, 135.0, 130.5, 129.6, 129.4, 129.0, 128.7, 127.7, 127.2, 127.1, 120.8, 117.1, 109.9, 108.4, 50.7, 41.5, 31.6. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SCl$, 528.1400; found, 528.1412.

*2-(4-Benzoyl-5-((4-fluorophenyl)amino)-3-phenylthiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4r**).* Isolated yield 187 mg (73%); yellow solid; mp 243−245 °C. IR (KBr, cm^{-1}) ν: 3445, 1597, 1568, 1538, 1509, 1227, 818, 740, 698. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.21 (s, 1H), 7.38 (s, 2H), 7.24−7.26 (m, 2H), 7.07−7.09 (m, 3H), 6.87−6.95 (m, 7H), 6.15 (s, 1H), 2.30 (s, 2H), 2.17 (s, 2H), 0.96 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.4, 193.2, 172.5, 164.5, 159.6 ($^1J_{C-F}$ = 244.8 Hz), 141.5, 140.0, 136.5, 135.2, 130.3, 129.4, 128.6, 127.7, 127.2, 127.1, 122.4 ($^3J_{C-F}$ = 6.5 Hz), 116.4 ($^2J_{C-F}$ = 23.2 Hz), 109.3, 108.6, 50.7, 41.6, 31.5, 28.2. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SF$, 512.1696; found, 512.1679.

*2-(4-Benzoyl-3-phenyl-5-(p-tolylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4s**).* Isolated yield 147 mg (58%); yellow solid; mp 223−224 °C. IR (KBr, cm^{-1}) ν: 3440, 1625, 1566, 1532, 1252, 738, 699. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.34 (s, 1H), 7.31−7.32 (d, 2H, J = 8.40 Hz), 7.24−7.25 (m, 2H), 7.18−7.20 (d, J = 8.30 Hz, 2H), 7.04−7.07 (m, 1H), 6.91−6.94 (m, 2H), 6.88 (s, 5H), 5.99 (s, 1H), 2.35 (s, 3H), 2.30 (s, 2H), 2.17 (s, 2H), 0.96 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.3, 193.0, 172.3, 164.5, 141.4, 139.9, 137.8, 135.3, 134.2, 130.1, 129.4, 128.6, 127.6, 127.2, 127.0, 120.4, 116.2, 109.1, 108.7, 50.7, 41.5, 31.5, 28.2, 20.9. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{32}H_{30}NO_3S$, 508.1946; found, 508.1952.

*2-(4-(4-Chlorobenzoyl)-5-((4-fluorophenyl)amino)-3-phenylthiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4t**).* Isolated yield 188 mg (69%); yellow solid; mp 231−233 °C. IR (KBr, cm^{-1}) ν: 3442, 1588, 1538, 1509, 1227, 792, 756, 700. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.23 (s, 1H), 7.38−7.40 (m, 2H), 7.16−7.17 (m, 2H), 7.08−7.11 (m, 2H), 6.98−7.00 (m, 1H), 6.89−6.95 (m, 4H), 6.84−6.86 (m, 2H), 6.05 (s, 1H), 2.30 (s, 2H), 2.18 (s, 2H), 0.97 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.3, 191.6, 172.4, 165.2, 160.7, 141.2, 138.1, 136.3, 135.0, 129.9, 128.6 ($^1J_{C-F}$ = 187.4 Hz), 127.4, 127.3, 122.7 ($^3J_{C-F}$ = 8.2 Hz), 116.4 ($^2J_{C-F}$ = 22.8 Hz), 116.1, 109.4, 108.5, 50.7, 41.5, 31.5, 28.2. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{26}NO_3SFCl$, 546.1306; found, 546.1312.

*3-Hydroxy-2-(4-(4-methoxybenzoyl)-3-phenyl-5-(p-tolylamino)-thiophen-2-yl)-5,5-dimethylcyclohex-2-enone (**4u**).* Isolated yield 140 mg (52%); yellow solid; mp 188−190 °C. IR (KBr, cm^{-1}) ν: 3442, 1605, 1586, 1533, 1251, 843, 792, 700. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 10.99 (s, 1H), 7.29−7.31 (m, 3H), 7.28 (s, 1H), 7.17−7.18 (m, 2H), 6.92−6.94 (m, 5H), 6.44−6.45 (m, 2H), 6.04 (s, 1H), 3.67 (s, 3H), 2.34 (s, 3H), 2.33 (s, 2H), 2.19 (s, 2H), 0.99 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.6, 192.0, 172.4, 163.4, 161.4, 141.4, 137.8, 135.3, 133.9, 132.3, 131.0, 130.1, 127.7, 127.0, 120.1, 116.4, 112.5, 108.8, 108.7, 55.2, 50.7, 41.5, 31.6, 20.9. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{33}H_{32}NO_4S$, 538.2052; found, 538.2046.

*2-(4-Benzoyl-5-(benzylamino)-3-phenylthiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4v**).* Isolated yield 160 mg (63%); yellow solid; mp 197−198 °C. IR (KBr, cm^{-1}) ν: 3439, 1591, 1567, 1523, 1492, 731, 698. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 9.71−9.74 (t, 1H, J = 5.53 Hz), 7.41−7.43 (d, 2H, J = 7.30 Hz), 7.36−7.39 (m, 2H), 7.30−7.33 (m, 1H), 7.16−7.17 (d, 2H, J = 7.30 Hz), 7.00−7.03 (d, J = 7.38 Hz, 1H), 6.84−6.90 (m, 7H), 6.05 (s, 1H), 4.52−4.53 (d, 2H, J = 5.55 Hz), 2.29 (s, 2H), 2.15 (s, 2H), 0.95 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.5, 192.3, 172.3, 169.9, 141.9, 140.0, 136.4, 135.5, 129.6, 129.3, 128.8, 128.3, 127.9, 127.7, 127.4, 127.0, 126.8, 114.0, 108.8, 108.6, 51.3, 50.6, 41.5, 31.4, 28.1, 26.9. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{32}H_{30}NO_3S$, 508.1946; found, 508.1952.

*2-(4-Benzoyl-3-(3-chlorophenyl)-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4w**).* Isolated yield 235 mg (89%); yellow solid; mp 237−239 °C. IR (KBr, cm^{-1}) ν: 3445, 1615, 1599, 1553, 1252, 856, 739, 698. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.96 (s, 1H), 10.01 (s, 1H), 7.39−7.41 (m, 2H), 7.23−7.32 (m, 5H), 7.12−7.15 (t, J = 7.50 Hz, 2H), 6.96−6.99 (m, 3H), 6.82−6.84 (m, 2H), 2.18 (s, 4H), 0.86 (s, 6H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 192.3, 156.2, 142.6, 139.4, 137.7, 135.7, 131.6, 131.3, 131.1, 129.9, 129.2, 128.0, 127.5, 122.7, 121.8, 118.3, 117.9, 107.1, 31.7, 28.2. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SCl$, 528.1400; found, 528.1405.

*2-(4-Benzoyl-3-(4-chlorophenyl)-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4x**).* Isolated yield 237 mg (90%); yellow solid; mp 249−251 °C. IR (KBr, cm^{-1}) ν: 3440, 1614, 1599, 1552, 856, 740, 698. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.43 (s, 1H), 7.38−7.40 (m, 4H), 7.21−7.23 (d, J = 7.50 Hz, 2H), 7.14−7.17 (m, 2H), 6.96−6.99 (t, J = 7.50 Hz, 2H), 6.84−6.85 (m, 2H), 6.78−6.79 (d, J = 7.70 Hz, 2H), 6.05 (s, 1H), 2.29 (s, 4H), 0.98 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.4, 193.0, 172.7, 163.9, 140.2, 140.0, 139.5, 133.7, 132.9, 130.6, 130.4, 129.6, 128.6, 127.7, 127.4, 124.4, 120.0, 116.5, 109.4, 108.3, 50.5, 41.4, 31.6, 28.2. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{31}H_{27}NO_3SCl$, 528.1400; found, 528.1396.

*2-(4-Benzoyl-3-(4-methoxyphenyl)-5-(phenylamino)thiophen-2-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**4y**).* Isolated yield 228 mg (87%); yellow solid; mp 236−238 °C. IR (KBr, cm^{-1}) ν: 3443, 1622, 1599, 1544, 1245, 857, 742, 699. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.39 (s, 1H), 7.36−7.42 (m, 4H), 7.24−7.25 (m, 2H), 7.08−7.14 (m, 2H), 6.95−6.98 (t, J = 7.65 Hz, 2H), 6.78−6.79 (d, J = 8.2 Hz, 2H), 6.41−6.43 (d, J = 8.5 Hz, 2H), 6.03 (s, 1H), 3.63 (s, 3H), 2.32 (s, 2H), 2.20 (s, 2H), 0.99 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 197.5, 193.2, 172.2, 163.5, 158.6, 140.9, 140.2, 139.7, 130.6, 130.2, 129.5, 128.7, 127.5, 124.1, 119.9, 116.7, 113.3, 108.8, 108.7, 55.1, 50.7, 41.5, 31.6, 28.3. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{32}H_{30}NO_4S$, 524.1896; found, 524.1902.

*3-(4-Benzoyl-3-phenyl-5-(phenylamino)thiophen-2-yl)-4-hydroxy-2H-chromen-2-one (**4ab**).* Isolated yield 191 mg (74%); yellow solid; mp 286−288 °C. IR (KBr, cm^{-1}) ν: 3438, 1670, 1608, 1542, 1492, 1252, 753, 699. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 11.33 (s, 1H), 7.59−7.61 (d, J = 7.90 Hz, 1H), 7.52−7.55 (t, J = 7.09 Hz, 1H), 7.38−7.44 (m, 4H), 7.30−7.34 (m, 3H), 7.18−7.21 (m, 1H), 7.13−7.16 (m, 1H), 7.08−7.11 (m, 1H), 6.95−6.99 (m, 4H), 6.88−6.89 (m, 3H), 6.39 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 193.2, 163.8, 162.4, 161.4, 153.2, 142.3, 140.0, 139.5, 134.5, 132.9, 130.5, 129.6, 129.1, 128.7, 128.1, 127.5, 127.2, 124.5, 124.0, 123.7, 120.1, 116.6, 116.4, 114.2, 108.0, 98.6. HRMS (ESI−TOF, [M + H]$^+$): calcd for $C_{32}H_{22}NO_4S$, 516.1270; found, 516.1265.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^1H and ^{13}C NMR spectra of all new compounds, and X-ray data for compound **4c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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