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Advanced Synthesis & Catalysis

[4+1] Cycloaddition of Enaminothiones and Aldehyde *N*-Tosylhydrazones Toward 3-Aminothiophenes

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Abstract: An efficient protocol toward trisubstituted 3-aminothiophenes has been developed through a [4+1] cycloaddition of enaminothiones and aldehyde *N*-tosylhydrazones under transition-metal-free conditions. 3-Aminothiophene derivatives as well as their chiral analogs were obtained in good to excellent yields. Direct interaction of the enaminothiones with the diazo compounds of α-carbonyl or ester group-functionalized aldehydes also efficiently afforded the same type of 3-aminothiophenes. The diversity of the synthetic methodology has been demonstrated by the broad substrate scopes and excellent chemoselectivity in cleavage of the C–S, C–O, and C–N bonds in enaminothiones.

Keywords: thiophenes; enaminothiones; hydrazones; cycloaddition; 3-aminothiophenes

Introduction

The thiophene ring is a fundamental scaffold in many pharmaceutical drugs,[1] functional materials,[2] and transition-metal complexes.[3] It is ranked the 19th in the top 100 list of the most frequently used rings in the synthesis of small molecule drugs.[4] Among the diverse types of substituted thiophene derivatives, aminothiophenes have exhibited potent bioactivity as the lead compounds for drug discovery.[5] Although various methods have been developed to construct a thiophene ring,[6,7] reports on chemoselective synthesis of aminothiophenes are limited. In this regard, continuous efforts have been made to access 2-aminothiophenes. The Gewald multicomponent reaction of a carbonyl compound with activated methylene, activated nitrile, and elemental sulfur in the presence of a base has been applied to synthesize substituted 2-aminothiophene derivatives which can be used as small molecular weight inhibitors,[8] and β-ketothioamides have been utilized for the same purpose.[9] The analogs of 2-aminothiophenes, that is, 3-aminothiophenes, have also been demonstrated to show a great potential for drug development (Figure 1). For example, 3-thienyl urea has been pharmaceutically tested as a potent inhibitor of p38 kinase,[10a] thiophene-carboxamide can be used as the inhibitor of IKKβ,[10b] and diarylated thiophenes can modulate the amyloidogenesis and cytotoxic effect of islet amyloid polypeptide (IAPP).[10c] Unfortunately, considerable attention has not been paid to the synthesis of 3-aminothiophenes in comparison with 2-aminothiophenes.

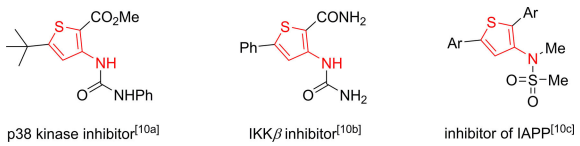


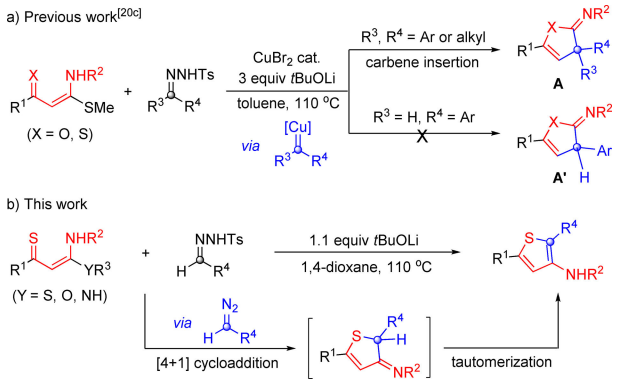
Figure 1. Selected bioactive 3-aminothiophenes.

To access substituted thiophene derivatives, two approaches may be applied: (i) modification of an intact thiophene ring by electrophilic/nucleophilic aromatic substitution or cross-coupling,[10c,11] and (ii)

ring closure of suitable precursor compounds.[12] Based upon such a principle, a few reports have been documented on the synthesis of 3-aminothiophenes.

Palladium-catalyzed amination of 3-bromothiophene with amines afforded 3-aminothiophenes with significant formation of the diarylation products in the case of using primary amines.[13] The domino reaction of vinyl azides and 1,4-dithiane-2,5-diol,[14a] and phase transfer catalysis assisted Thorpe reaction of 3-hydroxy-2-arylacrylonitriles and thioglycolates[14b] were reported for the preparation of functionalized 3-aminothiophenes. The multistep reaction of a dicyano-functionalized ketene dithioacetal was used for the same purpose.[14c] It has been known that α-oxo ketene S,S-acetals[15] can be used as the building blocks to establish a thiophene ring.[16] However, for their N,S-analogs,[17] only a few structurally specified ketene N,S-acetals have been documented for the synthesis of 2-aminothiophenes.[18] Although α-oxo ketene N,S-acetals cannot act as the building blocks to make a thiophene ring, the multi-component reactions of α-thioxo ketene N,S-acetals with activated methylene compounds and stoichiometric $Hg(OAc)_2$[19a–d] could be applied for the preparation of 3-aminothiophenes, and their reactions with diazo compounds were performed in the presence of $Rh_2(OAc)_4 \cdot 2H_2O$ catalyst for the same purpose.[19e]

During our ongoing investigation of the reactivity of S-functionalized internal alkenes,[15a,20] both α-oxo and thioxo ketene N,S-acetals were used to react with ketone *N*-tosylhydrazones under copper catalysis, forming five-membered 2-imino *O*- and *S*-heterocyclic compounds of type **A** *via* carbene insertion into the olefinic C=C bond, whereas aldehyde *N*-tosylhydrazones could not undergo the same type of reactions to give products of type **A′** which might tautomerize to a 2-aminothiophene product (Scheme 1a).[20c] Diazo compounds are amphiphilic and the negatively polarized diazo carbon atom is nucleophilic, while the metal carbene species generated from a diazo compound has an electron-deficient carbene center.[21] We



Scheme 1. Synthetic strategies for 3-aminothiophenes.

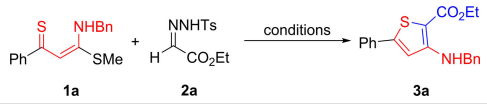
hypothesized that the nucleophilicity/electrophilicity of the intermediates generated *in situ* from *N*-tosylhydrazones, that is, the copper-carbene species in the presence of a copper catalyst, and the diazo species under transition-metal-free conditions, might be dramatically altered using the reaction conditions.[22] Interaction of the thiocarbonyl sulfur in an α-thioxo ketene N,S-acetal with the diazo carbon atom may result in a thiocar-bonyl ylide, that is, a sulfur-centered 1,3-dipole, which readily undergoes 1,5-dipolar electrocyclization.[23] Thus, it was envisioned that α-thioxo ketene N,S-acetals might react with aldehyde *N*-tosylhy-drazones to form five-membered S-heterocycles. Herein, we disclose the [4+1] cycloaddition of enaminothiones, that is, α-thioxo ketene N,S-acetals, and aldehyde *N*-tosylhydrazones for the chemoselective synthesis of 3-aminothiophenes under transition-metal-free conditions (Scheme 1b).

Results and Discussion

Initially, the reaction of enaminothione, that is, α-thioxo ketene N,S-acetal **1a**, and ethyl 2-(*N*-tosylhydrazono)acetate (**2a**) was conducted to optimize the reaction conditions (Table 1). Under an argon atmosphere, treatment of **1a** and **2a** in a 1:2 molar ratio in the presence of 2.0 equiv. *t*BuOLi in toluene at 110 °C for 3 h formed the target product ethyl 3-(benzylamino)-5-phenylthiophene-2-carboxylate (**3a**) in 89% yield (Table 1, entry 1). Increasing the amount of *t*BuOLi to 3 equiv. significantly diminished the yield to 56% (Table 1, entry 2), which is presumably attributed to that excess of *t*BuOLi base accelerated decomposition of the diazo intermediate generated *in situ* from **2a**. A loading of 1.1 equiv. *t*BuOLi was suitable for the reaction (Table 1, entries 3–5). The reaction efficiency could be obviously improved in 1,4-dioxane solvent, and **3a** was thus isolated in 96% yield (Table 1, entry 6). Either performing the reaction in air or lowering the reaction temperature to 100 °C dramatically reduced the product yield (Table 1, entries 7 and 8). Other bases such as K_3PO_4, LiOH, *t*BuONa, and Cs_2CO_3 were also investigated (Table 1, entries 9–12). Among them K_3PO_4 and LiOH exhibited a positive impact on the reaction efficiency, but they could not behave as efficiently as *t*BuOLi did.

Under the optimal conditions, the scope of enaminothiones, that is, α-thioxo ketene N,S-acetals (**1**), was explored (Table 2). Electron-donating substituents such as methyl and methoxy on the aryl group of the thiocarbonyl moiety in enaminothiones **1b–e** facilitated formation of the target products **3b–e** (91–97%). Electron-withdrawing 2-F and 3-CF_3 groups also favored the reactions to give 3-amino-thiophenes **3f** (92%) and **3g** (92%). Somehow, the 4-Br substituent lessened the yield of **3h** to 84%. Both 2-furyl and 2-thienyl-based α-thioxo ketene N,S-acetals **1i** and **1j**

Table 1. Screening of reaction conditions.[a]



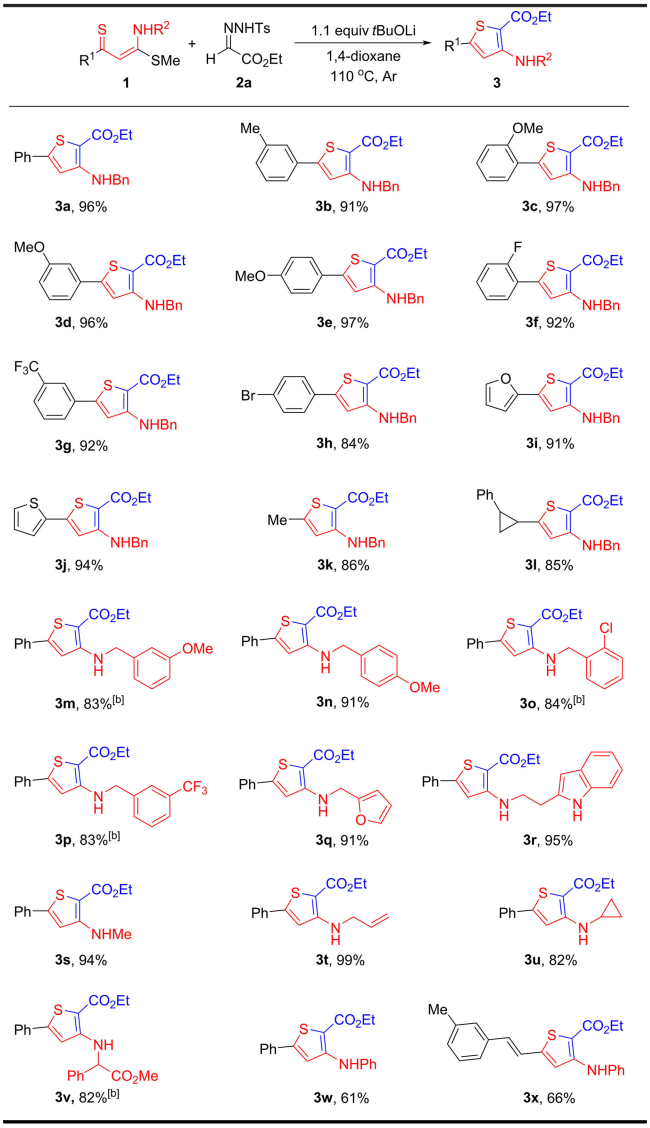
1a 2a 3a

Entry	2a [equiv.]	Base [equiv.]	Solvent	Yield[b] [%]
1	2.0	*t*BuOLi (2.0)	toluene	89
2	2.0	*t*BuOLi (3.0)	toluene	56
3	1.5	*t*BuOLi (1.5)	toluene	90
4	1.1	*t*BuOLi (1.1)	toluene	90
5	1.0	*t*BuOLi (1.0)	toluene	82
6	1.1	*t*BuOLi (1.1)	1,4-dioxane	99 (96)[c]
7[d]	1.1	*t*BuOLi (1.1)	1,4-dioxane	60
8[e]	1.1	*t*BuOLi (1.1)	1,4-dioxane	6
9	1.1	K_3PO_4 (1.1)	1,4-dioxane	94
10	1.1	LiOH (1.1)	1,4-dioxane	70
11	1.1	*t*BuONa (1.1)	1,4-dioxane	45
12	1.1	Cs_2CO_3 (1.1)	1,4-dioxane	13

[a] Conditions: **1a** (0.3 mmol), solvent (3 mL), 0.1 MPa argon, 110 °C, 3 h.
[b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxylbenzene as the internal standard.
[c] Isolated yield given in parentheses.
[d] In air.
[e] 100 °C.

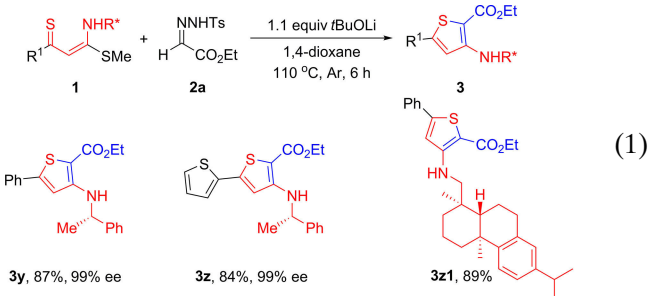
efficiently reacted with **2a**, forming **3i** and **3j** (91–94%), respectively. The alkyl α-thioxo substrates **1k** and **1l** behaved less efficiently than the aryl *α*-thioxo analogs, and their reactions with **2a** generated the target products **3k** and **3l** in 85–86% yields. 2- and 3-substituted benzyl amine-derived enaminothiones **1m**, **1o**, and **1p** exhibited a lower reactivity than the corresponding benzylamino substrates **1a** and **1n**, and their reactions with **2a** resulted in **3m**, **3o**, and **3p** in relatively low yields (83–84%) over a period of 6 h. Other aliphatic non-benzylamine-derived enaminothiones **1q–t** reacted efficiently to afford the target products **3q–t** in excellent yields (91–99%), and only the cyclopropyl functionality exhibited a negative steric effect on the yield of **3u** (82%). *α*-Aminoacid ester-derived enaminothione (**1v**) showed a relatively low reactivity to react with **2a** to form **3v** (82%) within 6 h. Both the aniline-based substrates **1w** and **1x** reacted much less efficiently than aliphatic amine-derived enaminothiones **1a–v**, yielding **3w** (61%) and **3x** (66%), respectively. Chiral enaminothiones were readily prepared from the corresponding ketene S,S-acetals and chiral amines, and they could also efficiently react with **2a**, giving the corresponding chiral 3-aminothiophenes **3y** and **3z** (84–87%) with 99% ee [Eq. (1)]. To our delight, the enaminothione of the resolving agent dehydroabietylamine, that is, enaminothione **1z1**, reacted with **2a** to afford a complex molecule **3z1** in 89% yield. These results

Table 2. Scope of *α*-thioxo ketene N,S-acetals (**1**).[a]



[a] Conditions: **1** (0.3 mmol), **2a** (0.33 mmol), *t*BuOLi (0.33 mmol), 1,4-dioxane (3 mL), 0.1 MPa argon, 110 °C, 3 h. Yields refer to the isolated products.
[b] 6 h.

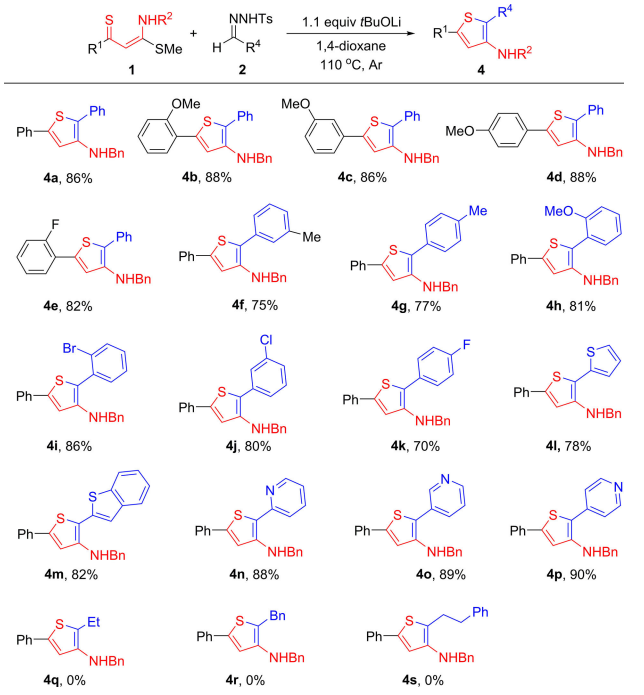
show the diversity of the present synthetic methodology and its potential application in the structural modification of dehydroabietylamine, pharmaceutical drugs and natural products that possess an amino group.[24]



(1)

Next, the protocol generality was investigated by carrying out the reactions of **1** with a variety of aldehyde *N*-tosylhydrazones (**2**) (Table 2). Enaminothione **1a** reacted with benzaldehyde *N*-tosylhydrazone (**2b**) to form the target 3-benzyl-aminothiophene **4a** (86%). The methoxy-substituted α-benzo-thioyl ketene N,S-acetals also efficiently reacted with **2b** to give products **4b–d** (86–88%), while the 2-F substituent exhibited a negative electronic effect on the product yield of **4e** (82%). Various substituents such as methyl, methoxy, bromo, chloro, and fluoro could be tolerated in the substituted benzaldehyde *N*-tosylhydrazones, rendering the formation of **4f–k** in 70–86% yields. Both the *N*-tosylhydrazones of thiophene-2-carboxaldehyde and benzothiophene-2-carboxaldehyde reacted with **1a** to produce **4l** (78%) and **4m** (82%) in good yields, whereas pyridine-carboxaldehyde *N*-tosylhydrazones reacted to afford the target products **4n–p** in excellent yields (88–90%). These results demonstrate a good substrate applicability of the synthetic protocol. However, the *N*-tosylhydrazones of aliphatic aldehydes could not react with **1a** under the standard conditions to give the corresponding products **4q–s**. This result may be attributed to the poor electrophilicity and instability of the diazo alkane intermediates generated *in situ* from the aliphatic aldehyde *N*-tosylhydrazones (Table 3). It is noteworthy that the molecular structures of compounds **3** and **4** are further confirmed by the X-ray single crystal structural determination of compound **4b** (Figure 2) (see the Supporting Information for details).[25]

Table 3. Scope of aldehyde *N*-tosylhydrazones (**2**).[a]



[a] Conditions: **1** (0.3 mmol), **2** (0.33 mmol), *t*BuOLi (0.33 mmol), 1,4-dioxane (3 mL), 0.1 MPa argon, 110 °C, 3 h. Yields refer to the isolated products.

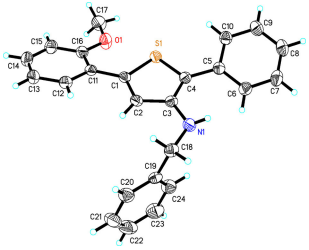
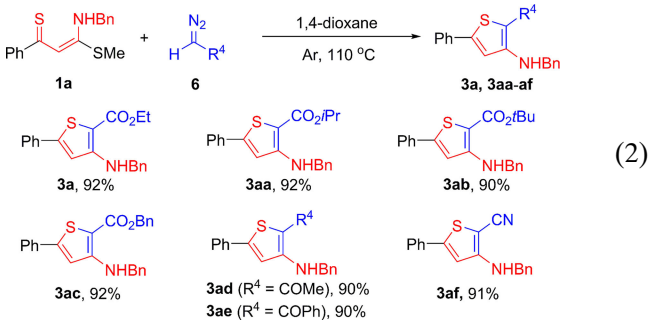


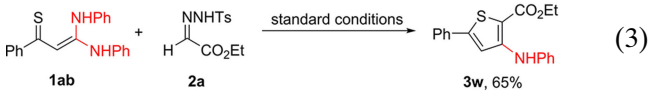
Figure 2. Molecular structure of compound **4b**.

To further explore the substrate scopes, other types of non-alkylthio-functionalized enaminothiones were reacted with **2a** under the standard conditions. In the case of using α-thioxo ketene N,O-acetal **1aa**, 3-benzylaminothiophene **3a** was obtained in 90% yield through removal of the ethoxy group [Eq. (2)]. The aniline-based α-thioxo ketene N,N-acetal **1ab** underwent a similar reaction to form 3-arylamino-thiophene **3w** (65%) by cleaving a C–N bond [Eq. (3)]. It should be noted that both secondary amine-derived α-thioxo ketene N,S-acetals and aliphatic amine-based α-thioxo ketene N,N-acetals could not be successfully prepared to react with the aldehyde *N*-tosylhydrazones. Unexpectedly, simple enaminothione **1ac** reacted with **2a** to yield the non-aminosubstituted thiophene product **5** in 69% yield through the C–N bond cleavage [Eq. (4)]. These results reveal that an alkylthio group is not an indispensable structural functionality at one terminus of the ketene moiety in an enaminothione substrate, but its presence facilitates formation of the target 3-aminothiophene products.

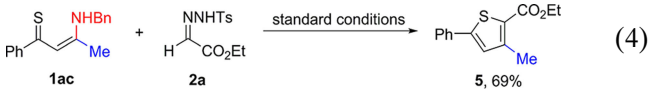
The direct reactions of enaminothione **1a** with readily available diazo compounds **6** were conducted in the absence of *t*BuOLi [Eq. (5)]. Such reactions proceeded very efficiently under the heating conditions, affording the corresponding 3-amino-thiophene products **3a** and **3aa–af** in excellent yields (90–92%). It should be noted that the reaction of diazoacetonitrile with **1a** also efficiently underwent, forming 2-cyano-3-aminothiophene (**3af**) in 91% yield, which can not be readily prepared by other methods. A one-pot, two-step procedure was applied to synthesize 3-aminothiophene **3a** by reacting ethyl 2-oxoacetate (**2aa**) with *N*-tosylhydrazine to initially form aldehyde *N*-tosylhydrazone **2a**, followed by treatment with *t*BuOLi at 110 °C for 3 h, giving **3a** in 97% yield [Eq. (6)]. This result has also demonstrated a promising application of the present protocol for the preparation of 3-aminothiophene derivatives in a concise way.



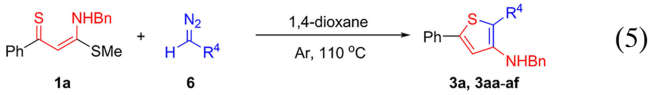
(2)



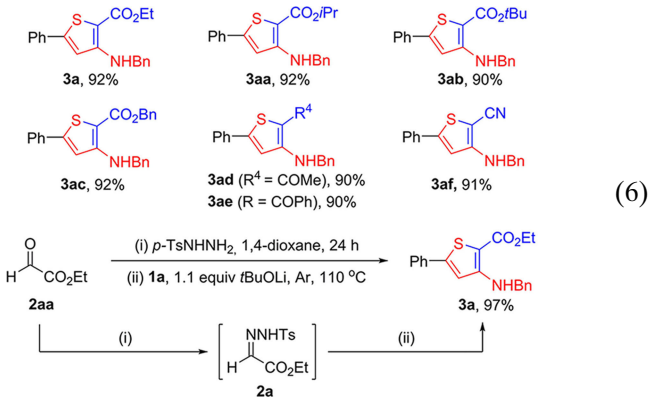
(3)



(4)

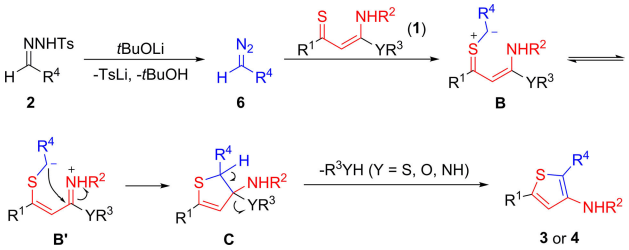


(5)



(6)

A plausible mechanism is proposed (Scheme 2). Interaction of aldehyde *N*-tosylhydrazone **2** with *t*BuOLi initially generates the intermediate diazo species **6** through Bamford-Stevens reaction.[26] Nucleophilic attack of the diazo carbon atom at the thiocarbonyl sulfur of enaminothione **1** forms thiocarbonyl ylide **B**, a sulfur-centered 1,3-dipole, which can tautomerize to exist in the form of species **B′**, and then undergoes 1,5-dipolar electrocycliza-tion[23b] to form species **C**, furnishing a [4+1] cycloaddition. In the cases of using alkylthio, alkoxy, and primary amino-fuctionalized enaminothiones, the leaving groups are the alkylthio, alkoxy, and primary amino, respectively. Thus, the reaction of enamino-thione **1** with aldehyde *N*-tosylhydrazone **2** gives 3-aminothiophene product **3** or **4**. When a simple enaminothione of type **1ac** is used as the substrate, the primary amino group is cleaved during the 1,5-dipolar electrocyclization, forming a non-amino-functionalized thiophene derivative of type **5**.



Scheme 2. Proposed mechanism.

Conclusion

In conclusion, we have developed a concise and highly efficient synthetic protocol to access trisubsti-tuted 3-aminothiophenes from the [4+1] cycloaddition of enaminothiones and aldehyde *N*-tosylhydra-zones. Due to easy manipulations, readily available reactants, excellent chemoselectivity, and transition-metal-free conditions, this work offers a promising method to construct a 3-aminothiophene motif.

Experimental Section

General Considerations

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a 400 MHz spectrometer and all chemical shift values refer to $CDCl_3$ ($\delta(^{1}H)$, 7.26 ppm and $\delta(^{13}C)$, 77.16 ppm). X-Ray crystallographic analysis was achieved by the Analysis Center, Dalian Institute of Chemical Physics, Chinese Academy of Sciences. The HRMS analysis was obtained by ESI on a GC-TOF mass spectrometer. Column chromatographic purifications were performed on silica gel. All the chemical reagents were purchased from commercial sources and used as received unless otherwise indicated.

General Procedure for the Synthesis of 3-Amino-Thiophenes and Derivatives 3-5

A mixture of **1** (0.3 mmol), **2** (0.33 mmol), and *t*BuOLi (0.33 mmol) in 3 mL of 1,4-dioxane was stirred at 110 °C for 3 h under an argon atmosphere. After cooled to ambient temperature, the mixture was evaporated to remove all the volatiles under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/ethyl acetate = 100:1, v/v) to afford the target product **3**, **4** or **5**.

Ethyl 3-(benzylamino)-5-phenylthiophene-2-carboxylate (3a): 97 mg, yield 96%, white solid, m.p.: 80–81 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.48, 7.29 and 7.16 (m, 2:7:2 H, aromatic CH and NH), 6.71 (s, 1 H, thienyl CH), 4.45 (d, J = 5.3 Hz, 2 H, $NHCH_2$), 4.23 (q, J = 7.1 Hz, 2 H, OCH_2), 1.28 (t, J = 7.1 Hz, 3 H, CH_3). $^{13}C\{^{1}H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.2 (Cq, CO_2), 156.4, 149.7, 139.0 and 133.7 (Cq),

129.0, 128.8, 127.5, 127.1 and 126.1 (aromatic CH), 112.3 (thienyl CH), 60.1 (OCH_2), 49.1 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{20}H_{19}NO_2S$ $[M+H]^+$: 338.1215; Found: 338.1216.

Ethyl 3-(benzylamino)-5-(*m*-tolyl)thiophene-2-carboxylate (3b): 96 mg, yield 91%, white solid, m.p.: 72–73 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.39 and 7.28 (m, 6:3 H, aromatic CH and NH), 7.18 (d, $J=7.5$ Hz, 1 H, aromatic CH), 6.83 (s, 1 H, thienyl CH), 4.57 (d, $J=6.0$ Hz, 2 H, $NHCH_2$), 4.34 (q, $J=7.1$ Hz, 2 H, OCH_2), 2.40 (s, 3 H, CH_3), 1.40 (t, $J=7.1$ Hz, 3 H, CH_2CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.2 (Cq, CO_2), 156.4, 149.9, 139.1, 138.8 and 133.7 (Cq), 129.9, 128.9, 128.8, 127.5, 127.1, 126.9 and 123.3 (aromatic CH), 112.2 (thienyl CH), 60.1 (OCH_2), 49.1 ($NHCH_2$), 21.5 (CH_3), 14.7 (CH_2CH_3). HRMS (EI) calcd for $C_{21}H_{21}NO_2S$ $[M+H]^+$: 352.1371; Found: 352.1372.

Ethyl 3-(benzylamino)-5-(2-methoxyphenyl)thiophene-2-carboxylate (3c): 107 mg, yield 97%, white solid, m.p.: 89–90 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.60 (dd, $J=7.7$ and 1.2 Hz, 1 H, aromatic CH), 7.33 and 7.95 (m, 6:2 H, aromatic CH), 7.22 (s, 1 H, NH), 7.03 (s, 1 H, thienyl CH), 4.54 (d, $J=5.9$ Hz, 2 H, $NHCH_2$), 4.34 (q, $J=7.1$ Hz, 2 H, OCH_2), 3.88 (s, 3 H, OCH_3), 1.39 (t, $J=7.1$ Hz, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.3 (Cq, CO_2), 156.5, 155.6, 145.2, 139.3 and 122.4 (Cq), 129.9, 128.7, 128.6, 127.3, 127.2, 120.9, 114.7 (aromatic CH), 111.8 (thienyl CH), 59.9 (OCH_2), 55.6 (OCH_3), 49.0 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{21}H_{21}NO_3S$ $[M+H]^+$: 368.1320; Found: 368.1320.

Ethyl 3-(benzylamino)-5-(3-methoxyphenyl)thiophene-2-carboxylate (3d): 106 mg, yield 96%, white solid, m.p.: 76–77 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.44–7.35 (m, 4H), 7.29 and 7.11 (m, 3:1 H, aromatic CH and NH), 7.20 (d, $J=7.9$ Hz, 1 H, aromatic CH), 6.92 (dd, $J=8.2$ and 1.9 Hz, 1 H, aromatic CH), 6.83 (s, 1 H, thienyl CH), 4.56 (d, $J=6.0$ Hz, 2 H, $NHCH_2$), 4.35 (q, $J=7.1$ Hz, 2 H, OCH_2), 3.86 (s, 3 H, OCH_3), 1.41 (t, $J=7.1$ Hz, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 156.0, 156.3, 149.5, 138.9, 135.0 (Cq), 130.0, 128.8, 127.4, 127.1, 118.6, 112.5 and 111.7 (aromatic CH), 114.6 (thienyl CH), 60.1 (OCH_2), 55.4 (OCH_3), 49.0 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{21}H_{21}NO_3S$ $[M+H]^+$: 368.1320; Found: 368.1320.

Ethyl 3-(benzylamino)-5-(4-methoxyphenyl)thiophene-2-carboxylate (3e): 107 mg, yield 97%, white solid, m.p.: 91–92 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.40 (d, $J=8.8$ Hz, 2 H, aromatic CH), 7.26 and 7.14 (m, 4:2 H, aromatic CH and NH), 6.78 (d, $J=8.8$ Hz, 2 H, aromatic CH), 6.61 (s, 1 H, thienyl CH), 4.42 (d, $J=6.0$ Hz, 2 H, $NHCH_2$), 4.21 (q, $J=7.1$ Hz, 2 H, OCH_2), 3.71 (s, 3 H, OCH_3), 1.27 (t, $J=7.1$ Hz, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 160.4, 156.5, 149.8, 139.1 and 126.5 (Cq), 128.8, 127.5, 127.4, 127.1 and 114.4 (aromatic CH), 111.2 (thienyl CH), 59.9 (OCH_2), 55.5 (OCH_3), 49.0 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{21}H_{21}NO_3S$ $[M+H]^+$: 368.1320; Found: 368.1319.

Ethyl 3-(benzylamino)-5-(2-fluorophenyl)thiophene-2-carboxylate (3f): 98 mg, yield 92%, white solid, m.p.: 76–77 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.61, 7.46–7.20 and 7.15 (m, 1:7:2 H, aromatic CH and NH), 7.02 (d, $J=0.7$ Hz, 1 H, thienyl CH), 4.56 (d, $J=5.8$ Hz, 2 H, $NHCH_2$), 4.35 (q, $J=7.1$ Hz, 2 H, OCH_2), 1.40 (t, $J=7.1$ Hz, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 159.7 (Cq and d, $J=252.1$ Hz, C–F), 155.9, 142.6 (d, $J=3.3$ Hz), 139.0, 130.2 (d, $J=8.7$ Hz) and 121.7 (d, $J=12.1$ Hz, Cq), 128.9, 128.9, 128.8, 127.5, 127.2, 124.6 (d, $J=3.5$ Hz), 121.7 (d, $J=12.1$ Hz), 116.6 (d, $J=22.4$ Hz) and 115.6 (d, $J=7.8$ Hz, aromatic CH and thienyl CH), 60.2 (OCH_2), 49.1 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{20}H_{18}FNO_2S$ $[M+H]^+$: 356.1121; Found: 356.1120.

Ethyl 3-(benzylamino)-5-(3-(trifluoromethyl)phenyl) thiophene-2-carboxylate (3g): 112 mg, yield 92%, white solid, m.p.: 94–95 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.69 (s, 1 H, aromatic CH), 7.60 (d, $J=7.8$ Hz, 1 H, aromatic CH), 7.47 (d, $J=7.7$ Hz, 1 H, aromatic CH), 7.36 (t, $J=7.8$ Hz, 1 H, aromatic CH), 7.25 and 7.21–7.05 (m, 4:2 H, aromatic CH and NH), 6.74 (s, 1 H, thienyl CH), 4.44 (d, $J=6.0$ Hz, 2 H, $NHCH_2$), 4.22 (q, $J=7.1$ Hz, 2 H, OCH_2), 1.27 (t, $J=7.1$ Hz, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.9 (Cq, CO_2), 156.2, 147.5, 138.8, 134.6, 131.5 (q, $J=32.5$ Hz, Cq), 129.6, 129.2, 128.9, 127.5, 127.1, 125.4 (q, $J=3.6$ Hz) and 122.8 (q, $J=3.8$ Hz, aromatic CH), 123.9 (Cq and q, $J=270.0$ Hz, CF_3), 113.1 (thienyl CH), 60.2 (OCH_2), 49.1 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{21}H_{18}F_3NO_2S$ $[M+H]^+$: 406.1089; Found: 406.1087.

Ethyl 3-(benzylamino)-5-(4-bromophenyl)thiophene-2-carboxylate (3h): 105 mg, yield 84%, white solid, m.p.: 126–127 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.51 and 7.43 (d each, $J=8.5$ Hz, 2:2 H, aromatic CH), 7.41–7.13 (m, 6 H, aromatic CH and NH), 6.79 (s, 1 H, thienyl CH), 4.55 (d, $J=6.0$ Hz, 2 H, $NHCH_2$), 4.34 (q, $J=7.1$ Hz, 2 H, OCH_2), 1.40 (t, $J=7.1$ Hz, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.0 (Cq, CO_2), 156.3, 148.2, 138.9, 132.7 and 123.1 (Cq), 132.2, 128.9, 127.5, 127.4 and 127.1 (aromatic CH), 112.6 (thienyl CH), 60.2 (OCH_2), 49.1 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{20}H_{18}BrNO_2S$ $[M+H]^+$: 416.0320; Found: 416.0319.

Ethyl 3-(benzylamino)-5-(furan-2-yl)thiophene-2-carboxylate (3i): 89 mg, yield 91%, white solid, m.p.: 109–110 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.44 (d, $J=1.2$ Hz, 1 H, aromatic CH), 7.37 and 7.30 (m each, 4:2 H, aromatic CH and NH), 6.78 (s, 1H, thienyl CH), 6.62 (d, $J=3.4$ Hz, 1 H, furyl CH), 6.46 (dd, $J=3.4$ and 1.8 Hz, 1 H, furyl CH), 4.54 (d, $J=6.0$ Hz, 2 H, $NHCH_2$), 4.33 (q, $J=7.1$ Hz, 2 H, OCH_2), 1.39 (t, $J=7.1$ Hz, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 156.0, 148.9, 138.9 and 138.5 (Cq), 142.9, 128.8, 127.4, 127.1, 112.1, 111.1 and 107.7 (aromatic CH), 60.1 (OCH_2), 49.0 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{18}H_{17}NO_3S$ $[M+H]^+$: 328.1007; Found: 328.1006.

Ethyl 4-(benzylamino)-[2,2′-bithiophene]-5-carboxylate (3j): 97 mg, yield 94%, white solid, m.p.: 160–107 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.54–7.13 and 7.68 (m, 8:1 H, aromatic CH and NH), 6.71 (s, 1 H, thienyl CH), 4.54 (d, $J=6.0$ Hz, 2H, $NHCH_2$), 4.34 (q, $J=7.1$ Hz, 2H, OCH_2), 1.40 (t, $J=7.1$ Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.9 (Cq, CO_2), 156.1, 142.7, 138.9 and 136.9 (Cq), 128.8, 128.1, 127.5, 127.1, 126.1, 125.3 and 112.4 (aromatic CH),

60.1 (OCH_2), 49.1 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{18}H_{17}NO_2S_2$ $[M+H]^+$: 344.0779; Found: 344.0773.

Ethyl 3-(benzylamino)-5-methylthiophene-2-carboxylate (3k): 71 mg, yield 86%, white solid, m.p.: 47–48 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.22 (m, 5 H, aromatic CH), 7.13 (br, 1 H, NH), 6.20 (s, 1 H, thienyl CH), 4.35 (d, J = 6.1 Hz, 2 H, $NHCH_2$), 4.17 (q, J = 7.1 Hz, 2 H, OCH_2), 2.27 (s, 3 H, CH_3), 1.24 (t, J = 7.1 Hz, 3 H, CH_2CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.9 (Cq, CO_2), 156.3, 147.4 and 139.2 (Cq), 128.8, 127.3 and 127.0 (aromatic CH), 115.4 (thienyl CH), 59.8 (OCH_2), 48.9 ($NHCH_2$), 16.4 (CH_3), 14.7 (CH_2CH_3). HRMS (EI) calcd for $C_{15}H_{17}NO_2S$ $[M+H]^+$: 276.1058; Found: 276.1058.

Ethyl 3-(benzylamino)-5-(2-phenylcyclopropyl)thiophene-2-carboxylate (3l): 96 mg, yield 85%, colorless liquid. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.38–7.15 (m, 7 H, aromatic CH and NH), 7.11 (m, 2 H, aromatic CH), 6.99 (d, J = 7.3 Hz, 2 H, aromatic CH), 6.28 (s, 1 H, thienyl CH), 4.35 (d, J = 6.0 Hz, 2 H, $NHCH_2$), 4.18 (q, J = 7.1 Hz, 2 H, OCH_2), 2.14 (t, J = 7.3 Hz, 2 H, cyclopropyl CH_2), 1.42 and 1.32 (m each, 1:1 H, cyclopropyl CH), 1.24 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.9 (Cq, CO_2), 156.2, 154.6, 141.1 and 139.1 (Cq), 128.8, 128.6, 127.4, 127.1, 126.3 and 125.9 (aromatic CH), 112.8 (thienyl CH), 59.8 (OCH_2), 48.9 ($NHCH_2$), 29.7, 24.6 and 19.7 (cyclopropyl CH_2 and cyclopropyl CH), 14.7 (CH_3). HRMS (EI) calcd for $C_{23}H_{23}NO_2S$ $[M+H]^+$: 378.1528; Found: 378.1527.

Ethyl 3-((3-methoxybenzyl)amino)-5-phenylthiophene-2-carboxylate (3m): 91 mg, yield 83%, colorless liquid. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.48, 7.32–7.06 and 6.70 (m each, 2:5:2 H, aromatic CH and NH), 6.85 (d, J = 7.6 Hz, 1 H, aromatic CH), 6.81 (s, 1 H, thienyl CH), 4.40 (d, J = 6.0 Hz, 2 H, $NHCH_2$), 4.22 (q, J = 7.1 Hz, 2 H, OCH_2), 3.69 (s, 3 H, OCH_3), 1.27 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 160.1, 156.3, 149.6, 140.7 and 133.7 (Cq), 129.9, 128.9, 126.1, 119.3, 112.8 and 112.7 (aromatic CH), 112.3 (thienyl CH), 60.1 (OCH_2), 55.3 (OCH_3), 48.9 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{21}H_{21}NO_3S$ $[M+H]^+$: 368.1320; Found: 368.1320.

Ethyl 3-((4-methoxybenzyl)amino)-5-phenylthiophene-2-carboxylate (3n): 100 mg, yield 91%, yellow solid, m.p.: 82–83 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.59 (d, J = 6.9 Hz, 2 H, aromatic CH), 7.46–7.27 (m, 5 H, aromatic CH), 7.18 (br, 1 H, NH), 6.90 (d, J = 8.5 Hz, 2 H, aromatic CH), 6.84 (s, 1 H, thienyl CH), 4.47 (d, J = 5.8 Hz, 2 H, $NHCH_2$), 4.32 (q, J = 7.1 Hz, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 1.38 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 158.9, 156.3, 149.6, 133.7 and 130.9 (Cq), 128.9, 128.4, 126.1 and 114.2 (aromatic CH), 112.3 (thienyl CH), 59.9 (OCH_2), 55.3 (OCH_3), 48.5 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{21}H_{21}NO_3S$ $[M+H]^+$: 368.1320; Found: 368.1320.

Ethyl 3-((2-chlorobenzyl)amino)-5-phenylthiophene-2-carboxylate (3o): 94 mg, yield 84%, white solid, m.p.: 76–77 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.47 (dd, J = 7.9 and 1.3 Hz, 2 H, aromatic CH), 7.34–7.18 and 7.13 (m each, 6:2 H, aromatic CH and NH), 6.67 (s, 1 H, thienyl CH), 4.52 (d, J = 6.4 Hz, 2 H, $NHCH_2$), 4.23 (q, J = 7.1 Hz, 2 H, OCH_2), 1.28 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 156.1, 149.8, 136.4, 133.6 and 133.1 (Cq), 129.7, 129.1, 129.0, 128.6, 128.5, 127.2 and 126.1 (aromatic CH), 112.1 (thienyl CH), 60.1 (OCH_2), 46.6 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{20}H_{18}ClNO_2S$ $[M+H]^+$: 372.0825; Found: 372.0821.

Ethyl 5-phenyl-3-((3-(trifluoromethyl)benzyl)amino) thiophene-2-carboxylate (3p): 101 mg, yield 83%, white solid, m.p.: 65–66 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.63 (s, 1 H, aromatic CH), 7.56 and 7.37 (m each, 4:3 H, aromatic CH), 7.47 (t, J = 7.7 Hz, 1 H, aromatic CH), 7.28 (br, 1 H, NH), 6.75 (s, 1 H, thienyl CH), 4.59 (d, J = 6.1 Hz, 2 H, $NHCH_2$), 4.33 (q, J = 7.1 Hz, 2 H, OCH_2), 1.39 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 155.9, 149.9, 140.2, 133.6 and 131.2 (q, J = 32.3 Hz, Cq), 130.4, 130.3, 129.4, 129.1, 129.1, 126.1, 124.4 (q, J = 3.8 Hz) and 123.9 (q, J = 3.7 Hz, aromatic CH), 124.2 (Cq and q, J = 272.3 Hz, CF_3), 112.0 (thienyl CH), 60.2 (OCH_2), 48.7 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{21}H_{18}F_3NO_2S$ $[M+H]^+$: 406.1089; Found: 406.1089.

Ethyl 3-((furan-2-ylmethyl)amino)-5-phenylthiophene-2-carboxylate (3q): 89 mg, yield 91%, colorless liquid. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.61 and 7.47–7.29 (m each, 2:4 H, aromatic CH), 7.14 (br, 1 H, NH), 6.93 (s, 1 H, thienyl CH), 6.33 (m, 1 H, furyl CH), 6.26 (d, J = 2.9 Hz, 1 H, furyl CH), 4.49 (d, J = 6.1 Hz, 2 H, $NHCH_2$), 4.31 (q, J = 7.1 Hz, 2 H, OCH_2), 1.37 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.0 (Cq, CO_2), 155.8, 152.4, 149.6 and 133.7 (Cq), 142.2, 129.0, 126.1, 112.2 and 110.5 (aromatic CH), 107.1 (thienyl CH), 60.1 (OCH_2), 42.3 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{18}H_{17}NO_3S$ $[M+H]^+$: 328.1007; Found: 328.1009.

Ethyl 3-((2-(1*H*-indol-2-yl)ethyl)amino)-5-phenylthiophene-2-carboxylate (3r): 111 mg, yield 95%, yellow solid, m.p.: 105–106 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 8.13 and 6.98 (br each, 1:1 H, NH), 7.70 (d, J = 7.8 Hz, 1 H, aromatic CH), 7.57 (dd, J = 7.8 and 1.4 Hz, 2 H, aromatic CH), 7.41 (m, 4 H, aromatic CH), 7.28 (t, J = 7.1 Hz, 1 H, aromatic CH), 7.23 (dd, J = 10.9 and 3.9 Hz, 1 H, aromatic CH), 7.07 (d, J = 2.0 Hz, 1 H, aromatic CH), 6.81 (s, 1 H, thienyl CH), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2), 3.69 (q, J = 6.7 Hz, 2 H, $NHCH_2$), 3.16 (t, J = 6.8 Hz, 2 H, CH_2), 1.40 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 156.5, 149.5, 136.5, 133.7 and 127.3 (Cq), 129.0, 128.9, 126.0, 122.5, 122.1, 119.5, 118.6, 112.8 and 112.2 (aromatic CH), 111.4 (thienyl CH), 59.9 (OCH_2), 45.5 ($NHCH_2$), 26.3 (CH_2), 14.7 (CH_3). HRMS (EI) calcd for $C_{23}H_{22}N_2O_2S$ $[M+H]^+$: 391.1480; Found: 391.1480.

Ethyl 3-(methylamino)-5-phenylthiophene-2-carboxylate (3s): 74 mg, yield 94%, yellow solid, m.p.: 62–63 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.72–7.56 and 7.47–7.29 (m, 2:3 H, aromatic CH), 6.86 (s, 1 H, thienyl CH), 6.69 (br, 1 H, NH), 4.30 (q, J = 7.1 Hz, 2 H, OCH_2), 3.02 (d, J = 5.2 Hz, 3 H, $NHCH_3$), 1.36 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 157.4, 149.7 and 133.8 (Cq), 129.0, 128.9 and 126.1 (aromatic CH), 111.7 (thienyl CH), 59.9 (OCH_2), 31.7 ($NHCH_3$), 14.7 (CH_3). HRMS (EI) calcd for $C_{14}H_{15}NO_2S$ $[M+H]^+$: 262.0902; Found: 262.0902.

Ethyl 3-(allylamino)-5-phenylthiophene-2-carboxylate (3t): 85 mg, yield 99%, colorless liquid. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.70–7.54 and 7.49–7.30 (m each, 2:3 H, aromatic CH), 6.95 (br, 1 H, NH), 6.84 (s, 1 H, thienyl CH), 5.95 (m, 1 H, *CH*=CH_2), 5.31 and 5.19 (m each, 1:1 H, CH=*CH_2*), 4.31 (q, J = 7.1 Hz, 2 H, OCH_2), 3.96 (m, 2 H, NH*CH_2*), 1.37 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 156.3, 149.6 and 133.8 (Cq), 135.0, 129.1, 129.0 and 126.1 (aromatic CH) and 116.3 (CH=CH_2), 112.3 (thienyl CH), 60.0 (OCH_2), 47.5 ($NHCH_2$), 14.7 (CH_3). HRMS (EI) calcd for $C_{16}H_{17}NO_2S$ $[M+H]^+$: 288.1058; Found: 288.1058.

Ethyl 3-(cyclopropylamino)-5-phenylthiophene-2-carboxylate (3u): 71 mg, yield 82%, colorless liquid. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.75–7.59 and 7.48–7.30 (m, 2:3 H, aromatic CH), 7.16 (s, 1 H, thienyl CH), 6.95 (br, 1 H, NH), 4.30 (q, J = 7.1 Hz, 2 H, OCH_2), 2.76–2.54 (m, 1 H, NH*CH*), 1.36 (t, J = 7.1 Hz, 3 H, CH_3), 0.90–0.75 and 0.71–0.54 (m each, 2:2 H, cyclopropyl CH_2). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.9 (Cq, CO_2), 157.1, 149.3 and 133.8 (Cq), 129.0, 128.9 and 126.1 (aromatic CH), 113.4 (thienyl CH), 60.0 (OCH_2), 26.2 (NHCH), 14.7 (CH_3), 7.8 (cyclopropyl CH_2). HRMS (EI) calcd for $C_{16}H_{17}NO_2S$ $[M+H]^+$: 288.1058; Found: 288.1057.

Ethyl 3-((2-methoxy-2-oxo-1-phenylethyl)amino)-5-phenylthiophene-2-carboxylate (3v): 97 mg, yield 82%, white solid, m.p.: 159–160 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.88 (br, 1 H, NH), 7.51 and 7.35 (m each, 4:6 H, aromatic CH), 6.58 (s, 1 H, thienyl CH), 5.23 (d, J = 6.6 Hz, 1 H, NH*CH*), 4.36 (q, J = 7.1 Hz, 2 H, OCH_2), 3.76 (s, 3 H, OCH_3), 1.40 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 171.3 and 164.8 (Cq, CO_2), 149.7, 137.4 and 133.6 (Cq), 129.3, 129.1, 129.0, 128.7, 127.2 and 126.1 (aromatic CH), 112.4 (thienyl CH), 62.0 and 60.3 (OCH_2 and OCH_3), 53.1 (NH*CH*), 14.7 (CH_3). HRMS (EI) calcd for $C_{22}H_{21}NO_4S$ $[M+H]^+$: 369.1270; Found: 369.1271.

Ethyl 3-methyl-5-phenylthiophene-2-carboxylate (3w): 59 mg, yield 61%, white solid, m.p.: 68–69 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 8.84 (s, 1 H, NH), 7.62 (dd, J = 7.9 and 1.3 Hz, 2 H, aromatic CH), 7.44–7.34 (m, 5 H, aromatic CH), 7.33 (s, 1 H, thienyl CH), 7.25 (t, J = 6.2 Hz, 2 H, aromatic CH), 7.10 (t, J = 7.4 Hz, 1 H, aromatic CH), 4.37 (q, J = 7.1 Hz, 2 H, OCH_2), 1.42 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.9 (Cq, CO_2), 151.7, 149.4, 141.6, 133.6 and 102.5 (Cq), 129.6, 129.1, 129.0, 126.2, 123.2, 120.6 and 113.7 (aromatic CH), 60.5 (OCH_2), 14.7 (CH_3). HRMS (EI) calcd for $C_{19}H_{17}NO_2S$ $[M+H]^+$: 324.1058; Found: 324.1059.

(*E*)-Ethyl 5-(3-methylstyryl)-3-(phenylamino)thiophene-2-carboxylate (3x): 72 mg, yield 66%, yellow solid, m.p.: 101–102 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 8.72 (br s, 1 H, NH), 7.26 (t, J = 7.8 Hz, 2 H, aromtic CH), 7.17 (m, 3 H, aromtic CH and CH=CH), 7.11 (t, J = 7.5 Hz, 2 H, aromtic CH), 6.95 (m, 5 H, aromtic CH and CH=CH), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2), 2.27 (s, 3 H, CH_3), 1.30 (t, J = 7.1 Hz, 3 H, CH_2CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.9 (Cq, CO_2), 151.5, 147.6, 141.5, 138.5, 136.1 and 101.4 (Cq), 131.9, 129.5, 129.4, 128.8, 127.6, 124.1, 123.2, 121.17, 120.58, 116.04 (aromtic CH and CH=CH), 60.4 (OCH_2), 21.5 (CH_3), 14.7 (CH_2CH_3). HRMS (EI) calcd for $C_{22}H_{21}NO_2S$ $[M+H]^+$: 364.1371; Found: 364.1370.

Ethyl 5-phenyl-3-((1-phenylethyl)amino)thiophene-2-carboxylate (3y): 92 mg, yield 87%, yellow solid, m.p.: 87–88 °C, 99% ee, $[\alpha]^{20}_D = +215.78$ (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.38 (dd, J = 7.7 and 1.3 Hz, 2 H, aromatic CH), 7.32–7.09 (m, 9 H, aromatic CH and NH), 6.50 (s, 1 H, thienyl CH), 4.57 (p, J = 6.6 Hz, 1 H, NH*CH*), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2), 1.50 (d, J = 6.8 Hz, 3 H, $CHCH_3$), 1.30 (t, J = 7.1 Hz, 3 H, CH_2CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.3 (Cq, CO_2), 155.7, 149.5, 144.9 and 133.7 (Cq), 128.9, 128.8, 128.7, 127.3, 126.1 and 125.9 (aromatic CH), 113.0 (thienyl CH), 60.0 (OCH_2), 54.9 (NHCH), 25.0 ($CHCH_3$), 14.7 (CH_2CH_3). HRMS (EI) calcd for $C_{21}H_{21}NO_2S$ $[M+H]^+$: 352.1371; Found: 352.1372. HPLC (AD-H column, ^{i}PrOH/*n*-hexane 3/97, 0.7 mL/min, 210 nm): t_1 = 10.04 min (major), t_2 = 11.03 min.

Ethyl 4-((1-phenylethyl)amino)-[2,2′-bithiophene]-5-carboxylate (3z): 90 mg, yield 84%, yellow solid, m.p.: 108–109 °C, 99% ee, $[\alpha]^{20}_D = +176.39$ (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.25, 7.19–7.10, 7.06 and 6.87 (m each, 4:3:1:1H, aromatic CH and NH), 6.37 (s, 1H, thienyl CH), 4.53 (p, J = 6.7 Hz, 1H, NH*CH*), 4.23 (q, J = 7.1 Hz, 2H, OCH_2), 1.49 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.28 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.1 (Cq, CO_2), 155.4, 144.8, 142.5, 136.9, 128.9, 128.0, 127.3, 126.1, 125.8 and 125.2 (aromatic CH), 113.1 (thienyl CH), 60.1 (OCH_2), 54.9 (NHCH), 24.9 ($CHCH_3$), 14.7 (CH_2CH_3). HRMS (EI) calcd for $C_{19}H_{19}NO_2S_2$ $[M+H]^+$: 358.0935; Found: 358.0935. HPLC (AD-H column, ^{i}PrOH/*n*-hexane 3/97, 0.7 mL/min, 210 nm): t_1 = 10.13 min (major), t_2 = 11.12 min.

Ethyl 3-((((1R,4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)amino)-5-phenylthiophene-2-carboxylate (3z1): 138 mg, yield 89%, colorless liquid. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.69 (d, J = 7.1 Hz, 2 H, aromatic CH), 7.42 (m, 3 H, aromatic CH), 7.24 (d, J = 8.3 Hz, 1 H, aromatic CH), 7.12 (br, 1 H, NH), 7.06 (d, J = 8.1 Hz, 1 H, aromatic CH), 6.95 (s, 2 H, aromtic CH), 4.34 (q, J = 7.1 Hz, 2 H, OCH_2), 3.26 (qd, J = 13.2 and 6.5 Hz, 2 H, NH*CH_2*), 3.06–2.81, 1.93–1.60 and 1.49 (m each, 3:6:2 H, alkyl CH and CH_2), 2.35 (d, J = 12.8 Hz, 1 H, alkyl CH), 1.40 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.31, 1.30, 1.29, 1.09 (s each, 3:3:3:3 H, CH_3). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 165.2 (Cq, CO_2), 157.3, 149.5, 147.2, 145.6, 134.7 and 133.8 (Cq), 129.0, 128.9, 126.9, 126.1, 124.4 and 123.9 (aromatic CH), 111.9 (thienyl CH), 59.9 (OCH_2), 56.9 ($NHCH_2$), 45.9 ($NHCH_2$), 38.4, 38.1, 37.7, 36.4, 33.5, 30.4, 25.5, 24.1, 19.4, 18.8, 18.7 and 14.69 (alkyl CH, CH_2 and CH_3). HRMS (EI) calcd for $C_{33}H_{41}NO_2S$ $[M+H]^+$: 516.2936; Found: 516.2937.

***N*-Benzyl-2,5-diphenylthiophen-3-amine (4a)**: 88 mg, yield 86%, yellow liquid. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.65, 7.46 and 7.34 (m each, 4:8:4 H, aromatic CH and NH), 7.09 (s, 1 H, thienyl CH), 4.48 (s, 2 H, CH_2). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 144.4, 141.8, 139.8 and 134.5 (Cq), 129.2, 128.8, 128.7, 127.9, 127.6, 127.5, 127.4, 126.5 and 125.4 (aromatic CH), 115.3 (thienyl CH), 51.2

(CH_2). HRMS (EI) calcd for $C_{23}H_{19}NS$ $[M+H]^+$: 342.1316; Found: 342.1316.

***N*-Benzyl-5-(2-methoxyphenyl)-2-phenylthiophen-3-amine (4b)**: 98 mg, yield 88%, yellow solid, m.p.: 95–96 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.60, 7.42, 7.31 and 7.15 (m, 2:6:3:1 H, aromatic CH), 7.22 (d, $J=7.9$ Hz, 1 H, aromatic CH), 7.05 (s, 1 H, thienyl CH), 6.87 (dd, $J=8.1$ and 1.9 Hz, 1 H, aromatic CH), 4.44 (s, 3 H, NHCH_2 and NH), 3.88 (s, 3 H, OCH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 159.9, 144.3, 141.5, 139.7, 135.8, 134.5 and 115.5 (Cq), 129.9, 129.2, 128.8, 127.8, 127.5, 127.4, 126.5, 118.0, 115.4, 113.0 and 111.1 (aromatic CH and thienyl CH), 55.4 (OCH_3), 51.2 ($NHCH_2$). HRMS (EI) calcd for $C_{24}H_{21}NOS$ $[M+H]^+$: 372.1422; Found: 372.1422.

***N*-Benzyl-5-(3-methoxyphenyl)-2-phenylthiophen-3-amine (4c)**: 96 mg, yield 86%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.47, 7.30–7.18, 7.10, 6.81 (m each, 3:6:4:2 H, aromatic CH), 4.25 (s, 3 H, NHCH_2 and NH), 3.72 (s, 3 H, OCH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 155.9, 143.6, 140.1, 137.2, 134.8, 123.4 and 116.2 (Cq), 129.2, 128.8, 128.4, 128.0, 127.9, 127.6, 127.3, 126.4, 121.1 and 117.8 (aromatic CH), 111.8 (thienyl CH), 55.7 (OCH_3), 51.3 ($NHCH_2$). HRMS (EI) calcd for $C_{24}H_{21}NOS$ $[M+H]^+$: 372.1422; Found: 372.1420.

***N*-Benzyl-5-(4-methoxyphenyl)-2-phenylthiophen-3-amine (4d)**: 98 mg, yield 88%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.43 (d, $J=7.4$ Hz, 2 H, aromatic CH), 7.38 (d, $J=8.7$ Hz, 2 H, aromatic CH), 7.26, 7.14 and 6.78 (m, 6:2:3 H, aromatic CH), 4.27 (s, 3 H, NHCH_2 and NH), 3.70 (s, 3 H, OCH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 159.3, 144.3, 141.8, 139.8, 134.7, 127.5 and 114.3 (Cq), 129.2, 128.8, 127.8, 127.6, 127.4, 126.7, 126.3, 114.4 and 114.3 (aromatic CH and thienyl CH), 55.4 (OCH_3), 51.2 ($NHCH_2$). HRMS (EI) calcd for $C_{24}H_{21}NOS$ $[M+H]^+$: 372.1422; Found: 372.1421.

***N*-Benzyl-5-(2-fluorophenyl)-2-phenylthiophen-3-amine (4e)**: 88 mg, yield 82%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.65, 7.45, 7.34, 7.26, 7.19 (m each, 3:6:2:2 H, aromatic CH), 4.46 (s, 3 H, NHCH_2 and NH). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 159.2 (d and Cq, $J=250.3$ Hz, C–F), 144.1, 139.7, 134.8 (d, $J=3.3$ Hz), 134.3 and 122.4 (d, $J=12.3$ Hz, Cq), 129.3, 128.8, 128.6 (d, $J=8.4$ Hz), 128.2 (d, $J=3.4$ Hz), 127.9, 127.6, 127.4, 126.7, 124.5 (d, $J=3.5$ Hz), 118.5 (d, $J=7.4$ Hz) and 116.4 (d, $J=22.4$ Hz, aromatic CH), 51.2 ($NHCH_2$). HRMS (EI) calcd for $C_{23}H_{18}FNS$ $[M+H]^+$: 360.1222; Found: 360.1222.

***N*-Benzyl-5-phenyl-2-(*m*-tolyl)thiophen-3-amine (4f)**: 80 mg, yield 75%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.48, 7.30 and 7.21 (m each, 2:8:3 H, aromatic CH), 6.99 (d, $J=7.4$ Hz, 1 H, aromatic CH), 6.92 (s, 1 H, thienyl CH), 4.33 (s, 3 H, NHCH_2 and NH), 2.30 (s, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 144.3, 141.6, 139.9, 138.9, 134.6, 134.4 and 115.7 (Cq), 129.2, 128.9, 128.8, 128.7, 127.5, 127.4, 127.3, 125.4 and 124.9 (aromatic CH), 115.3 (thienyl CH), 51.3 ($NHCH_2$), 21.7 (CH_3). HRMS (EI) calcd for $C_{24}H_{21}NS$ $[M+H]^+$: 356.1473; Found: 356.1473.

***N*-Benzyl-5-phenyl-2-(*p*-tolyl)thiophen-3-amine (4g)**: 82 mg, yield 77%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.60, 7.40 and 7.32 (m each, 2:6:2 H, aromatic CH), 7.47 (d, $J=8.1$ Hz, 2 H, aromatic CH), 7.26 (d, $J=8.0$ Hz, 2 H, aromatic CH), 7.04 (s, 1 H, thienyl CH), 4.41 (s, 2 H, NHCH_2), 4.40 (br, 1 H, NH), 2.41 (s, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 144.2, 141.3, 139.9, 136.4, 134.7, 131.5 and 115.8 (Cq), 129.9, 128.9, 128.8, 127.9, 127.6, 127.5, 127.4 and 125.4 (aromatic CH), 115.3 (thienyl CH), 51.3 ($NHCH_2$), 21.3 (CH_3). HRMS (EI) calcd for $C_{24}H_{21}NS$ $[M+H]^+$: 356.1473; Found: 356.1473.

***N*-Benzyl-2-(2-methoxyphenyl)-5-phenylthiophen-3-amine (4h)**: 90 mg, yield 81%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.55 (d, $J=7.5$ Hz, 2 H, aromatic CH), 7.45 (dd, $J=7.6$ and 1.6 Hz, 1 H, aromatic CH), 7.41–7.19 and 6.98 (m, 10:3 H, aromatic CH), 4.41 (s, 3 H, NHCH_2 and NH), 3.83 (s, 3 H, OCH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 156.3, 145.5, 142.5, 140.2, 134.8, 122.9 and 111.8 (Cq), 132.1, 128.9, 128.7, 128.6, 127.5, 127.4, 127.2, 125.5, 121.4 and 114.8 (aromatic CH), 111.7 (thienyl CH), 55.8 (OCH_3), 50.9 ($NHCH_2$). HRMS (EI) calcd for $C_{24}H_{21}NOS$ $[M+H]^+$: 372.1422; Found: 372.1421.

***N*-Benzyl-2-(2-bromophenyl)-5-phenylthiophen-3-amine (4i)**: 108 mg, yield 86%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.72 (dd, $J=8.0$ and 1.1 Hz, 1 H, aromatic CH), 7.61, 7.40, 7.30 and 7.21 (m, 2:7:2:1 H, aromatic CH), 7.49 (dd, $J=7.6$ and 1.7 Hz, 1 H, aromatic CH), 7.04 (s, 1 H, thienyl CH), 4.43 (s, 2 H, $NHCH_2$), 3.86 (br, 1 H, NH). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 145.3, 142.7, 139.8, 134.4, 134.3, 125.5 and 113.4 (Cq), 133.7, 133.4, 129.5, 128.9, 128.7, 127.7, 127.6, 127.3 and 125.4 (aromatic CH), 114.4 (thienyl CH), 50.9 ($NHCH_2$). HRMS (EI) calcd for $C_{23}H_{18}BrNS$ $[M+H]^+$: 420.0422; Found: 420.0422.

***N*-Benzyl-2-(3-chlorophenyl)-5-phenylthiophen-3-amine (4j)**: 90 mg, yield 80%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.57, 7.46–7.27 and 7.22 (m, 3:10:1 H, aromatic CH), 7.00 (s, 1 H, thienyl CH), 4.43 (s, 2 H, NHCH_2), 4.38 (br, 1 H, NH). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 144.9, 142.5, 139.6, 136.4, 135.1, 134.3 and 113.6 (Cq), 130.4, 129.0, 128.8, 127.8, 127.6, 127.5, 127.4, 126.4, 125.7 and 125.5 (aromatic CH), 115.3 (thienyl CH), 51.0 ($NHCH_2$). HRMS (EI) calcd for $C_{23}H_{18}ClNS$ $[M+H]^+$: 376.0927; Found: 376.0925.

***N*-Benzyl-2-(4-fluorophenyl)-5-phenylthiophen-3-amine (4k)**: 75 mg, yield 70%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.60, 7.53, 7.41, 7.32 and 7.14 (m each, 2:2:6:3:2 H, aromatic CH and NH), 7.04 (s, 1 H, thienyl CH), 4.43 (s, 2 H, NHCH_2). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 162.8 (d and Cq, $J=301.4$ Hz, C–F), 159.8, 144.3, 141.7, 139.7 and 134.5 (Cq), 129.7 (d, $J=8.0$ Hz), 128.9, 128.8, 127.7, 127.6, 127.5, 125.4, 116.3, 116.1 (d, $J=21.5$ Hz) and 115.3 (aromatic CH and thienyl CH), 51.3 ($NHCH_2$). HRMS (EI) calcd for $C_{23}H_{18}FNS$ $[M+H]+$: 360.1222; Found: 360.1220.

***N*-Benzyl-5-phenyl-[2,2′-bithiophen]-3-amine (4l)**: 81 mg, yield 78%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.55, 7.36, 7.29 and 7.24 (m each, 2:4:2:1 H, aromatic CH), 7.42 (d, $J=7.2$ Hz, 2 H, aromatic CH), 7.12 (d, $J=2.7$ Hz, 1 H, aromatic CH), 7.07 (dd, $J=5.1$ and 3.6 Hz, 1 H, aromatic CH), 6.98 (s, 1 H, thienyl CH), 4.46 (s, 2 H,

NHCH_2). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 144.7, 141.7, 139.5, 136.3 and 134.2 (Cq), 129.0, 128. 8, 127.89, 127.7, 127.5, 127.4, 125.5, 123.8 and 123.7 (aromatic CH), 114.9 (thienyl CH), 50.9 (NHCH_2). HRMS (EI) calcd for $C_{21}H_{17}NS_2$ $[M+H]^+$: 348.0881; Found: 348.0881.

2-(Benzo[*b*]thiophen-2-yl)-*N*-benzyl-5-phenylthiophen-3-amine (4m): 98 mg, yield 82%, yellow solid, m.p.: 168–169 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.79 (d, *J* = 7.9 Hz, 1 H, aromatic CH), 7.73 (d, *J* = 7.8 Hz, 1 H, aromatic CH), 7.58 (d, *J* = 7.4 Hz, 2 H, aromatic CH), 7.45 (d, *J* = 7.3 Hz, 2 H, aromatic CH), 7.43–7.25 (m, 9 H, aromatic CH), 6.99 (s, 1 H, thienyl CH), 4.70 (br, 1 H, NH), 4.51 (d, *J* = 5.5 Hz, 2 H, NHCH_2). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 145.9, 142.9, 140.5, 139.4, 138.7, 136.7, 134.1 and 108.8 (Cq), 129.0, 128.9, 127.9, 127.5, 127.4, 125.6, 124.8, 123.9, 123.1, 122.1 and 119.2 (aromatic CH), 114.9 (thienyl CH), 50.8 (NHCH_2). HRMS (EI) calcd for $C_{25}H_{19}NS_2$ $[M+H]^+$: 398.1037; Found: 398.1034.

***N*-Benzyl-5-phenyl-2-(pyridin-2-yl)thiophen-3-amine (4n)**: 90 mg, yield 88%, yellow solid, m.p.: 121–122 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 8.85 (s, 1 H, aromatic CH), 8.46 (d, *J* = 4.0 Hz, 1 H, aromatic CH), 7.82 (dd, *J* = 7.9 and 1.6 Hz, 1 H, aromatic CH), 7.58, 7.40 and 7.27 (m each, 2:6:3 H, aromatic CH), 7.03 (s, 1 H, thienyl CH), 4.41 (s, 2 H, NHCH_2), 4.34 (br, 1 H, NH). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 148.6, 147.3, 145.4, 143.1, 139.3, 134.8, 134.1, 130.9, 123.9 and 111.1 (Cq), 129.0, 128.8, 127.9, 127.5 and 125.5 (aromatic CH), 115.3 (thienyl CH), 51.1 (NHCH_2). HRMS (EI) calcd for $C_{22}H_{18}N_2S$ $[M+H]^+$: 343.1269; Found: 343.1270.

***N*-Benzyl-5-phenyl-2-(pyridin-3-yl)thiophen-3-amine (4o)**: 91 mg, yield 89%, yellow solid, m.p.: 126–127 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 8.85 (s, 1 H, aromatic CH), 8.47 (d, *J* = 3.7 Hz, 1 H, aromatic CH), 7.82 (d, *J* = 7.9 Hz, 1 H, aromatic CH), 7.58 (d, *J* = 7.5 Hz, 2 H, aromatic CH), 7.47–7.26 (m, 9 H, aromatic CH), 7.03 (s, 1 H, thienyl CH), 4.41 (s, 2 H, NHCH_2), 4.33 (s, 1 H, NH). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 148.6, 147.3, 145.4, 143.1, 139.3, 134.7, 134.1, 130.9, 123.9 and 111.1 (Cq), 128.9, 128.8, 127.9, 127.5 and 125.5 (aromatic CH), 115.3 (thienyl CH), 51.1 (NHCH_2). HRMS (EI) calcd for $C_{22}H_{18}N_2S$ $[M+H]^+$: 343.1269; Found: 343.1269.

***N*-Benzyl-5-phenyl-2-(pyridin-4-yl)thiophen-3-amine (4p)**: 92 mg, yield 90%, yellow solid, m.p.: 121–122 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 8.57 (s, 2 H, aromatic CH), 7.57 (d, *J* = 7.4 Hz, 2 H, aromatic CH), 7.51–7.19 (m, 10 H, aromatic CH), 6.99 (s, 1 H, thienyl CH), 4.55 (br, 1 H, NH), 4.45 (d, *J* = 5.1 Hz, 2 H, NHCH_2). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 146.8, 144.3, 142.4, 139.2, 133.9, 120.9 and 111.6 (Cq), 150.6, 129.1, 129.0, 128.3, 127.7, 127.5 and 125.7 (aromatic CH), 115.2 (thienyl CH), 50.9 (NHCH_2). HRMS (EI) calcd for $C_{22}H_{18}N_2S$ $[M+H]^+$: 343.1269; Found: 343.1270.

Ethyl 3-methyl-5-phenylthiophene-2-carboxylate (5): 51 mg, yield 69%, white solid, m.p.: 43–44 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.62 (d, *J* = 7.2 Hz, 2 H, aromatic CH), 7.36 (m, 3 H, aromatic CH), 7.12 (s, 1 H, thienyl CH), 4.35 (q, *J* = 7.1 Hz, 2 H, OCH_2), 2.57 (s, 3 H, CH_3), 1.39 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 162.9, 148.2, 147.1, 133.6 and 125.9 (Cq), 129.1, 128.7, 127.8 and 126.2 (aromatic CH and thienyl CH), 60.8 (OCH_2), 16.3 (CH_3), 14.5 (CH_2CH_3). HRMS (EI) calcd for $C_{14}H_{14}O_2S$ $[M+H]^+$: 247.0793; Found: 247.0793.

General Procedure for the Synthesis of 3-Aminothiophenes 3a and 3aa–af from the Diazo Compounds

A mixture of **1** (0.3 mmol) and **6** (0.33 mmol) in 3 mL of 1,4-dioxane was stirred at 110 °C for 3 h under an argon atmosphere. After cooled to ambient temperature, the mixture was evaporated to remove all the volatiles under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/ethyl acetate = 100:1, v/v) to afford the target product.

Isopropyl 3-(benzylamino)-5-phenylthiophene-2-carboxylate (3aa): 97 mg, yield 92%, yellow solid, m.p.: 76–77 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.47, 7.33–7.17 (m each, 2:8 H, aromatic CH), 7.14 (br s, 1 H, NH), 6.71 (s, 1 H, thienyl CH), 5.16 (m, 1 H, CH), 4.44 (d, *J* = 5.6 Hz, 2 H, CH_2), 1.26 (d, *J* = 6.3 Hz, 6 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.8 (CO_2), 156.2, 149.5, 139.1 and 133.8 (Cq), 129.1, 129.0, 128.8, 127.4, 127.1 and 126.1 (aromatic CH), 112.3 (thienyl CH), 67.5 (OCH), 49.1 (CH_2), 22.3 (CH_3). HRMS (EI) calcd for $C_{21}H_{21}NO_2S$ $[M+H]^+$: 352.1371; Found: 352.1370.

Tert-butyl 3-(benzylamino)-5-phenylthiophene-2-carboxylate (3ab): 99 mg, yield 90%, yellow liquid. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.59 and 7.35 (m each, 2:8 H, aromatic CH), 7.17 (br s, 1 H, NH), 6.81 (s, 1 H, thienyl CH), 4.53 (d, *J* = 5.6 Hz, 2 H, CH_2), 1.60 (s, 9 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.8 (CO_2), 155.8, 148.9, 139.2 and 133.9 (Cq), 129.0, 128.8, 128.7, 127.4, 127.2 and 126.1 (aromatic CH), 112.4 (thienyl CH), 80.7 (Cq, C–O), 49.1 (CH_2), 28.7 (CH_3). HRMS (EI) calcd for $C_{22}H_{23}NO_2S$ $[M+H]^+$: 366.1528; Found: 366.1526.

Benzyl 3-(benzylamino)-5-phenylthiophene-2-carboxylate (3ac): 110 mg, yield 92%, yellow solid, m.p.: 93–94 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.61 and 7.56–7.04 (m each, 2:14 H, aromatic CH and NH), 6.84 (s, 1 H, thienyl CH), 5.36 (s, 2 H, OCH_2), 4.56 (d, *J* = 5.4 Hz, 2 H, NHCH_2). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 164.8 (CO_2), 156.7, 150.2, 138.9, 136.7 and 133.6 (Cq), 129.1, 129.0, 128.8, 128.6, 128.1, 127.9, 127.5, 127.1 and 126.1 (aromatic CH), 112.2 (thienyl CH), 65.6 (OCH_2), 49.1 ($NHCH_2$). HRMS (EI) calcd for $C_{25}H_{21}NO_2S$ $[M+H]^+$: 400.1371; Found: 400.1370.

1-(3-(Benzylamino)-5-phenylthiophen-2-yl)ethanone (3ad): 83 mg, yield 90%, yellow solid, m.p.: 101–102 °C. ^1H NMR (400 MHz, 23 °C, $CDCl_3$) δ 8.67 (br s, 1 H, NH), 7.58, 7.38 and 7.28 (m, 2:7:1 H, aromatic CH), 6.82 (s, 1 H, thienyl CH), 4.55 (d, *J* = 5.9 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, 23 °C, $CDCl_3$) δ 190.4 (CO), 156.7, 150.5, 138.7, 133.4 and 110.1 (Cq), 129.4, 129.0, 128.8, 127.4, 126.9 and 126.2 (aromatic CH), 112.3 (thienyl CH), 48.8 (CH_2), 28.4 (CH_3). HRMS (EI) calcd for $C_{19}H_{17}NOS$ $[M+H]^+$: 308.1109; Found: 308.1109.

(3-(Benzylamino)-5-phenylthiophen-2-yl)(phenyl)methanone (3ae): 100 mg, yield 90%, yellow solid, m.p.: 113–114 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 9.20 (t, J = 5.4 Hz, 1 H, NH), 7.94, 7.61, 7.53, 7.49 and 7.37 (m each, 2:2:1:2:5 H, aromatic CH), 7.43 (d, J = 7.4 Hz, 2 H, aromatic CH), 7.31 (t, J = 7.3 Hz, 1 H, aromatic CH), 6.91 (s, 1 H, thienyl CH), 4.64 (d, J = 5.9 Hz, 2 H, CH_2). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 188.1 (CO), 158.8, 153.1, 141.4, 138.8, 133.3 and 108.9 (Cq), 130.8, 129.5, 129.0, 128.8, 128.4, 127.9, 127.5, 127.1, 126.2 and 111.9 (aromatic CH and thienyl CH), 48.9 (CH_2). HRMS (EI) calcd for $C_{24}H_{19}NOS$ $[M+H]^+$: 370.1266; Found: 370.1262.

3-(Benzylamino)-5-phenylthiophene-2-carbonitrile (3af): 79 mg, yield 91%, yellow solid, m.p.: 115–116 °C. ^{1}H NMR (400 MHz, 23 °C, $CDCl_3$) δ 7.51 and 7.48–7.27 (m each, 2:8 H, aromatic CH), 6.74 (s, 1 H, thienyl CH), 4.98 (s, 1 H, NH), 4.53 (s, 2 H, CH_2). ^{13}C{^{1}H} NMR (100 MHz, 23 °C, $CDCl_3$) δ 157.3, 150.4, 138.0, 132.7, 115.9 and 78.2 (Cq), 129.4, 129.1, 128.9, 127.8, 127.3 and 126.1 (aromatic CH), 112.2 (thienyl CH), 49.5 (CH_2). HRMS (EI) calcd for $C_{18}H_{14}N_2S$ $[M+H]^+$: 291.0956; Found: 291.0955.

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