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Synthesis of Thieno-Fused Five- and Six-Membered Nitrogen and Oxygen Heterocycles via Intramolecular Heteroannulation of 4,5-Substituted 3-Amino or 3-Hydroxy 2-Functionalized Thiophenes

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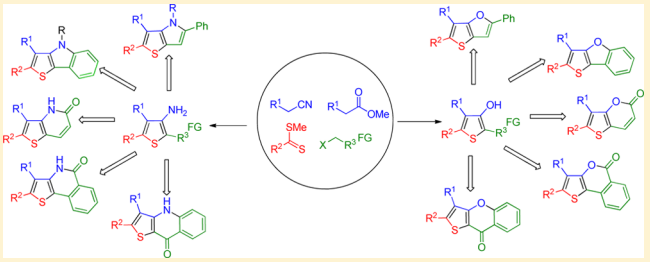
Supporting Information

ABSTRACT: Diverse general high-yield routes for novel thieno-fused five- and six-membered nitrogen and oxygen heterocycles such as thieno[3,2-*b*]pyrroles, thieno[3,2-*b*]-furans, thieno[3,2-*b*]indoles, thieno[3,2-*b*]benzofurans, thieno-[3,2-*b*]pyridine-5-ones, thieno[3,2-*b*]pyran-5-ones, thieno[3,2-*b*]isoquinolin-5-ones, thieno[3,2-*b*]chromen-5-ones, thieno-[3,2-*b*]quinolin-9-ones, and thieno[3,2-*b*]chromen-9-ones have been developed via in situ or stepwise intramolecular heteroannulation of newly synthesized 4,5-substituted 3-amino- or 3-hydroxy 2-functionalized thiophenes. These substituted 3-amino/hydroxythiophenes were readily obtained in high yields from easily accessible precursors, in a sequential one-pot process, by treatment of a range of (het)aryl/unsubstituted acetonitriles or acetates with (het)aryl dithioesters in the presence of LDA, followed by in situ alkylation−intramolecular condensation of the resulting enethiolate salts with functionalized activated methylene halides. The functionalized activated methylene halides employed in these reactions for the synthesis of various thieno-fused heterocycles were cinnamyl bromide, 2-bromobenzyl chloride, bromocrotonate, 2-(bromomethyl)benzoate, and 2-chlorophenacyl bromide. A few of the 4,5-substituted 3-amino/hydroxy-2-stryrylthiophenes (or 2-acrylates) displayed strong fluorescence, and their absorption/emission spectra have also been examined.



INTRODUCTION

The thiophene structural motif constitutes an important class of five-membered heterocycles that is prevalent in several bioactive natural products, pharmaceuticals, and some of the top selling marketed drugs (Plavix, Spriva, raloxifene, zileuton, clopidogrel).[1] Also, the bioisosteric replacement of a benzene ring by thiophene in some biologically active compounds has become a routine strategy in modern drug design, as the physiological effects of thiophenes are similar to those of benzene bioisosteres, sometimes with an altered biological profile/selectivity and frequently with a marked increase in potency along with enhanced pharmacodynamics/pharmacokinetics and toxicological properties.[2] Similarly, the fusion of thiophene and benzothiophene rings with various five- and six-membered heterocycles such as benzothieno-/thieno-fused thiophenes, furans, pyrroles, indoles, quinolines/quinolones, xanthones, pyrones, and pyrimidines furnishes a series of new lead structures with a broad spectrum of biological activity.[3]

Moreover, because of their structural rigidity and specific electronic properties, thiophene derivatives also find applications as excellent structural units in design and synthesis of novel organic materials, such as organic field effect transistors (OFET), organic photovoltaics (OPV), organic light emitting diodes (OLED), solar cells, liquid crystals, molecular wires, and organic semiconductors.[1] The fusion of a thiophene ring with a different five-membered heterocycle in place of traditionally α-linked segments has been commonly utilized for tuning the properties of conjugated oligomers and polymers.[4a] Thus, thiophene-fused heteroaromatic compounds such as thieno-[3,2-*b*]benzothiophene (TBT) and 1-benzothieno[3,2-*b*]-benzothiophene (BTBT) have been employed as key components in a wide range of molecular architectures in OFETs, OLEDs, and photovoltaic cells, including high-performance materials such as porous hydrogen storage hosts.[4,5] Similarly, the fusion of a thiophene ring with other five-membered heterocycles has also been investigated; for example, 4*H*-thieno[3,2-*b*]pyrrole[6] and selenopheno[3,2-*b*]-thiophenes have been synthesized and their properties have been studied through experimental and computational methods.[4a,b,6] The corresponding one oxygen replaced analogs, i.e., thieno[3,2-*b*]benzofurans (TBF) and benzothieno[3,2-*b*]-benzofurans (BTBF), and their derivatives are also of considerable interest, displaying luminescent and liquid crystalline properties as well as interesting reactivity toward electrophilic substitution.[7] Similarly, some of the benzothieno-fused indoles and their copolymers have been shown to be potential high-performance semiconductors and low-band-gap organic solar cells. Therefore, in view of the established utility of the thieno-fused heterocycles in medicinal chemistry, as well as their potential for incorporation into design of novel

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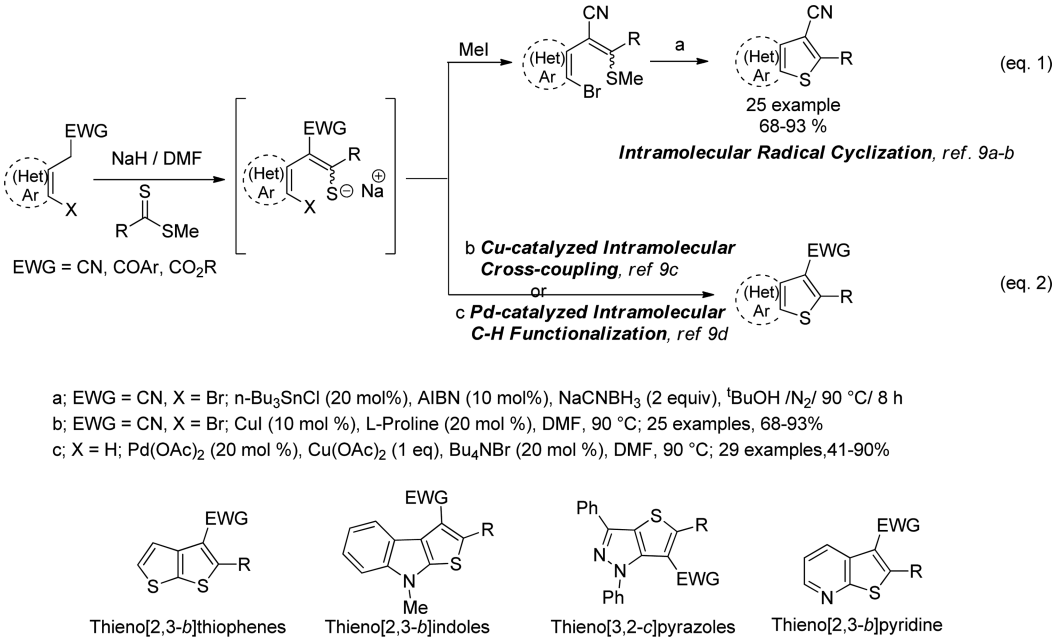
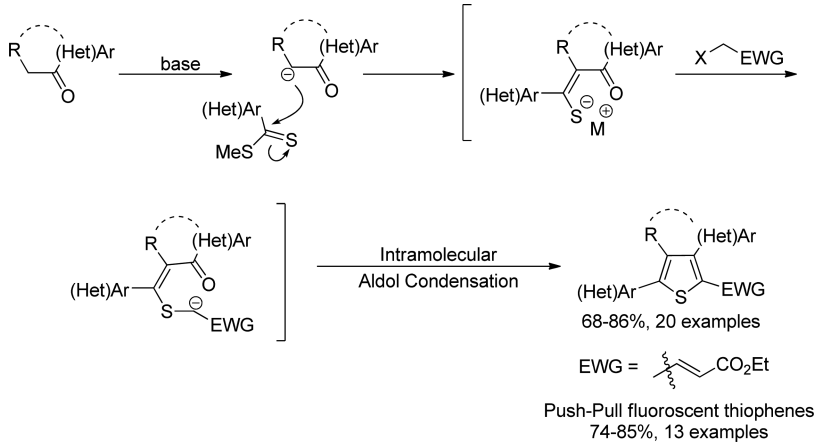
Scheme 1. Synthesis of Substituted Benzothiophenes and Thieno-Fused Heterocycles



Scheme 2. Sequential One-Pot Synthesis of Tri- and Tetrasubstituted Thiophenes



materials, these classes of compounds have become important targets in organic synthesis.

During the course of our investigation on exploring new synthetic methods for five- and six-membered heterocycles by employing easily accessible organosulfur synthons,[8] we have previously described a new efficient protocol for the synthesis of 2,3-substituted benzo[*b*]thiophenes and thieno-fused heterocycles such as thieno[2,3-*b*]thiophenes, thieno[2,3-*b*]indoles, and thieno[3,2-*c*]pyrazoles via radical-mediated intramolecular cyclization of 2-[*o*-bromo(het)aryl]-3-(methylthio)-3-(het)arylacrylonitriles (Scheme 1, eq 1).[9a,b] Subsequently, we have also developed the synthesis of these substituted benzo[*b*]-thiophenes and the corresponding hetero-fused derivatives via copper-catalyzed intramolecular cross-coupling[9c] or by intramolecular C−H activation/C−S bond formation[9d] of in situ generated enethiolates (Scheme 1, eq 2). In continuation of these studies, recently, we have also reported a sequential one-pot three-component synthesis of tri- and tetrasubstituted thiophenes and fluorescent push−pull thiophene acrylates via base-mediated condensation of active methylene ketones with a range of (het)aryl dithioesters as thiocarbonyl partners and subsequent alkylation of the resulting enethiolate salts with a variety of activated methylene halides followed by in situ intramolecular aldol condensation (Scheme 2).[1]

During the course of this work, we further conceived of developing a diverse general approach for thieno-fused five- and six-membered nitrogen and oxygen heterocycles as depicted in Scheme 3. Since amino and hydroxyl functionalities are central to organic synthesis, we first proposed to synthesize the corresponding 3-amino or 3-hydroxythiophenes such as **A** or **B**, bearing suitable functionalities at the 2-position, which are capable of undergoing intramolecular annulation with 3-amino or 3-hydroxy groups (Scheme 3). Thus, by employing a range of (het)arylacetonitriles **1** or the corresponding (het)-arylacetates **2** as active methylene partners in base-mediated condensation with various (het)aryl dithioesters **3**, followed by alkylation with functionalized activated methylene halides, in situ intramolecular cyclocondensation of the resulting alkylated intermediates **6**/**7** would afford the corresponding 3-amino or 3-hydroxythiophenes such as **A** and **B**, respectively (Scheme 3). The subsequent in situ or stepwise intramolecular hetero-annulation of **A** or **B** involving 3-amino/hydroxy groups and

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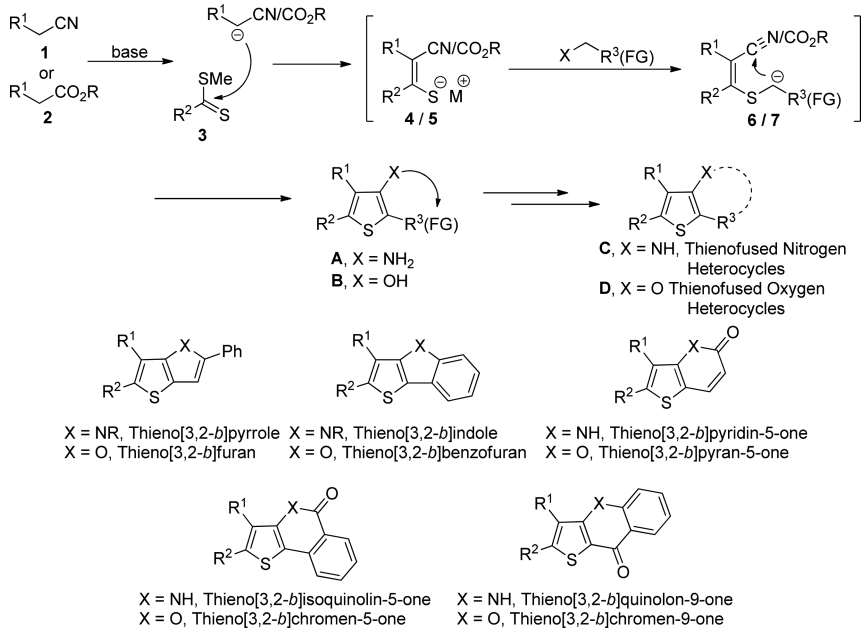
Scheme 3. Proposed Strategy for the Synthesis of Thieno-Fused Five- and Six-Membered Nitrogen and Oxygen Heterocycles



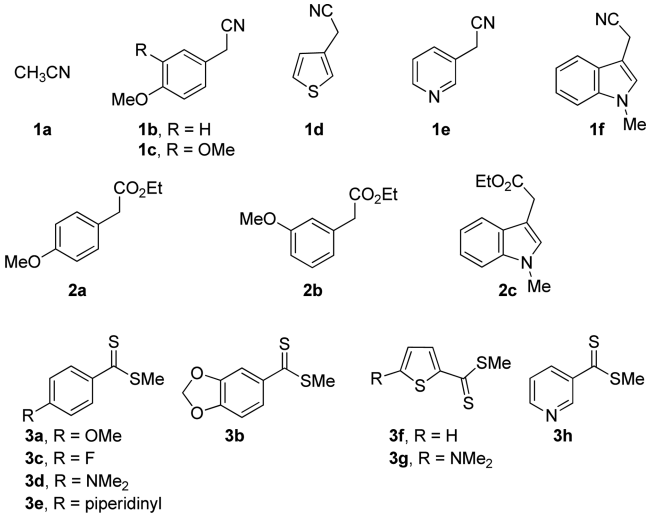
various functionalities present at the 2-position in the presence of various reagents would furnish the corresponding thieno-fused five- or six-membered heterocycles such as **C** or **D** (Scheme 3). We have successfully realized this goal and reported, in this paper, short concise syntheses of a range of thieno-fused nitrogen and oxygen heterocycles such as thieno[3,2-*b*]pyrroles, thieno[3,2-*b*]furans, thieno[3,2-*b*]-indoles, thieno[3,2-*b*]benzofurans, thieno[3,2-*b*]pyridin-5-ones, thieno[3,2-*c*]isoquinolin-5-ones, thieno[3,2-*b*]pyran-5-ones, thieno[3,2-*c*]isochromen-5-ones, thieno[3,2-*b*]quinolin-9-ones, and thieno[3,2-*b*]chromen-9-ones (Schemes 4−13).

RESULTS AND DISCUSSION

For the synthesis of various substituted thieno-fused nitrogen and oxygen heterocycles, we required substituted 3-amino/hydroxy 2-functionalized thiophenes as precursors (Scheme 3). Our literature survey at this stage revealed that only limited methods are available for these compounds, most of them involve base-mediated condensation of activated methylene nitriles/esters such as malononitrile, cyanoacetate or diethyl malonate with carbon disulfide (Gompper's method),[10] or aryl isothiocyanates followed by subsequent in situ or stepwise alkylation/cyclocondensation with activated methylene halides such as bromoacetate, chloroacetonitrile, or phenacyl bromide, affording 3-amino/hydroxy 2-substituted 4-cyano/carboethoxy/phenyl-5-alkylthio/(arylamino)thiophenes in moderate to good yields. However, these methods suffer from several drawbacks, such as moderate to low yields, along with the formation of side products, and limited substituent diversity at various positions of the thiophene ring. Recently a few of the 2-cyano-3-amino-4-alkyl/aryl 5-unsubstituted thiophenes have been synthesized in moderate to good yields via the sequential reaction of few alkyl/arylacetonitriles with *O*-ethyl thioformate and 2-chloroacetonitriles in the presence of LDA.[11]

For our synthesis of various 2-functionalized 4,5-bis(het)aryl-3-amino/hydroxythiophenes, we employed a range of (het)aryl dithioesters **3** as thioacyl precursors[1,8] and (het)-arylacetonitriles/acetates **1**−**2** as active methylene partners, which were condensed in the presence of LDA, followed by in situ one-pot alkylation−cyclocondensation with various functionalized activated methylene halides (Schemes 4−13). The (het)arylacetonitriles **1**, (het)arylacetates **2**, and the dithioesters **3** selected for these studies are shown in Chart 1.

Chart 1. (Het)Arylacetonitriles/Acetates and (Het)Aryl Dithioesters Employed for the Synthesis of 4,5-Substituted 3-Amino/Hydroxy 2-Functionalized Thiophenes



We first undertook the synthesis of substituted thieno-fused five-membered heterocycles such as thieno[3,2-*b*]pyrroles **11**-**12** and thieno[3,2-*b*]furans **14**, which are shown to be privileged scaffolds in medicinal chemistry (Schemes 4 and 5). Thus, thieno[3,2-*b*]pyrroles exhibit the hepatitis virus polymerase inhibitor[3f,g] and CRTH2 receptor antagonist activity.[12a] Thieno[3,2-*b*]pyrrole-fused borondipyrromethenedifluoride (BODIPY) dyes have been successfully applied for preclinical optical imaging and for photodynamic therapy to effectively control subcutaneous tumors.[12b] A few of the

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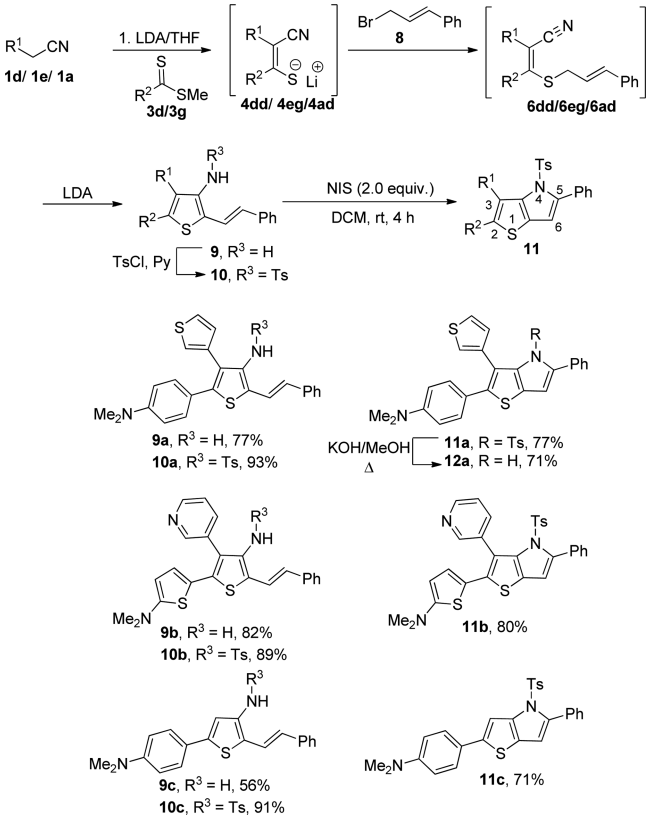
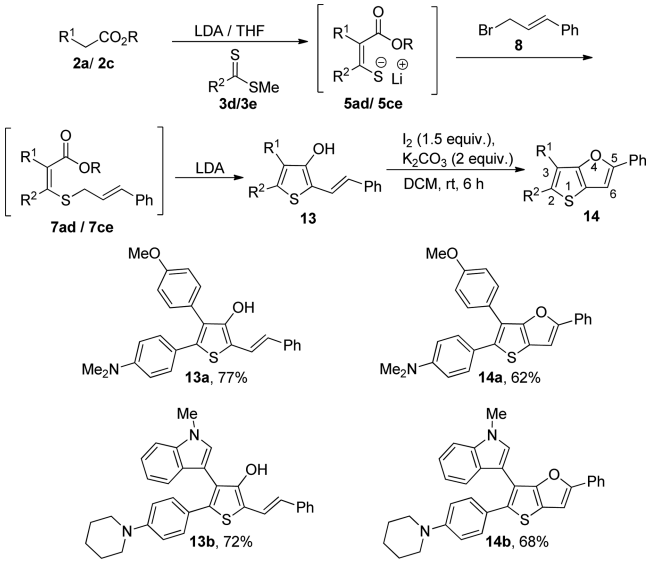
Scheme 4. Synthesis of Substituted Thieno[3,2-*b*]pyrroles



Scheme 5. Synthesis of Substituted Thieno[3,2-*b*]furans



bispyrrolothiophene compounds have also been implemented into solution processed OFETS.[4b]

Substituted thieno[3,2-*b*]pyrroles have been synthesized by reductive cyclization or nitrene-mediated Cadogan type thermal/photochemical cyclization of 3-nitro 2-functionalized thiophenes,[3f,13a−c] by the Hemetsberger−Knittel reaction of thiophene α-azidoacrylate,[3g,6c,12b,13d−f] or recently by rhodium(II)-catalyzed intramolecular C−H bond amination of thiophene azidoacrylate.[6a]

In our approach for the synthesis of 4,5-substituted thieno[3,2-*b*]pyrroles **11a** and **12a**, the anion generated from thiophene-3-acetonitrile **1d** in the presence of LDA (2.2 equiv) at 0 °C was reacted with the 4-(dimethylamino)phenyl dithioester **3d** and the resulting enethiolate anion **4dd**, forming S-alkylation with cinnamyl bromide **8** to give the intermediate enethioether **6dd**, which underwent in situ intramolecular cyclization, furnishing the corresponding 5-(4-dimethylaminophenyl)-4-(3-thienyl)-2-styryl-3-aminothiophene **9a** in 77% yield (Scheme 4). Thiophene **9a** was transformed into the corresponding N-tosylated derivative **10a**, which was subjected to intramolecular iodocyclization in the presence of *N*-iodosuccinimide (NIS) at room temperature, furnishing the corresponding *N*-tosyl 2,3,5-trisubstituted 4*H*-thieno[3,2-*b*]pyrrole **11a** in 77% yield (Scheme 4). Detosylation of **11a** in the presence of KOH/MeOH afforded the corresponding *NH*-thieno[3,2-*b*]pyrrole **12a** in 71% yield (Scheme 4). The corresponding 4-*N*-tosyl-3-(3-pyridyl)-2-(5-dimethylamino-2-thienyl)-5-phenylthieno[3,2-*b*]pyrrole derivative **11b** was also synthesized in good yield following a similar strategy via intramolecular iodocyclization of 3-(*N*-tosyl)-2-styryl 4,5-disubstituted thiophene **10b**, obtained in high yield from the corresponding 3-pyridylacetonitrile **1e**, dithioester **3g**, and cinnamyl bromide under identical conditions (Scheme 4). Similarly, we could also synthesize 3-unsubstituted 4-*N*-tosylthieno[3,2-*b*]pyrrole **11c** in good yield by condensing simple acetonitrile **1a** with the dithioester **3d** and cinnamyl bromide **8** with subsequent intramolecular iodocyclization of the resulting 3-*N*-tosyl 4-unsubstituted 2-styrylthiophene **10c** under identical conditions.

We next synthesized the corresponding 2,3,5-substituted thieno[3,2-*b*]furans **14** following a similar protocol via intramolecular iodocyclization of the corresponding 3-hydroxy-2-styryl 4,5-substituted thiophenes **13** as shown in Scheme 5. It should be noted that unlike thieno[3,2-*b*]pyrroles, the corresponding thieno[3,2-*b*]furans have not been explored much and the unsubstituted thieno[3,2-*b*]furan has been shown to be an unstable compound.[14a] Matzger and co-workers have only recently reported the optimized synthetic methodology, isolation, and functionalization of thieno[3,2-*b*]furan via intramolecular acid-mediated cyclization of 3-(2,2-diethoxyethoxy)thiophene.[4a] Other isolated examples of the synthesis of substituted thieno[3,2-*b*]furans include palladium-catalyzed hydroxylation and intramolecular cyclization of 3-bromo-2-(phenylethynyl)thiophene[14b] and a two-step elaboration of 3-hydroxythiophene-2,5-dicarboxylate.[14a]

Thus, the enolate anion generated from 4-methoxyphenyl acetate **2a** in the presence of LDA was reacted with 4-(dimethylamino)phenyl dithioester **3d** to give enethiolate **5ad**, which underwent facile S-alkylation with cinnamyl bromide and subsequent in situ intramolecular cyclocondensation at ester moiety, yielding the corresponding 4,5-disubstituted 3-hydroxy-2-styrylthiophene **13a** in excellent yield under one-pot conditions (Scheme 5). Subsequent intramolecular iodocyclization of **13a** in the presence of iodine and potassium carbonate afforded 2,5,6-triarylthieno[3,2-*b*]furan **14a** in 62% yield. Following a similar strategy, the corresponding 2,5-bis(aryl)-3-(3-indolyl)thieno[3,2-*b*]furan **14b** could also be synthesized in good yield, under identical conditions, starting from 3-indolyl acetate precursor **2c** and dithioester **3e** (Scheme 5).

After successfully establishing the synthesis of substituted thieno[3,2-*b*]pyrroles and thieno[3,2-*b*]furans via intramolecular iodocyclization of 2-styryl-3-amino/3-hydroxythiophenes, respectively (Schemes 4 and 5), we next focused our attention toward the synthesis of substituted thieno[3,2-*b*]indoles and

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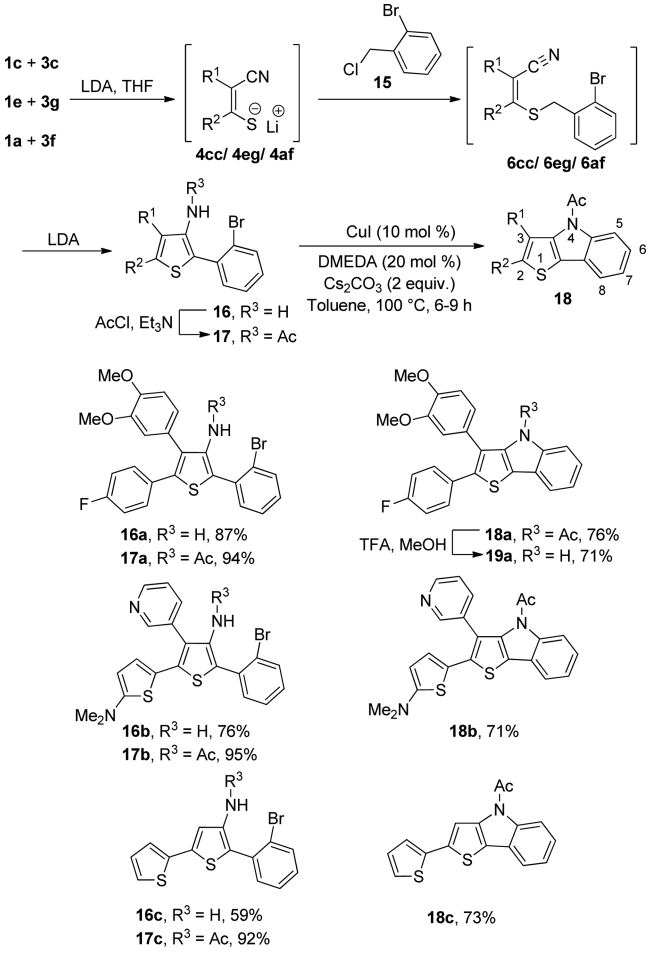
thieno[3,2-*b*]benzofurans as shown in Schemes 6 and 8, respectively. Heteroannulated indole and carbazole alkaloids

Scheme 6. Synthesis of Substituted Thieno[3,2-*b*]indoles

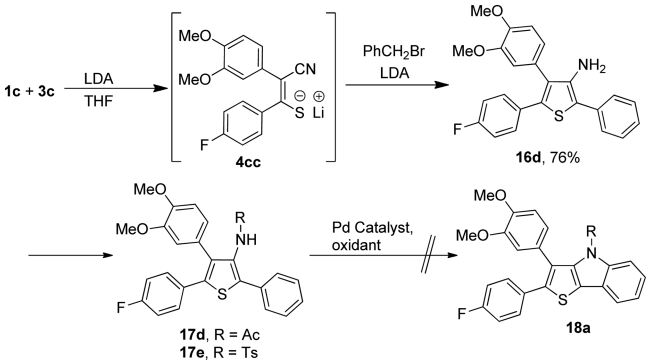


constitute an important class of heterocycles, due to the broad range of biological activities displayed by this class of compounds, especially their affinity toward DNA.[2d] Donor–acceptor type copolymers based on 6-(2-thienyl)-4*H*-thieno-[3,2-*b*]indoles have also been utilized for the photovoltaics[15a] and in organic solar cells.[15b] However, only limited methods exist for their synthesis, although several new methodologies have been developed for the corresponding benzo-fused indolo[3,2-*b*]benzo[*b*]thiophenes via palladium- or rhodium-catalyzed C–C/C–N/C–H bond formations.[2d,4c,16] In a few isolated cases, 6-(2-thienyl)-4*H*-thieno[3,2-*b*]indole has been synthesized by nitrene-mediated Cadogan cyclization of 2-(2-thienyl)nitrobenzene derivatives,[15b] whereas the corresponding unsubstituted thieno[3,2-*b*]indole framework has been obtained either via Rh(II)- or copper-catalyzed intramolecular C–H amination of 2-(2-thienyl)phenyl azide[17a] and 2-(2-aminophenyl)thiophene, respectively.[17b]

In our strategy toward thieno[3,2-*b*]indoles and thieno[3,2-*b*]benzofurans, we proposed to synthesize these heterocyclic cores via intramolecular copper- or palladium-catalyzed C–N or C–O bond formation of the corresponding 4,5-disubstituted 3-amino-2-(2-bromophenyl)thiophenes **16** and the 3-hydroxy-2-(2-bromophenyl)thiophene **20**, respectively, as shown in Schemes 6 and 8. Thus, the desired 4,5-disubstituted 3-amino-2-(2-bromophenyl)thiophene **16a** was synthesized in high yield, by alkylation of the thioenolate anion **4cc** (generated by condensation of 3,4-dimethoxyphenylacetonitrile **1c** and 4-fluorophenyl dithioester **3c** in the presence of LDA) with 2-bromobenzyl chloride **15** followed by in situ intramolecular cyclocondensation of the resulting S-benzylated enethioether **6cc** (Scheme 6). Subsequent N-acylation of **16a** afforded the N-acylated thiophene **17a**, which was subjected to intramolecular C–N bond formation in the presence of cuprous iodide (10 mol %) and DMEDA, furnishing the desired 2,3-bis(aryl)-4-*N*-acyl-4*H*-thieno[3,2-*b*]indole **18a** in 76% yield. Deprotection of the *N*-acyl group in **18a** with TFA at room temperature gave the corresponding NH thieno[3,2-*b*] indole **19a** in good yield (Scheme 6). The corresponding 4-*N*-acyl-2-[5-(dimethylamino)-2-thienyl]-3-(3-pyridyl)thieno[3,2-*b*]-indole **18b** and the 3-unsubstituted analog **18c** were also synthesized in overall good yield, following a similar strategy via copper-catalyzed intramolecular cross-coupling/C–N bond formation of the newly synthesized 2-(2-bromophenyl)-3-(acylamino)thiophene **17b** and **17c**, respectively (Scheme 6).

We also attempted the synthesis of substituted thieno[3,2-*b*]indoles via palladium- or copper-catalyzed intramolecular C–H activation/C–N bond formation of the corresponding 3-amino-2-phenyl 4,5-disubstituted thiophene **16d** or its *N*-acyl/tosyl derivatives **17d–e** (Scheme 7).[17b,18] The desired 3-amino-2-phenylthiophene **16d** was prepared in good yield following a protocol similar to that for thiophenes **16a–c** by employing benzyl bromide as the alkylating agent (Scheme 7). However,

Scheme 7. Attempted Synthesis of Thieno[3,2-*b*]indoles via Intramolecular C–H Activation/Amination



all our attempts to obtain the desired thieno[3,2-*b*]indole **18a** in the presence of various palladium(II) catalysts/oxidants/additives were not successful in yielding only either unreacted **17d** or an unisolable mixture of several products.

The synthesis of substituted thieno[3,2-*b*]benzofurans was next undertaken following a protocol similar to that described for thieno[3,2-*b*]indoles **18** (Scheme 6), via the intramolecular copper-catalyzed cross-coupling of the corresponding 3-hydroxyl-2-(2-bromophenyl) 4,5-substituted thiophenes **20** (Scheme 8). It should be noted that thieno[3,2-*b*]benzofuran and its derivatives, like their thieno[3,2-*b*]furan counterparts, have been underrepresented in the literature.[7,19a,b] A few of the benzothieno[3,2-*b*]furan derivatives are found to display potent inhibitory activity toward IKKβ in enzymatic and cellular assays.[19c] In an isolated example, 6-methoxythieno[3,2-*b*]-benzofuran-2-carboxylate has been synthesized via a conventional multistep procedure.[20] Recently, a few of the substituted thieno[3,2-*b*]benzofurans have been obtained in moderate

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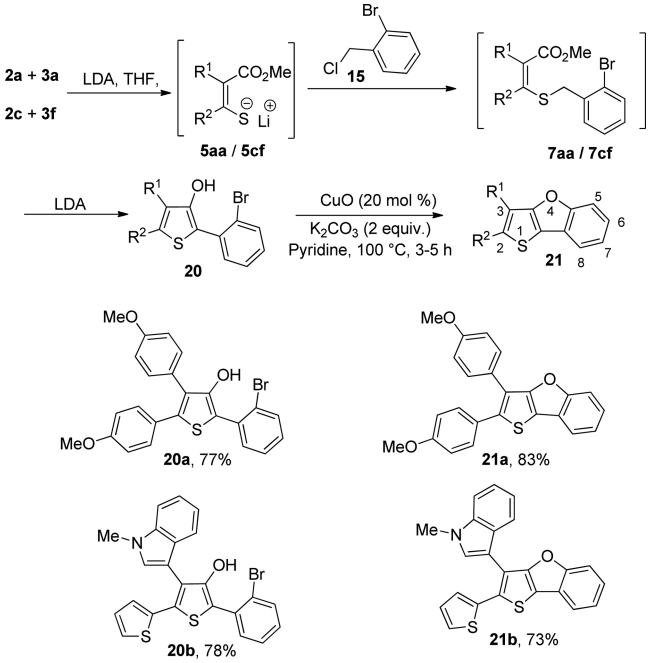
Scheme 8. Synthesis of Substituted Thieno[3,2-*b*]benzofurans



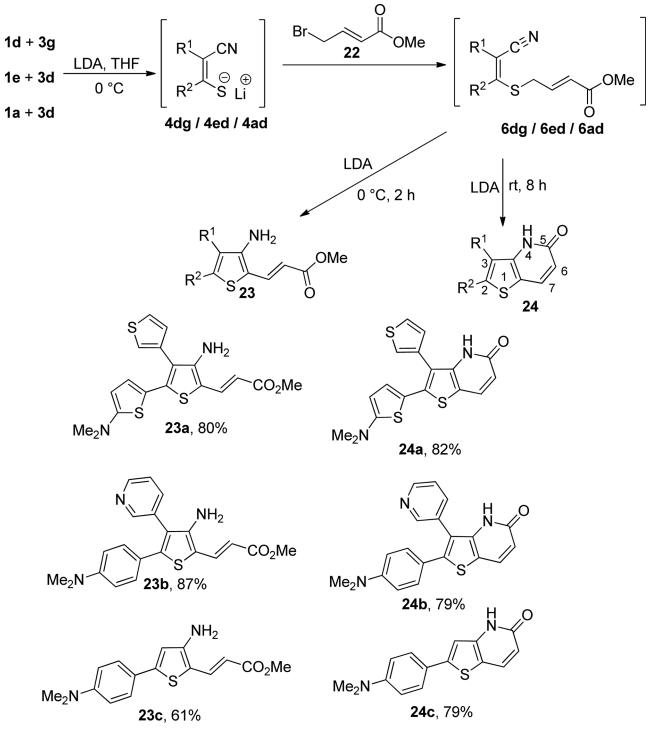
yields via palladium-catalyzed intramolecular C−H/C−H coupling of 3-aryloxythiophenes.[7]

The desired 4,5-disubstituted 2-(2-bromophenyl)-3-hydroxythiophenes **20a,b** were obtained in good yields via base-mediated one-pot sequential S-alkylation of the corresponding thioenolates **5aa** and **5cf** (obtained from appropriate (het)arylacetates and dithioesters) with 2-bromobenzyl chloride and subsequent in situ intramolecular acylation of the resulting S-benzylthioenol ethers. These 3-hydroxythiophenes **20a,b** underwent smooth copper-catalyzed intramolecular C−O bond formations, furnishing the desired 2,3-bis(hetaryl)-thieno[3,2-*b*]benzofurans **21a,b** in high yields (Scheme 8).

After successfully achieving the synthesis of thieno-fused five-membered nitrogen and oxygen heterocycles, we next turned our attention toward synthesis of thieno-fused six-membered heterocycles such as thieno[3,2-*b*]pyridinones and thieno[3,2-*c*]isoquinolin-5-ones (Schemes 9 and 10). Substituted thieno-[3,2-*b*]pyridinones are pharmacologically important molecules displaying a broad range of biological activities such as calcium channel inhibitors, immune modulators, γ-aminobutyric acid ligands, and herbicides.[21a] A few of the 4-substituted thieno-[2,3-*b*]pyridine-6-one derivatives are shown to be Checkpoint kinase 1 (Chk1) inhibitors[3b] and glycine antagonists.[2a] There are only two reports of the syntheses of the thieno[3,2-*b*]pyridine-5-one ring system described in the literature, although the synthesis of a few hetero-fused thienopyridones have been reported.[21] Recently, 3-(triazolyl)thieno[3,2-*b*]-pyridinone has been synthesized by copper-catalyzed domino cycloaddition/C−N coupling/cyclization of 2-bromoarylketones, 2-azidoacetamides, and acetylenes.[22a] Also, there is one example of the synthesis of 7-methylthieno[3,2-*b*]pyridine-5-one by Ru(II)-catalyzed intermolecular cyclization of 3-acetylaminothiophene and methyl propiolate.[22b]

The synthetic strategy for thieno[3,2-*b*]pyridinones **24** developed by us is depicted in Scheme 9. Thus, the thioenolate salt **4dg** generated from the condensation of thiophene-3-acetonitrile **1d** and 5-(dimethylamino)-2-thienyl dithioester **3g**

Scheme 9. Synthesis of Substituted Thieno[3,2-*b*]pyridin-5-ones



in the presence of LDA was S-alkylated with bromocrotonate **22**[1,23] and the reaction mixture was stirred at room temperature for 5−6 h, which after workup, directly afforded thienopyridinone **24a** in 82% yield via intramolecular cyclocondensation of in situ generated 3-amino-4,5-bis(het)arylthiophene-2-acrylate **23a**. Similarly, the corresponding 3-pyridyl/3-unsubstituted thieno[3,2-*b*]-pyridin-5-ones **24b−c** were also obtained in high yields in a sequential one-pot domino reaction involving the formation of two rings and four bonds (Scheme 9). However, when the reaction mixture after addition of bromocrotonate was stirred at 0 °C for 3−4 h, acyclic 3-aminothiophene-2-acrylates **23a−c** were obtained exclusively in overall good yields (Scheme 9). 3-Aminothiophene-2-acrylates **23a−c** were found to be highly fluorescent compounds (Table 1, Figure 1).

We next extended our studies toward the synthesis of thieno-fused isoquinolones **27** as shown in Scheme 10. It should be noted that thieno[3,2-*c*]isoquinolin-5-ones have not been often documented in the literature, although the syntheses of a few benzothieno[3,2-*c*]isoquinolin-5(6*H*)-ones have been reported recently.[24] Substituted 3-methyl-thieno[3,2-*c*]isoquinolone-2-carboxamides are shown to display nanomolar PARP-1 inhibitory activity.[3c] The corresponding thieno-fused isoquinolone-2-carboxylate precursor has been synthesized through a multistep process involving the intramolecular reductive cyclization of 2-(3-nitro-2-thienyl)benzoate.[3c]

Thus, the enethiolate salt **4ce** generated from the condensation of arylacetonitrile **1c** and dithioester **3e** in the presence of LDA was subjected to S-alkylation−intramolecular condensation with 2-(bromomethyl)benzoate **25** at room temperature for 8 h; the workup of the reaction mixture afforded the 4,5-substituted thieno[3,2-*c*]isoquinolone **27a** as the major product in 79% yield, along with the trace of open-chain 3-amino-2-(2-carboethoxy)phenylthiophene **26a** (7%).

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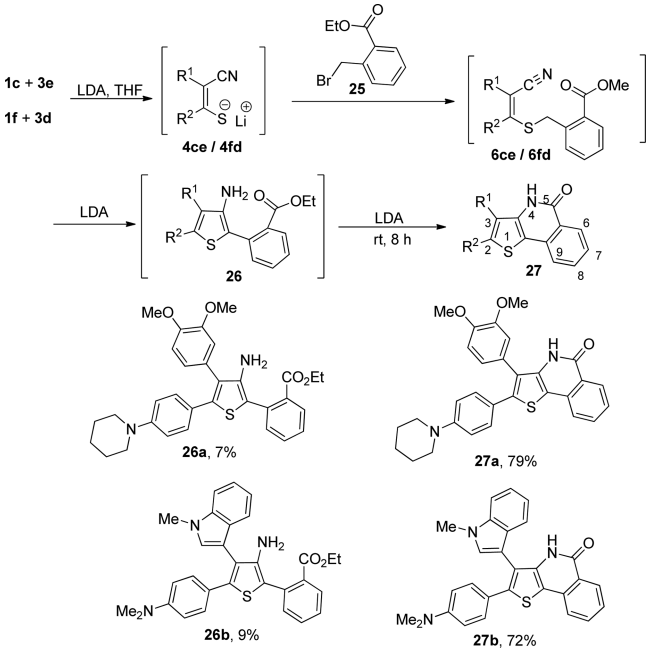
Scheme 10. Synthesis of Substituted Thieno[3,2-*c*]isoquinolin-5-ones



When the same reaction was conducted at 0 °C, for a prolonged time (14 h), **27a** was still formed as the major product (57%), along with traces of uncyclized **26a** and unreacted starting material. Apparently, because of the presence of the bulkier (2-carboethoxy)phenyl group in the 2-position, intramolecular cyclization of 3-aminothiophene **26a** is very facile even at lower temperatures. The corresponding 3-(3-indolyl)-2-[(4-dimethylamino)phenyl]thieno[3,2-*c*]-isoquinolone **27b** was similarly obtained in high yield from the appropriate precursors, following a similar protocol, along with 3-amino-2-(2-carboalkoxyphenyl)thiophene **26b** in low yield (Scheme 10).

With the successful synthesis of thieno-fused pyridinones **24** and isoquinolones **27** in hand (Schemes 9 and 10), we next proceeded to explore the synthesis of the corresponding oxa analogs, i.e., thieno[3,2-*b*]pyran-5-ones **29** and thieno[3,2-*c*]isochromen-5-ones **31**, following a similar strategy (Scheme 11). There are only a few reports of the thieno[3,2-*b*]-pyran-5-one ring system in the literature, and the unsubstituted compound has been synthesized in moderate yields, either by intramolecular cyclization of 3-hydroxythiophene-2-aldehyde with acetic anhydride/sodium acetate at higher temperatures[25a] or by condensation of 3-hydroxy-5-(methylthio)thiophene with methoxymethylene Meldrum's acid and subsequent FVP of the adduct (650 °C).[25b] The corresponding 7-hydroxy-5*H*-thieno-[3,2-*b*]pyran-5-one derivatives, which are synthesized by intramolecular−condensation-cyclization of 3-hydroxythiophene-2-carboxylate with various active methylene compounds, have been shown to display potent antihelmintic activity against *Trichostrongylus colubriformis* in sheeps and dogs.[3a,26]

In our approach for the synthesis of thieno[3,2-*b*]pyran-5-ones **29**, the thioenolate anion **5ad** generated by the treatment of 4-methoxyphenyl acetate **2a** and 4-dimethylaminophenyl dithioester **3d** in the presence of LDA was S-alkylated with bromocrotonate **22** with a view to obtain thieno[3,2-*b*]pyrone **29a** directly via the domino intramolecular cyclization of the resulting 3-hydroxythiophene-2-acrylate **28a** as observed in the synthesis of thieno[3,2-*b*]pyridones **24** (Scheme 9). However, the workup of the reaction mixture did not furnish **29a** but did furnish the corresponding 4,5-disubstituted 3-hydroxythiophene-2-acrylate **28a** in 87% yield (Scheme 11). We, therefore, attempted intramolecular cyclization of **28a** under different conditions by heating in xylene or in toluene in the presence of H_2SO_4, which did not afford the desired thieno[3,2-*b*]pyrone **29a**, yielding only the intractable reaction mixture.

Finally, 3-hydroxythiophene-2-acrylate **28a** could be cyclized in the presence of tri(*n*-butyl)phosphine in refluxing methanol,[27] affording the corresponding thienopyrone **29a** in moderate yield (50%), which could not be improved further. Similarly the corresponding 3-(3-indolyl)-2-[(5-dimethylamino)-2-thienyl]thieno[3,2-*b*]pyrone **29b** could also be synthesized in 55% yield from 4-(3-indolyl-)3-hydroxythiophene-2-acrylate **28b** (77%) following the identical procedure (Scheme 11). Both 3-hydroxythiophene-2-acrylates **28a**,**b** display strong fluorescence in the yellow-red region (Table 1, Figure 1).

The synthesis of thieno[3,2-*c*]isochromene-5-ones **31a**,**b** was next undertaken as shown in Scheme 11. π-Conjugated coumarin type frameworks are shown to be excellent structural units for organic photovoltaics and field-effect transistors (OFETS).[28a,b] The thieno[3,2-*c*]isochromene-5-one ring system, however, is only scarcely known in the literature,[28c] although the corresponding 5*H*-dithieno[3,2-*b*:2′,3′-*d*]pyran (DTP) and the corresponding 5*H*-pyrone derivatives (DTPO) are known to be among the most efficient donors for organic photovoltaics.[28a] Recently, these coumarin type structures such as benzothienochromene-5-one, DTPO, and the corresponding thieno[3,2-*c*]isochromene-5-one have been synthesized in good yields via palladium-catalyzed intramolecular oxidative C−H lactonization of the corresponding 2-(het)arylbenzoic acids.[28a,c]

We followed an approach for the synthesis of thieno[3,2-*c*]isochromenones **31** similar to that described for thieno[3,2-*c*]isoquinolones **27** (Scheme 10). Thus, when the thioenolates anion **5ag** [derived from 4-methoxyphenyl acetate **2a** and (5-dimethylamino)-2-thienyl dithioester **3g**] was reacted with 2-(bromomethyl) benzoate **25**, the workup of the reaction mixture did not furnish the desired thienoisochromenone **31a**, yielding only the uncyclized 4,5-substituted 2-(2-carboethoxyphenyl)-3-hydroxythiophene **30a** in 71% yield (Scheme 11). Hydroxythiophene **30a** could be cyclized to the corresponding 2,3-substituted thieno[3,2-*c*]isochromen-5-one **31a** in good yield, in the presence of sulfuric acid in refluxing methanol. Similarly, the corresponding 3-(3-indolyl)-2-[4-(dimethylamino)phenyl]thienoisochromenone **31b** could also be synthesized in good yield following a similar procedure (Scheme 11).

We next focused our attention toward the synthesis of linearly fused thieno[3,2-*b*]quinolin-9-ones **35** and their oxa analogs such as thieno[3,2-*b*]benzopyran-9-ones **37** as depicted in Schemes 12 and 13. Although the thieno[3,2-*b*]quinolin-9-one ring system is only scarcely documented in the literature,[29] the synthesis and biological activity of the corresponding benzothieno[3,2-*b*]quinolones and their 5-*N*-methylquinolium salts have been extensively studied as sulfur isosteres of cryptolepine and quindoline alkaloids, displaying equipotent anti-infective and antifungal activities with low cytotoxicity.[3d,e,30] There is only one isolated report of the synthesis of 8-fluoro-7-methoxythieno[3,2-*b*]quinolin-9-one obtained by the intramolecular cyclization of substituted benzyne (generated from 5-(3-fluoro-4-methoxyphenyl)thianthrenium perchlorate

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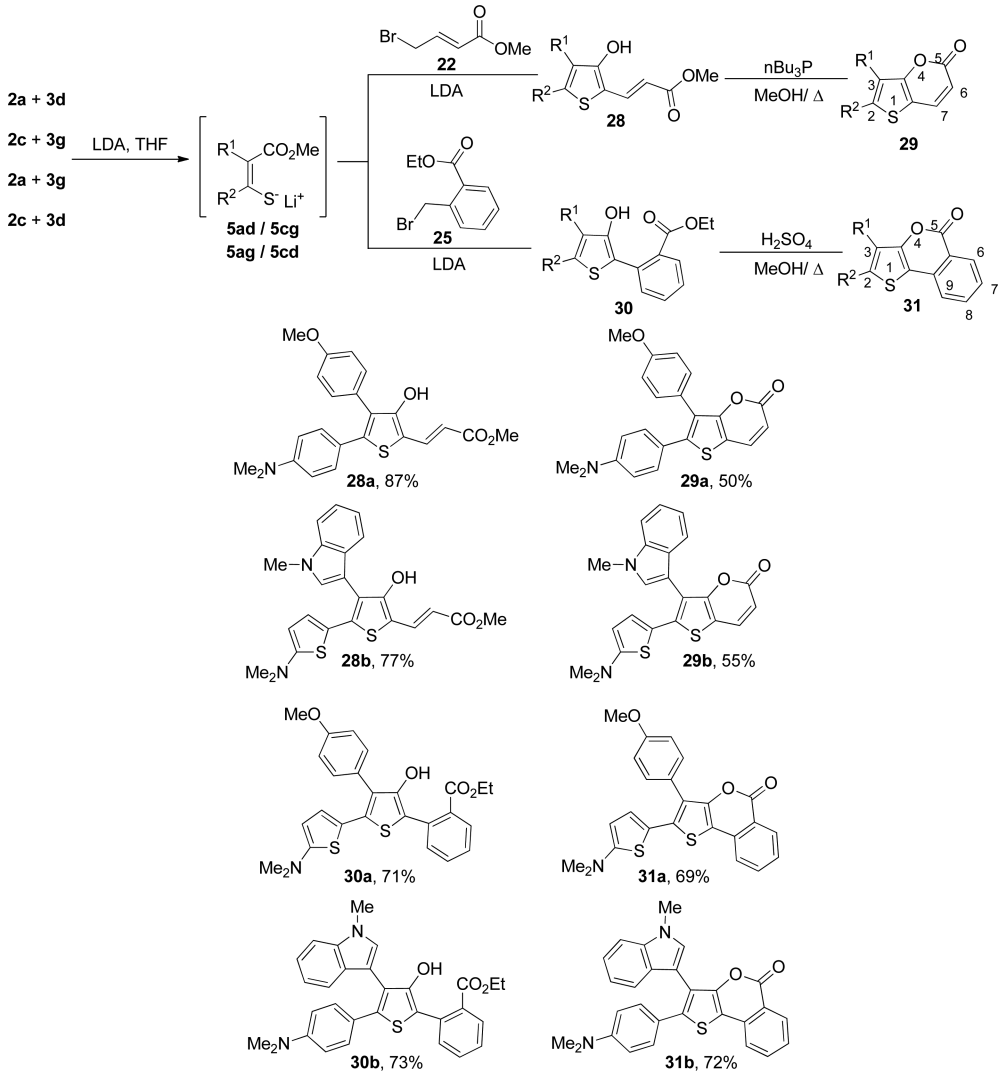
Scheme 11. Synthesis of Substituted Thieno[3,2-*b*]pyran-5-ones and Thieno[3,2-*c*]isochromen-5-ones



by treatment with LDA) with methyl 3-aminothieno-2-carboxylate.[29]

In our synthetic design for 2,3-substituted thieno[3,2-*b*]quinolones **35a,b**, we planned to construct this heterocyclic core via the intramolecular cycloannulation of the corresponding 3-amino-2-(2-chlorobenzoyl)thiophenes **33a,b** or their *N*-acyl derivatives **34a,b**, respectively (Scheme 12). Thus, the desired 3-amino-4,5-subtituted 2-(2-chlorobenzoyl)thiophene **33a** was obtained in high yield via the in situ S-alkylation-intramolecular cyclization of the corresponding thiolate salt **4ba** (derived from arylacetonitrile **1b** and dithioester **3a** in the presence of LDA) with 2-chlorophenacyl bromide **32.** 3-Aminothiophene **33a** was acylated with acetyl chloride to afford 3-(*N*-acyl)thiophene **34a**, which on copper-catalyzed intramolecular amination furnished the 2,3-bis(4-methoxyphenyl)-4*H*,9*H*-thieno[3,2-*b*]quinolin-9-one **35a** in 81% yield. Similarly, the corresponding 2-(3-pyridyl)-3-(*N*-methyl-3-indolyl)-thienoquinolone **35b** was also synthesized in high yield from the newly synthesized 3-(*N*-acylamino) 2-substituted thiophene **34b**, following the identical procedure (Scheme 12).

Thieno[3,2-*b*]chromen-9-ones, the thiophene analogs of xanthones, like their nitrogen counterparts have not been explored much; however, the corresponding benzothieno-fused derivatives (5-oxa-11-thiabenzo[*b*]fluoren-10-ones) have been recently shown to be selective estrogen receptor *β*-(ER*β*) ligands.[31] There is only one report of the synthesis of thieno[3,2-*b*]chromen-9-one, involving the 2-lithiation of 3-(*p*-tolyloxy)thiophene followed by the carbonation with CO_2 and subsequent intramolecular condensation of 3-aryloxythiophene-2-carboxylic acids with PPE.[32]

We followed a similar protocol for the synthesis of thieno[3,2-*b*]benzopyrones **37a,b** as described for thieno[3,2-*b*]quinolones **35a,b** via intramolecular base-mediated heterocyclization of the newly synthesized 3-hydroxy-2-(2-chlorobenzoyl)-4,5-substituted thiophenes **36a,b** (Scheme 13). Thus, one-pot alkylation−cyclocondensation of *β*-thienoacrylate salt **5ab** with 2-chlorophenacyl bromide **32** afforded the 4,5-disubstituted 3-hydroxy-2-(2-chlorobenzoyl)thiophene **36a** in 82% yield. The hydroxythiophene **36a** underwent facile intramolecular nucleophilic substitution in the presence of K_2CO_3/DMSO at 90 °C, furnishing the corresponding 2,3-bis(aryl)thieno[3,2-*b*]chromen-9-one **37a** in 80% yield. Similarly, the thienochromenone **37b** bearing a 3-pyridyl- and a 3-indolyl- moiety at 2,3-positions, respectively, was also obtained in excellent yield from 3-hydroxythiophene **36b** under identical conditions from the appropriate precursors (Scheme 13).

During the course of these studies, we observed that few of the substituted 3-amino/3-hydroxythiophenes (**10a,b**, **23a−c**,

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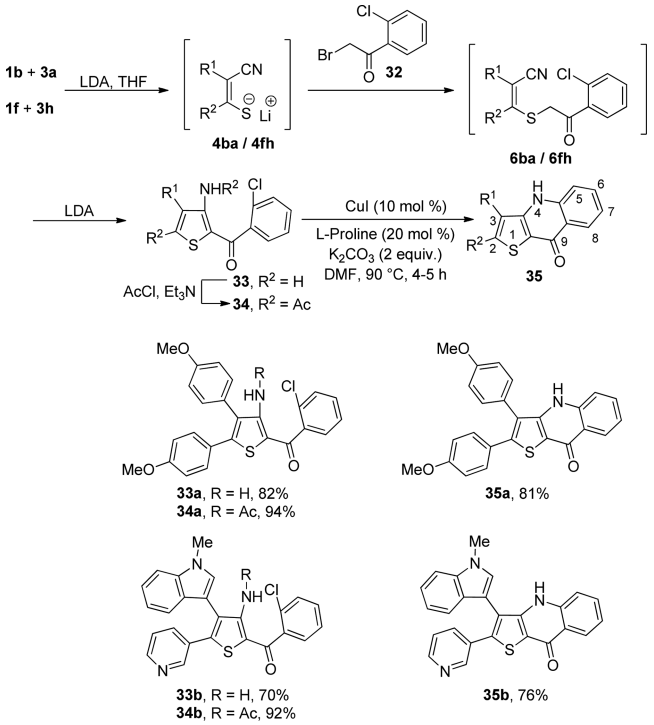
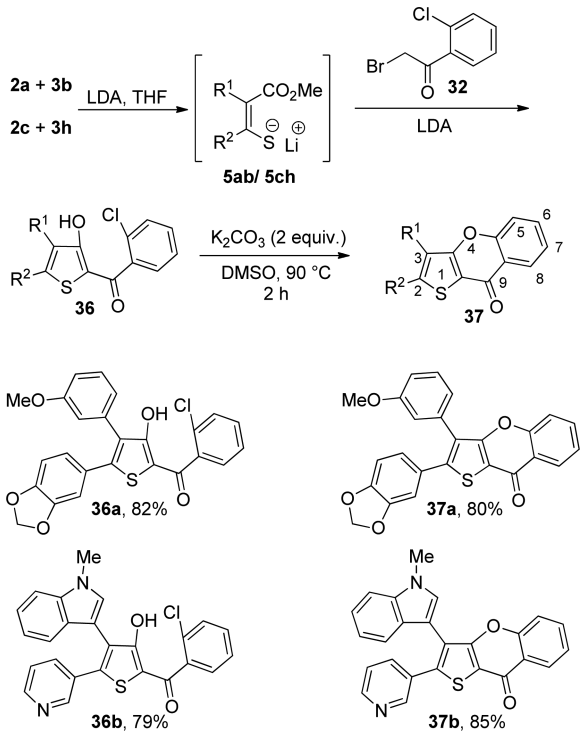
Scheme 12. Synthesis of Substituted Thieno[3,2-*b*]quinolin-9-ones

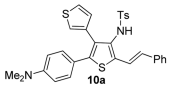
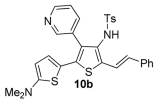
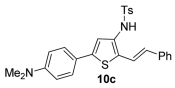
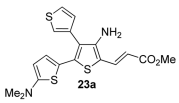
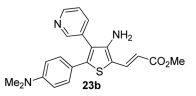
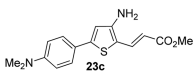
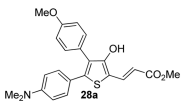
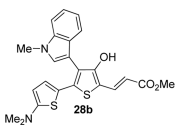


Scheme 13. Synthesis of Substituted Thieno[3,2-*b*]chromen-9-ones



28a,b) with extended conjugation display pronounced yellow-green, yellow, and red fluorescence, as observed in our previous study.[1] We therefore examined UV−vis absorption and emission spectra of these compounds, which are depicted in Table 1 and Figure 1A−F.

Table 1. UV−Vis Absorption and Emission Properties of Compounds 10a,b, 23a−c, and 28a,b

entry	compound	absorption $\lambda_{max,abs}$ (nm) ε ($Lmol^{-1}cm^{-1}$)[a]	emission $\lambda_{max,em}$ (nm)[b]	Stokes shift $\Delta(cm^{-1})$
1		303 (13,400), 465 (17,800)	627	5556
2		310 (17,900), 395 (19,700)	610	8923
3		308 (25,400) 415 (24,600)	604	7540
4		313 (25,700), 472 (31,500)	557	3233
5		292 (28,700), 415 (38,400)	593	7232
6		302 (29,800), 419 (36,200)	609	7445
7		306 (21,500), 451 (22,400)	606	5671
8		337 (25,400), 478 (33,500)	663	5837

[a]Recorded in MeCN, T = 293 K, c = 12.5 × 10^{-6} M. [b]Recorded in MeCN, T = 293 K, c = 12.5 × 10^{-6} M.

These 2,4,5-substituted 3-amino/3-hydroxythiophenes display strong absorption and emission properties because of their push−pull character due to the presence of electron-donating substituents (such as 4-(dimethylamino)phenyl- or 5-(dimethylamino)-2-thienyl- groups) and electron-withdrawing functionalities such as styryl/acrylate groups at the 5- and 2-positions, respectively. Thus, 3-*N*-tosyl-5-(4-dimethylamino)-phenyl-4-(3-thienyl)-2-styrylthiophene **10a** shows absorption bands at 303 and 465 nm with a high molar extinction coefficient of 13 400 and 17 800 L mol^{-1} cm^{-1}, respectively, and an emission band in the region of 627 nm (Table 1, Figure 1A,B). Further, it was found that the nature of the substituent at the 4-positon of these thiophenes affects the wavelength of the absorption band. Thus, in the UV spectrum of the 4-(3-pyridyl)-5-[(5-dimethylamino)-2-thienyl] derivative **10b**, the higher wavelength absorption band is blue-shifted to 395 nm in comparison to the corresponding 4-(3-thienyl) derivative **10a** (Table 1, entry 1 vs 2), probably due to the electron-withdrawing effect of the 4-(3-pyridyl) group. Its emission band is also present at a lower wavelength of 610 nm (Table 1, entry 2). The 4-unsubstituted 3-*N*-tosylaminothiophene **10c** also shows absorption bands at 308 and 415 nm and emission at 604 nm with a Stokes shift of 7540 cm^{-1} (Table 1, entry 3). Similarly, the corresponding 3-amino/3-hydroxythiophene-2-

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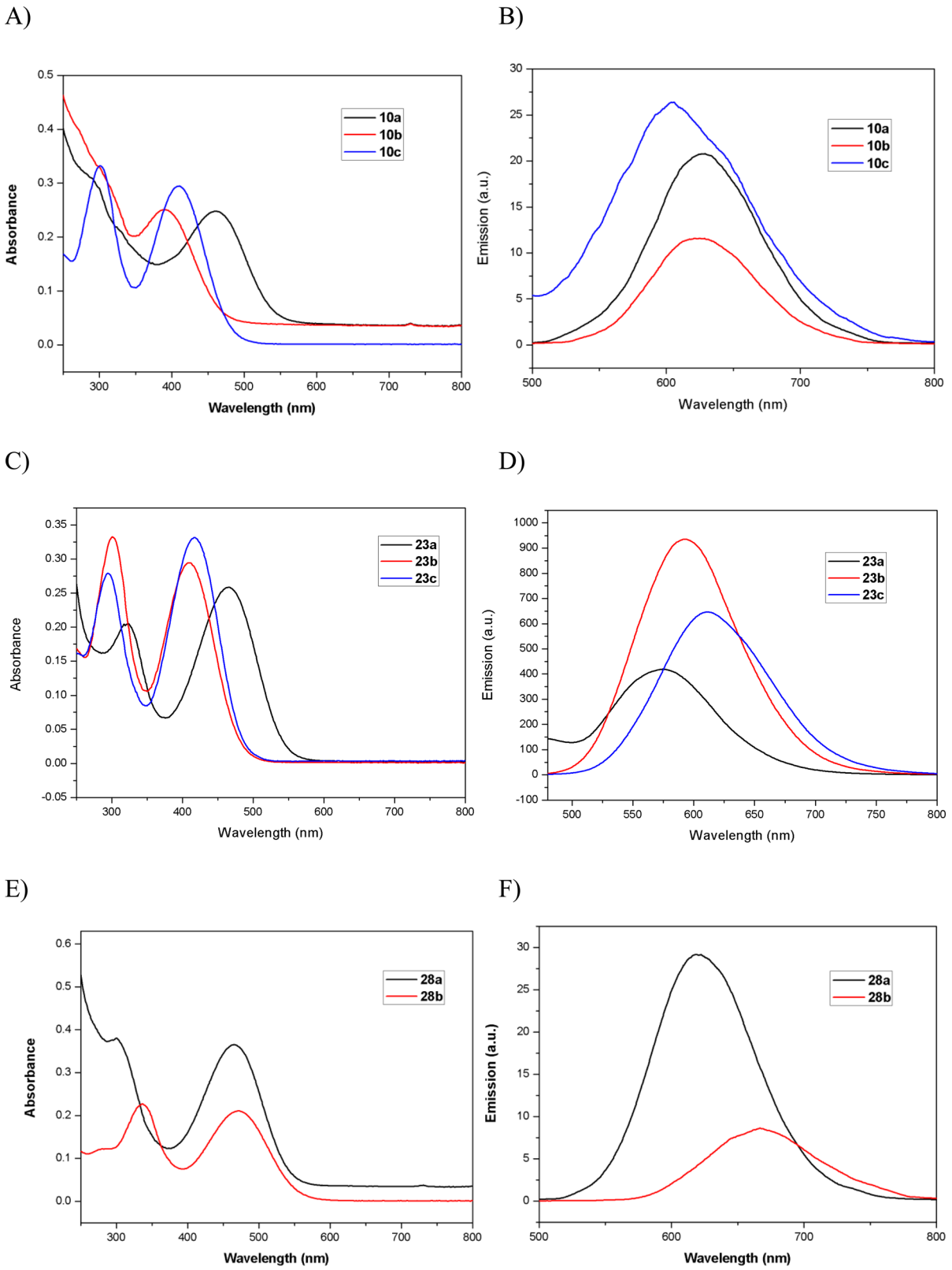

Figure 1. UV−vis absorption and emission spectra of compounds **10a,b**, **23a−c**, and **28a,b**: (A) UV−vis absorption spectra of **10a−c**; (B) emission spectra of **10a−c**; (C) UV−vis absorption spectra of **23a−c**; (D) emission spectra of **23a−c**; (E) UV−vis absorption spectra of **28a,b**; (F) emission spectra of **28a,b**. Recorded in MeCN, T = 293 K, c = 12.5 × 10^{-6} M. Excitation at longest absorption wavelength of all compounds.

acrylates **23a−c** and **28a,b** also display excellent UV−vis absorption and emission properties (Table 1, entries 4−8, Figure 1C−F).[1] Thus, 4,5-substituted 3-aminothiophene-2-acrylates **23a−c** show absorption in the range 302−472 nm with very high molar extinction coefficients (25 700−38 400 L mol^{-1} cm^{-1}). Here, also, we observe a trend similar to that of the thiophene-2-acrylate (**23b**) containing 4-(3-pyridyl) group, displaying lower wavelength absorption bands at 292 and 415

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nm in comparison to the corresponding 4-(3-thienyl)-thiophene-2-acrylate **23a** (Table 1, entry 4 vs 5). All three 3-aminothiophene-2-acrylates **23a−c** display strong emission bands at 557, 593, and 609 nm, respectively (Table 1, Figure 1D). The corresponding 4,5-substituted 3-hydroxythiophene-2-acrylates **28a,b** also show a similar trend in their UV−vis spectra displaying absorption bands at 306 and 451 nm and 337 and 478 nm, respectively (Table 1, entries 7 and 8). The higher wavelength absorption band present in the UV spectrum of **28b** may be attributed due to the presence of stronger electron-donating 4-(3-indolyl)- and 5-[(dimethylamio)-2-thienyl] groups at the 4- and 5-positions, respectively. The emission spectra of **28a,b** also display emission at 606 and 663 nm, respectively (Table 1, Figure 1F).

CONCLUSION

In summary, we have successfully developed simple general protocols to access a diverse range of novel thieno-fused five- and six-membered nitrogen and oxygen heterocycles, involving in situ or stepwise intramolecular heterocyclization of newly generated 4,5-substituted 3-amino or 3-hydroxy 2-functionalized thiophenes. These 3-amino/hydroxy thiophenes are readily assembled in high yields from easily accessible precursors, in a sequential one-pot process, by treatment of a range of (het)aryl/unsubstituted acetonitriles or acetates with het(aryl)dithioesters in the presence of LDA, followed by alkylation−intramolecular condensation of the resulting enethiolate salts with functionalized activated methylene halides.

It should be noted that, although there are few reports of a stepwise elaboration of 3-amino 4-substituted thiophenes to thieno-fused nitrogen heterocycles such as thienopyrimidines[11] and 4-hydroxythienopyridones,[21,22] corresponding 3-hydroxy 2-functionalized thiophenes are virtually unexplored as precursors for the synthesis of oxa-annulated thienoheterocycles. Also, the activated methylene halides commonly employed previously as alkylating agents in the synthesis of 3-amino/hydroxy 2-substituted thiophenes are bromoacetate, chloro/bromoacetonitrile, phenacyl bromide, or chloroacetamide,[10,11] whereas the present syntheses, utilizing cinnamyl bromide, bromocrotonate,[1,23] 2-bromobenzyl chloride, and 2-(bromomethyl)-benzoate[24b] as activated methylene halide coupling partners, further expand the scope of the synthesis of substituted 3-amino/hydroxythiophenes with built-in functionalities at the 2-position for their direct cycloannulation to thieno-fused heterocycles. Besides, the het(aryl)/alkyl dithioesters, which are scarcely investigated,[1] serve as useful precursors for introduction of substituent diversity at 5-position of 3-amino/hydroxythiophenes and the corresponding thienoheterocycles.

We expect that the synthetic strategies developed herein will provide facile access to a variety of appealing and potentially useful thieno-fused heterocycles, which will find applications in medicinal chemistry for library synthesis and in material science, serving as an additional means of tailoring the molecules and bulk properties of conjugated oligomers and polymers. Further work to extend these protocols for the synthesis of other novel thieno/thiazolo-fused heterocycles is in progress in our laboratory.

EXPERIMENTAL SECTION

General Information. All the reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography (TLC) using standard TLC silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100−200 mesh). Nuclear magnetic resonance spectra were recorded on a (400 MHz) FT-NMR spectrometer with $CDCl_3$, DMSO-d_6, or acetone-d_6 as solvent. Chemical shifts were reported in δ (ppm) using residual solvent protons as the internal standard (δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-d_6, and δ 2.05 for acetone-d_6 in ^{1}H NMR, δ 77.16 for $CDCl_3$, δ 39.52 for DMSO-d_6, and δ 206.68/δ 29.92 for acetone-d_6 in ^{13}C NMR). Coupling constants were reported as J values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet), and br (broad). Infrared spectra of neat samples were recorded in attenuated total reflectance (ATR) mode using a FT-IR instrument, and HRMS spectra were recorded using a Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and were uncorrected. Electronic absorption spectra were recorded on a UV−vis−NIR spectrometer. Emission spectra were recorded on a luminescence spectrometer.

Acetonitrile **1a** and (het)arylacetonitriles **1c**, **1d**, and **1e** were commercially purchased, whereas **1b** and **1f**[33] and (het)arylacetates **2a−c** were synthesized according to the reported procedure. All the (het)aryldithioesters **3a−h** were also prepared according to the literature procedure.[34]

General Procedure for the Synthesis of 4,5-Substituted 3-Amino/3-Hydroxy 2-Functionalized thiophenes 9a−c, 13a,b, 16a−c, 20a,b, 23a−c, 26a,b, 28a,b, 30a,b, 33a,b, and 36a,b. To a stirring solution of LDA (2.2 mmol) in THF (3 mL) at 0 °C was added (het)arylacetonitrile/acetate (1.0 mmol) in THF (3 mL), and the reaction mixture was further stirred for 10 min at 0 °C, followed by dropwise addition of a solution of (het)aryl dithioester (1.0 mmol) in THF (3 mL) and further stirring for 0.5 h, while maintaining the temperature at 0 °C (monitored by TLC). A solution of the halo alkylating agent (1.0 mmol) in THF (2 mL) was added dropwise to the reaction mixture followed by further stirring for 0.5 h at 0 °C and then at room temperature for 4−6 h (monitored by TLC). The reaction mixture was diluted with saturated NH_4Cl solution (25 mL) and extracted using ethyl acetate (3 × 25 mL). The combined organic layer was washed with water (3 × 25 mL) and brine and dried over Na_2SO_4, and the solvent was removed under vacuum. The crude residues were purified by column chromatography using hexane/ethyl acetate as eluents.

*2-(4-(Dimethylamino)phenyl)-5-styryl-3-(3-thienyl)thiophene-4-amine (**9a**).* Obtained from acetonitrile **1d** and dithioester **3d**: orange solid (309 mg, 77%); mp 143−145 °C; R_f 0.38 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H), 7.36 (dd, J = 8.0, 2.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 3H), 7.19 (d, J = 7.2 Hz, 1H), 7.17−7.09 (m, 3H), 6.96 (dd, J = 4.0, 0.4 Hz, 1H), 6.70 (d, J = 15.6 Hz, 1H), 6.56 (d, J = 8.8 Hz, 2H), 3.77 (s, 2H), 2.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 142.3, 139.2, 138.2, 135.6, 129.4, 129.3, 128.8, 126.8, 126.3, 125.9, 124.3, 124.1, 122.3, 119.1, 113.7, 112.1, 40.4; IR (neat, cm^{-1}) 3407, 336, 1604, 1275, 802; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2S_2$ $[M + H]^+$ 403.1302, found 403.1303.

*2-(2-(5-Dimethylamino)thienyl)-3-(pyridin-3-yl)-5-styrylthiophene-4-amine (**9b**).* Obtained from acetonitrile **1e** and dithioester **3g**: reddish brown solid (331 mg, 82%); mp 138−140 °C; R_f 0.36 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.4 Hz, 1H), 8.53 (dd, J = 4.4, 0.8 Hz, 1H), 7.84−7.81 (m, 1H), 7.66 (d, J = 4.8 Hz, 1H), 7.58−7.56 (m, 2H), 7.51−7.43 (m, 4H), 7.21 (dd, J = 8.4, 4.8 Hz, 1H), 6.73 (d, J = 16 Hz, 1H), 5.98 (d, J = 4.4 Hz, 1H), 3.09 (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 152.9, 151.1, 147.9, 138.8, 136.0, 135.8, 134.1, 131.4, 131.3, 131.2, 129.23, 129.21, 128.7, 128.64, 128.60, 124.9, 121.1, 105.4, 42.1; IR (neat, cm^{-1}) 3392, 3167, 1578, 1457, 1128, 747; HRMS (ESI) m/z calcd for $C_{23}H_{22}N_3S_2$ $[M + H]^+$ 404.1255, found 404.1249.

*5-(4-(Dimethylamino)phenyl)-2-styrylthiophen-3-amine (**9c**).* Obtained from acetonitrile **1a** and dithioester **3d**: yellow solid (180 mg, 56%); mp 103−105 °C; R_f 0.31 (1:4 EtOAc/hexane); ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 16 Hz, 1H), 7.56−7.54 (m, 2H),

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7.42−7.40 (m, 4H), 7.29 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 16 Hz, 1H), 2.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.2, 134.2, 131.8, 130.9, 130.0, 129.1, 128.5, 127.8, 127.1, 117.5, 114.4, 112.3, 108.8, 40.7; IR (neat, cm^{-1}) 3412, 3243, 1589, 1432, 750; HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2S$ $[M + H]^+$ 321.1425, found 321.1419.

*2-(2-Bromophenyl)-4-(3,4-dimethoxyphenyl)-5-(4-fluorophenyl)-thiophen-3-amine (**16a**).* Obtained from acetonitrile **1c** and dithioester **3c**: off-white solid (420 mg, 87%); mp 115−117 °C; R_f 0.72 (2:8 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.69 (m, 1H), 7.56 (dd, J = 7.6, 1.2 Hz, 1H), 7.40−7.36 (m, 1H), 7.24−7.20 (m, 3H), 6.92−6.88 (m, 4H), 6.79 (1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 160.9, 149.4, 148.7, 141.0, 137.2, 134.7, 133.6, 133.5, 130.5, 130.4, 130.0, 129.5, 129.0, 127.8, 127.7, 126.3, 125.0, 122.6, 115.5, 115.3, 113.6, 113.0, 111.8, 56.04, 56.00; IR (KBr, cm^{-1}) 3469, 3375, 1508, 1253, 1139, 755; HRMS (ESI) m/z calcd for $C_{24}H_{20}BrFNO_2S$ $[M + H]^+$ 484.0322 and 486.0362, found 484.0318 and 486.0361.

*5-(2-Bromophenyl)-2-(2-(5-dimethylamino)thienyl)-3-(pyridin-3-yl)-thiophene-4-amine (**16b**).* Obtained from acetonitrile **1e** and dithioester **3g**: reddish brown solid (345 mg, 76%); mp 185−187 °C; R_f 0.31 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.4 Hz, 1H), 8.53 (dd, J = 4.4, 1.2 Hz, 1H), 7.82 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.66 (d, J = 4.8 Hz, 1H), 7.39 (dd, J = 5.2, 1.2 Hz, 1H), 7.21−7.18 (m, 1H), 7.11−7.07 (m, 1H), 6.75 (dd, J = 8.0, 1.6 Hz, 1H), 6.63−6.59 (m, 1H), 5.98 (d, J = 4.8 Hz, 1H), 4.08 (br s, 2H), 3.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 147.9, 144.2, 138.7, 132.6, 121.3, 128.6, 128.4, 127.6, 127.0, 124.9, 122.7, 121.0, 119.3, 115.8, 109.3, 105.4, 42.0; IR (neat, cm^{-1}) 3457, 3295, 1600, 1192, 1021, 754; HRMS (ESI) m/z calcd for $C_{21}H_{19}BrN_3S_2$ $[M + H]^+$ 456.0204 and 458.0183, found 456.0202 and 456.0180.

*5-(2-Bromophenyl)-[2,2′-bithiophen]-4-amine (**16c**).* Obtained from acetonitrile **1a** and dithioester **3f**: off-white solid (197 mg, 59%); mp 132−134 °C; R_f 0.53 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 7.6, 1.6 Hz, 1H), 7.23 (dd, J = 5.2, 1.2 Hz, 1H), 7.13−7.08 (m, 2H), 7.06 (dd, J = 7.6, 1.2 Hz, 1H), 6.87 (dd, J = 6.4, 3.6 Hz, 1H), 6.76 (dd, J = 8.0, 1.6 Hz, 1H), 6.65−6.60 (m, 2H), 4.07 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 144.2, 132.7, 130.0, 129.2, 128.4, 127.7, 127.1, 123.2, 119.5, 116.3, 115.9, 112.2, 109.4; IR (neat, cm^{-1}) 3389, 3216, 1605, 1523, 1216, 755; HRMS (ESI) m/z calcd for $C_{14}H_{11}BrNS_2$ $[M + H]^+$ 335.9516 and 337.9496, found 335.9508 and 337.9485.

*2-Phenyl-4-(3,4-dimethoxyphenyl)-5-(4-fluorophenyl)thiophen-3-amine (**16d**).* Obtained from acetonitrile **1c** and dithioester **3c**: off-white solid (308 mg, 76%); mp 193−195 °C; R_f 0.55 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.61 (m, 2H), 7.46−7.42 (m, 2H), 7.28−7.25 (m, 2H), 7.23−7.19 (m, 2H), 6.92−6.88 (m, 3H), 6.802−6.799 (m, 1H), 3.91 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 160.9, 149.5, 148.8, 139.9, 136.5, 134.7, 131.2, 130.73, 130.69, 130.4, 130.3, 129.3, 127.7, 127.6, 126.6, 122.7, 115.6, 115.3, 114.7, 113.5, 111.8, 56.04, 56.00; IR (neat, cm^{-1}) 3426, 3345, 2624, 1595, 1493, 1024, 759; HRMS (ESI) m/z calcd for $C_{24}H_{21}FNO_2S$ $[M + H]^+$ 406.1277, found 406.1276.

*Methyl 4-Amino-2(2-(5-dimethylamino)thienyl)3-thienylthiophene-2-acrylate (**23a**).* Obtained from acetonitrile **1d** and dithioester **3g**: orange solid (312 mg, 80%); mp 187−189 °C; R_f 0.63 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 16 Hz, 1H), 7.24−7.22 (m, J = 1H), 7.06−7.04 (m, 1H), 6.87 (dd, J = 3.6, 5.2 Hz, 1H), 6.14 (d, J = 16 Hz, 1H), 5.98 (d, J = 4.8 Hz, 1H), 3.76 (s, 3H), 3.09 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 133.8, 133.2, 132.5, 131.2, 130.8, 129.9, 128.2, 127.7, 127.1, 125.4, 123.4, 120.5, 112.2, 105.4, 55.9, 42.1; IR (neat, cm^{-1}) 3482, 3359, 1688, 1585, 1163, 750; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O_2S_3$ $[M + H]^+$ 391.0609, found 391.0599.

*Methyl 3-Amino-5-(4-(dimethylamino)phenyl)-4-(pyridin-3-yl)-thiophen-2-acrylate (**23b**).* Obtained as E/Z mixture in 73:27 ratio from acetonitrile **1e** and dithioester **3d**: orange solid (330 mg, 87%); mp 105−107 °C; R_f 0.43 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61−8.59 (m, 1H), 8.54−8.53 (m, 1H), 7.80 (d, J = 15.2 Hz, 1H), 7.79−7.63 (m, 0.54H), 7.33 (ddd, J = 8.0, 4.8, 0.8 Hz, 0.73H), 7.31−7.28 (m, 0.27H), 7.12 (d, J = 9.2 Hz, 0.54H), 7.01 (d, J = 9.2 Hz, 1.46H), 6.60 (d, J = 9.2 Hz, 0.54H), 6.51 (d, J = 9.2 Hz, 1.46H), 5.95 (d, J = 15.2 Hz, 1H), 4.04 (br s, 2H), 3.78 (s, 3H), 2.97 (s, 1.34H), 2.93 (s, 4.66H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 151.2, 150.9, 150.4, 149.0, 147.1, 145.3, 141.0, 138.2, 137.7, 134.3, 131.2, 129.8, 129.3, 124.7, 124.1, 120.6, 1, 112.0, 110.4, 110.2, 51.5, 40.3; IR (neat, cm^{-1}) 3398, 3195, 1673, 1585, 1165, 750; HRMS (ESI) m/z calcd for $C_{21}H_{22}N_3O_2S$ $[M + H]^+$ 380.1433, found 380.1431.

*Methyl 3-Amino-5-(4-(dimethylamino)phenyl)thiophen-2-acrylate (**23c**).* Obtained from acetonitrile **1a** and dithioester **3d**: orange solid (184 mg, 61%); mp 117−119 °C; R_f 0.58 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79−7.71 (m, 3H), 7.26 (s, 1H), 6.74 (d, J = 8.8 Hz, 2H), 6.14 (d, J = 15.6 Hz, 1H), 3.80 (s, 3H), 3.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 155.6, 151.7, 143.4, 130.7, 128.8, 116.8, 116.2, 112.2, 106.7, 51.9, 40.3; IR (neat, cm^{-1}) 3264, 3121, 1652, 1543, 1109, 753; HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O_2S$ $[M + H]^+$ 303.1167, found 303.1167.

*Ethyl 2-(3-Amino-4-(3,4-dimethoxyphenyl)-5-(4-(piperidin-1-yl)-phenyl)thiophen-2-yl)benzoate (**26a**).* Obtained from acetonitrile **1c** and dithioester **3e**: brown solid (38 mg, 7%); mp 199−201 °C; R_f 0.23 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 9.2 Hz, 2H), 7.85 (dd, J = 8.0, 1.6 Hz, 1H), 7.61 (dd, J = 8.0, 1.6 Hz, 1H), 7.19 (td, J = 8.0, 1.2 Hz, 1H), 7.04−7.00 (9m, 1H), 6.99−6.96 (m, 2H), 6.77 (d, J = 9.2 Hz, 2H), 6.72 (d, J = 7.6 Hz, 1H), 4.69 (br s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.35 (s, 3H), 3.37−3.35 (br m, 4H), 1.66 (br s, 6H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 154.5, 149.8, 148.4, 140.4, 134.5, 132.8, 129.9, 129.8, 129.5, 128.9, 128.4, 127.7, 127.0, 123.4, 114.9, 1112.8, 112.6, 112.2, 101.2, 61.1, 56.1, 56.1, 48.6, 25.4, 19.8, 14.6; IR (neat, cm^{-1}) 3351, 3134, 1721, 1592, 1426, 1158, 750; HRMS (ESI) m/z calcd for $C_{32}H_{35}N_2O_4S$ $[M + H]^+$ 543.2318, found 543.2315.

*Ethyl 2-(3-Amino-5-(4-(dimethylamino)phenyl)-4-(1-methyl-1H-indol-3-yl)thiophen-2-yl)benzoate (**26b**).* Obtained from acetonitrile **1f** and dithioester **3d**: brown solid (44 mg, 9%); mp 216−218 °C; R_f 0.23 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.0, 1.2 Hz, 1H), 7.60 (dd, J = 8.0, 1.2 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.32−7.24 (m, 4H), 7.20−7.14 (m, 2H), 7.05 (s, 1H), 6.97 (td, J = 8.0, 1.2 Hz, 1H), 6.56 (d, J = 8.8 Hz, 2H), 4.73 (br s, 2H), 4.01 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 2.90 (s, 6H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 157.2, 149.6, 140.4, 137.1, 132.8, 131.7, 129.7, 129.5, 128.4, 127.4, 127.0, 126.5, 122.4, 119.7, 118.3, 118.2, 114.1, 109.7, 108.5, 103.0, 61.1, 40.6, 32.8, 14.3; IR (neat, cm^{-1}) 3382, 3201, 1719, 1560, 1432, 1167, 770; HRMS (ESI) m/z calcd for $C_{30}H_{30}N_3O_2S$ $[M + H]^+$ 496.2059, found 496.2050.

*(3-Amino-4,5-bis(4-methoxyphenyl)thiophen-2-yl)(2-chlorophenyl)methanone (**33a**).* Obtained from acetonitrile **1b** and dithioester **3a**: yellow solid (368 mg, 82%); mp 175−177 °C; R_f 0.35 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.32−7.29 (m, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.43 (br s, 2H), 3.84 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 160.1, 159.6, 155.5, 149.4, 140.5, 131.4, 131.0, 130.6, 130.2, 129.8, 128.5, 127.6, 126.6, 125.9, 125.6, 115.1, 114.0, 109.9, 55.42, 55.37; IR (neat, cm^{-1}) 3451, 3316, 1604, 1586, 1246, 1025, 751; HRMS (ESI) m/z calcd for $C_{25}H_{21}ClNO_3S$ $[M + H]^+$ 450.0931 and 452.0901, found 450.0929 and 452.0909.

*(3-Amino-4-(1-methyl-1H-indol-3-yl)-5-(pyridin-3-yl)thiophen-2-yl)(2-chlorophenyl)methanone (**33b**).* Obtained from acetonitrile **1f** and dithioester **3h**: yellow solid (310 mg, 70%); mp 186−188 °C; R_f 0.35 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.48 (br s, 1H), 8.38 (br s, 1H), 7.67−7.65 (m, 1H), 7.61−7.58 (m, 1H), 7.56−7.49 (m, 3H), 7.47−7.44 (m, 2H), 7.21−7.17 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 6.97−6.37 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 186.8, 157.3, 150.4, 149.5, 145.4, 141.6, 138.4, 136.1, 131.9, 130.9, 130.6, 129.4, 128.0, 127.7, 124.8, 124.3, 123.0, 120.7, 120.3, 110.9, 106.4, 33.3; IR (neat, cm^{-1}) 3464, 3287, 1599, 1447, 1260, 749; HRMS (ESI) m/z calcd for $C_{25}H_{19}ClN_3OS$ $[M + H]^+$ 444.0937 and 446.0908, found 444.0938 and 446.0917.

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*5-(4-(Dimethylamino)phenyl)-4-(4-methoxyphenyl)-2-styrylthiophen-3-ol (**13a**).* Obtained from acetate **2a** and dithioester **3d**: yellow solid (329 mg, 77%); mp 183−185 °C; R_f 0.33 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68−7.67 (m, 2H), 7.60 (d, J = 16 Hz, 1H), 7.46−7.41 (m, J = 5H), 7.29 (d, J = 9.2 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.65 (J = 9.2 Hz, 2H), 6.53 (d, J = 16 Hz, 1H), 3.75 (s, 3H), 2.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 149.6, 147.1, 134.2, 132.3, 131.8, 130.8, 129.9, 129.1, 128.5, 127.7, 127.1, 117.5, 115.8, 114.3, 112.9, 112.2, 108.7, 55.5, 40.7; IR (neat, cm^{-1}) 3458−2651 (br), 2925, 1585, 1461, 1105, 749; HRMS (ESI) m/z calcd for $C_{27}H_{26}NO_2S$ $[M + H]^+$ 428.1684, found 428.1680.

*4-(1-Methyl-1H-indol-3-yl)-5-(4-(piperidin-1-yl)phenyl)-2-styrylthiophen-3-ol (**13b**).* Obtained from acetate **2c** and dithioester **3e**: brown solid (353 mg, 72%); mp 192−194 °C; R_f 0.28 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 7.6 Hz, 2H), 7.68−7.67 (m, 2H), 7.61 (d, J = 5.6 Hz, 1H), 7.58 (s, 1H), 7.45−7.41 (m, 4H), 7.34 (s, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 16 Hz, 1H), 3.77 (s, 3H), 3.42−3.41 (m, 4H), 1.59−1.57 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 137.2, 134.5, 134.1, 132.6, 130.8, 129.2, 129.1, 128.6, 128.4, 127.6, 127.4, 127.1, 127.0, 126.5, 122.5, 119.8, 118.3, 117.4, 112.9, 109.7, 103.0, 48.6, 32.9, 25.4, 14.3; IR (neat, cm^{-1}) 3461−2521 (br), 2851, 1614, 1588, 1437, 1107, 750; HRMS (ESI) m/z calcd for $C_{32}H_{31}N_2OS$ $[M + H]^+$ 491.2157, found 491.2155.

*2-(2-Bromophenyl)-4,5-bis(4-methoxyphenyl)thiophen-3-ol (**20a**).* Obtained from acetate **2a** and dithioester **3a**: off-white solid (359 mg, 77%); mp 197−199 °C; R_f 0.21 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55−7.52 (m, 2H), 7.51−7.46 (m, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 5.61 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 147.3, 133.4, 133.2, 131.4, 131.1, 130.6, 130.1, 130.0, 129.9, 129.4, 127.6, 126.3, 124.3, 114.4, 114.0, 113.9, 113.7, 55.2; IR (neat, cm^{-1}) 3481−2782 (br), 1654, 1452, 1198, 753; HRMS (ESI) m/z calcd for $C_{24}H_{20}BrO_3S$ $[M + H]^+$ 467.0317 and 469.0296, found 467.0311 and 469.0291.

*5-(2-Bromophenyl)-3-(1-methyl-1H-indol-3-yl)-2-(2-thienyl)-thiophen-4-ol (**20b**).* Obtained from acetate **2c** and dithioester **3f**: brown semisolid (362 mg, 78%); R_f 0.21 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.43−7.34 (m, 3H), 7.30−7.21 (m, 1H), 7.17 (m, 2H), 7.10 (d, J = 7.6 Hz, 1H), 7.08−7.06 (m, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.84 (t, J = 4.0 Hz, 1H), 5.06 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 137.4, 136.7, 133.5, 133.2, 132.1, 129.6, 129.4, 128.3, 127.5, 126.9, 125.3, 125.1, 124.5, 122.5, 121.9, 120.3, 113.4, 109.7, 106.3, 33.3; IR (neat, cm^{-1}) 3458−2621 (br), 3010, 1684, 1467, 1275, 749; HRMS (ESI) m/z calcd for $C_{23}H_{17}BrNOS_2$ $[M + H]^+$ 465.9935 and 467.9914, found 465.9930 and 467.9907.

*Methyl 3-(5-(4-(Dimethylamino)phenyl)-3-hydroxy-4-(4-methoxyphenyl)thiophen-2-yl)acrylate (**28a**).* Obtained from acetate **2a** and dithioester **3d**: black solid (356 mg, 87%); mp 192−194 °C; R_f 0.38 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 6.33 (d, J = 16 Hz, 1H), 6.19 (d, J = 16 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 2.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.7, 149.6, 132.3, 131.7, 130.8, 129.9, 128.3, 127.7, 127.0, 115.8, 114.1, 112.8, 112.2, 108.5, 55.5, 51.7, 40.6; IR (neat, cm^{-1}) 3487−2518 (br), 1714, 1613, 1588, 1432, 1156, 750; HRMS (ESI) m/z calcd for $C_{23}H_{24}NO_4S$ $[M + H]^+$ 410.1426, found 410.1425.

*Methyl 3-(5′-(Dimethylamino)-4-hydroxy-3-(1-methyl-1H-indol-3-yl)-2-(2-thienyl)thiophen-5-acrylate (**28b**).* Obtained from acetate **2c** and dithioester **3g**: black solid (337 mg, 77%); mp 215−217 °C; R_f 0.29 (3:2 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, J = 4.8 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H), 6.33 (d, J = 16 Hz, 1H), 6.27 (d, J = 4.8 Hz, 1H), 6.19 (d, J = 16 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 137.1, 135.7, 131.2, 130.8, 129.9, 128.3, 127.7, 127.4, 127.0, 126.5, 122.4, 119.7, 118.3, 112.1, 109.7, 105.4, 103.0, 51.7, 42.0, 32.8; IR (neat, cm^{-1}) 3430−2621 (br), 1728, 1601, 1542, 1425, 1106, 753; HRMS (ESI) m/z calcd for $C_{23}H_{23}N_2O_3S_2$ $[M + H]^+$ 439.1150, found 439.1149.

*Ethyl 2-(5′-(Dimethylamino)-4-hydroxy-3-(4-methoxyphenyl)-[2,2′-bithiophen]-5-yl)benzoate (**30a**).* Obtained from acetate **2a** and dithioester **3g**: black solid (340 mg, 71%); mp 201−203 °C; R_f 0.32 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.70 (d, J = 4.8 Hz, 1H), 7.66 (dd, J = 7.6, 1.6 Hz, 1H), 7.54−7.50 (m, 1H), 7.44 (d, J = 9.2 Hz, 2H), 7.00−6.94 (m, 1H), 6.90 (d, J = 9.2 Hz, 2H), 6.27 (d, J = 4.8 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.10 (s, 6H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 152.9, 140.6, 140.4, 140.0, 132.8, 131.2, 129.9, 129.5, 128.5, 127.7, 127.1, 116.5, 114.9, 112.2, 105.4, 112.2, 105.4, 61.1, 55.8, 42.1, 14.6; IR (neat, cm^{-1}) 3489, 1718, 1535, 1426, 1108, 750; HRMS (ESI) m/z calcd for $C_{26}H_{26}NO_4S_2$ $[M + H]^+$ 480.1303, found 480.1301.

*Ethyl 2-(5-(4-(Dimethylamino)phenyl)-3-hydroxy-4-(1-methyl-1H-indol-3-yl)thiophen-2-yl)benzoate (**30b**).* Obtained from acetate **2c** and dithioester **3d**: black solid (168 mg, 80%); mp 219−221 °C; R_f 0.21 (3:2 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.54−7.50 (m, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.30−7.28 (m, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.01−6.94 (m, 2H), 6.66−6.64 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 2.87 (s, 6H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 149.6, 140.4, 137.2, 132.8, 131.7, 129.9, 129.8, 129.5, 128.5, 127.7, 127.4, 127.1, 126.5, 122.5, 119.8, 118.3, 114.2, 112.2, 109.7, 108.6, 103.0, 101.2, 61.1, 32.9, 14.3; IR (neat, cm^{-1}) 3489−2572 (br), 1722, 1539, 1425, 1110, 748; HRMS (ESI) m/z calcd for $C_{30}H_{29}N_2O_3S$ $[M + H]^+$ 497.1899, found 497.1899.

*(5-(Benzo[d][1,3]dioxol-5-yl)-3-hydroxy-4-(3-methoxyphenyl)-thiophen-2-yl)(2-chlorophenyl)methanone (**36a**).* Obtained from acetate **2a** and dithioester **3b**: off-white solid (380 mg, 82%); mp 93−95 °C; R_f 0.37 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.71−7.69 (m, 1H), 7.63−7.61 (m, 2H), 7.57−7.52 (m, 1H), 7.31 (td, J = 7.6, 1.2 Hz, 1H), 6.95−6.92 (m, 2H), 6.90−6.89 (m, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.01 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 190.5, 166.3, 160.8, 150.9, 149.9, 149.0, 139.0, 134.4, 133.0, 131.3, 131.2, 130.5, 129.9, 129.6, 128.2, 127.7, 124.2, 123.3, 116.7, 114.5, 113.9, 109.7, 109.5, 102.8, 55.6; IR (neat, cm^{-1}) 3454, 2924, 1651, 1599, 1245, 753; HRMS (ESI) m/z calcd for $C_{25}H_{18}ClO_5S$ $[M + H]^+$ 465.0563 and 467.0534, found 465.0562 and 467.0532.

*(2-Chlorophenyl)(3-hydroxy-4-(1-methyl-1H-indol-3-yl)-5-(pyridin-3-yl)thiophen-2-yl)methanone (**36b**).* Obtained from acetate **2c** and dithioester **3h**: yellow solid (350 mg, 79%); mp 113−115 °C; R_f 0.32 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 8.63 (br s, 1H), 8.45 (br s, 1H), 7.60−7.59 (m, 2H), 7.53 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.20−7.17 (m, 2H), 7.10−7.08 (m, 2H), 6.95 (t, J = 7.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.17, 166.5, 148.9, 144.3, 137.9, 137.2, 135.6, 131.2, 130.7, 129.5, 128.7, 126.9, 124.9, 123.4, 122.2, 120.5, 120.0, 114.2, 109.7, 105.4, 33.2; IR (neat, cm^{-1}) 3467, 1648, 1452, 1236, 748; HRMS (ESI) m/z calcd for $C_{25}H_{18}ClN_2O_2S$ $[M + H]^+$ 445.0778 and 447.0748, found 445.0780 and 447.0753.

General Procedure for the N-Tosylation of 3-Aminothiophenes 9a−c. To a solution of 3-aminothiophenes **9a−c** (0.3 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.1 mL, 1.2 mmol) and tosyl chloride (62 mg, 0.33 mmol), and the reaction mixture was stirred at room temperature for 3−4 h (monitored by TLC). The solvent was removed in vacuo, and the residue was diluted with water and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with 10% aq HCl, water, and brine, dried, and concentrated under reduced pressure. The crude products were purified by column chromatography using hexane/ethyl acetate as eluents.

*N-(2-(4-(Dimethylamino)phenyl)-5-styryl-3-(3-thienyl)thiophen-4-yl)-4-methylbenzenesulfonamide (**10a**):* off-white solid (155 mg, 93%); mp 157−159 °C; R_f 0.34 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H) 7.37 (d, J = 7.2 Hz, 2H),

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7.32−7.28 (m, 3H), 7.24−7.21 (m, 2H), 7.17 (dd, J = 4.8, 3.2 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.10 (D, J = 8.8 Hz, 2H), 6.87 (d, J = 15.6 Hz, 1H), 6.79−6.78 (m, 1H), 6.52 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 5.2 Hz, 1H), 6.18 (s, 1H), 2.92 (s, 6H), 2.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 143.8, 138.6, 137.2, 136.9, 137.2, 136.9, 135.6, 134.4, 129.8, 129.7, 129.1, 129.0, 128.7, 128.2, 127.7, 127.5, 126.7, 125.9, 124.2, 121.6, 120.4, 112.0, 40.3, 21.6; IR (neat, cm^{-1}) 3243−2690 (br), 1604, 1516, 1160, 749; HRMS (ESI) m/z calcd for $C_{31}H_{29}N_2O_2S_3$ $[M + H]^+$ 557.1391, found 557.1383.

*N-(2-(2-(5-Dimethylamino)thienyl-3-(pyridin-3-yl)-5-styrylthiophen-4-yl)-4-methylbenzenesulfonamide (**10b**):* pale yellow solid (149 mg, 89%); mp 161−163 °C; R_f 0.29 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.53 (d, J = 4.4 Hz, 1H), 7.83−7.81 (m, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 4.8 Hz, 1H), 7.58−7.56 (m, 3H), 7.48 (d, J = 16 Hz, 1H), 7.44−7.43 (m, 3H), 7.24−7.18 (m, 2H), 6.72 (d, J = 16 Hz, 1H), 5.97 (d, J = 4.4 Hz, 1H), 3.07 (s, 6H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 150.8, 147.7, 139.1, 139.0, 136.8, 134.4, 131.3, 130.9, 130.6, 129.9, 128.3, 127.0, 125.0, 123.5, 121.1, 119.12, 119.09, 118.02, 117.96, 105.3, 42.1, 21.0; IR (neat, cm^{-1}) 3415−2698 (br), 1600, 1519, 1251, 750; HRMS (ESI) m/z calcd for $C_{30}H_{28}N_3O_2S_3$ $[M + H]^+$ 558.1344, found 558.1340.

*N-(5-(4-(Dimethylamino)phenyl)-2-styrylthiophen-3-yl)-4-methylbenzenesulfonamide (**10c**):* pale yellow solid (129 mg, 91%); mp 125−127 °C; R_f 0.41 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.10 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.8 Hz, 4H), 7.61 (d, J = 16 Hz, 1H), 7.43−7.42 (m, 3H), 6.78 (d, J = 8.4 Hz, 2H), 6.54 (d, J = 16 Hz, 1H), 3.04 (s, 6H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 147.1, 136.9, 134.2, 131.8, 131.3, 130.92, 130.85, 130.0, 129.1, 128.5, 127.8, 127.1, 119.2, 117.5, 114.3, 112.3, 108.8, 40.7, 21.0; IR (neat, cm^{-1}) 3321−2236 (br), 1594, 14329, 1214, 750; HRMS (ESI) m/z calcd for $C_{27}H_{27}N_2O_2S_2$ $[M + H]^+$ 475.1514, found 475.1515.

General Procedure for the Synthesis of Thieno[3,2-*b*]-pyrroles 11a−c from 3-*N*-Tosylaminothiophenes 10a−c via Iodocyclization. To a stirring solution of 3-*N*-tosylaminothiophenes **10a−c** (0.1 mmol) in CH_2Cl_2 (5.0 mL) was added NIS (45 mg, 0.2 mmol) under air. The reaction mixture was stirred at room temperature for 4 h (monitored by TLC) and concentrated under reduced pressure to give crude residues, which were purified by column chromatography on silica gel to give the corresponding thieno[3,2-*b*]pyrroles **11a−c**.

*2-(4-(Dimethylamino)phenyl-5-phenyl-3-(thiophen-3-yl)-4-tosyl-4H-thieno[3,2-b]pyrrole (**11a**):* brown solid (43 mg, 77%); mp 148−150 °C; R_f 0.32 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 77.44−7.42 (m, 3H), 7.37−7.33 (m, 5H), 7.21 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.04−7.00 (m, 4H), 6.59 (d, J = 8.8 Hz, 2H), 6.48 (s, 1H), 2.95 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 144.3, 143.8, 142.3, 135.8, 134.2, 132.9, 130.1, 129.6, 128.8, 128.2, 127.8, 127.1, 124.3, 124.1, 123.2, 122.7, 112.0, 111.9, 40.5, 21.7; IR (neat, cm^{-1}) 1605, 1522, 1346, 1094, 759; HRMS (ESI) m/z calcd for $C_{31}H_{27}N_2O_2S_3$ $[M + H]^+$ 555.1235, found 555.1229.

*2-(5-(Dimethylamino)-2-thienyl-5-phenyl-3-(pyridin-3-yl)-4-tosyl-4H-thieno[3,2-b]pyrrole (**11b**):* brown solid (44 mg, 80%); R_f 0.23 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.53 (d, J = 4.8 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.84−7.81 (m, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.67−7.65 (m, 3H), 7.63−7.59 (m, 1H), 7.50−7.46 (m, 2H), 7.22−7.19 (m, 1H), 5.98 (d, J = 4.8 Hz, 1H), 3.09 (s, 6H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 148.0, 144.2, 138.8, 137.3, 136.9, 132.7, 131.3, 130.9, 130.0, 128.4, 127.8, 127.1, 126.7, 124.9, 121.1, 119.5, 119.2, 115.9, 112.3, 109.4, 105.4, 42.1, 21.0; IR (neat, cm^{-1}) 1598, 1431, 1219, 1025, 746; HRMS (ESI) m/z calcd for $C_{30}H_{26}N_3O_2S_3$ $[M + H]^+$ 556.1187, found 556.1180.

*2-(4-(Dimethylamino)phenyl-5-phenyl-4-tosyl-4H-thieno[3,2-b]-pyrrole (**11c**):* brown solid (33 mg, 71%); R_f 0.39 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.78−7.66 (m, 4H), 7.65−7.59 (m, 4H), 7.59−7.46 (m, 2H), 6.70 (d, J = 8.8 Hz, 2H), 3.08 (s, 6H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 139.3, 136.9, 132.1, 131.8, 131.5, 131.3, 130.9, 130.7, 129.9, 129.5, 127.7, 127.1, 127.0, 119.1, 114.2, 112.2, 108.6, 40.6, 21.0; IR (neat, cm^{-1}) 1610, 1472, 1261, 1051, 739; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_2S_2$ $[M + H]^+$ 473.1357, found 473.1355.

*Detosylation of Thieno[3,2-b]pyrrole **11a** to 4-NH-Thieno[3,2-b]pyrrole **12a**.* A suspension of **11a** (55 mg, 0.1 mmol) in 20% aq KOH (10 mL) was refluxed at 80 °C for 6 h (monitored by TLC). The reaction mixture was cooled to room temperature and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to give crude product, which was purified by column chromatography using hexane/EtOAc as eluents.

*2-(4-(Dimethylamino)phenyl-5-phenyl-3-(thiophen-3-yl)-4H-thieno[3,2-b]pyrrole (**12a**):* pale yellow solid (28 mg, 71%); mp 165−167 °C; R_f 0.43 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.64 (m, 3H), 7.62−7.57 (m, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.22 (dd, J = 5.6, 1.2 Hz, 1H), 7.04 (dd, J = 3.6, 1.2 Hz, 1H), 6.86 (dd, J = 5.6, 3.6 Hz, 1H), 6.57 (d, J = 8.8 Hz, 2H), 2.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 140.4, 132.8, 132.1, 132.0, 129.9, 129.8, 129.5, 128.6, 127.8, 127.7, 125.3, 112.2, 111.1, 40.1; IR (neat, cm^{-1}) 3421−2651 (br), 1581, 1462, 1215, 1109, 750; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2S_2$ $[M + H]^+$ 401.1146, found 401.1141.

General Procedure for the Synthesis of Thieno[3,2-*b*]furans 14a,b from 3-Hydroxythiophene 13a,b via Iodocyclization. To a stirring solution of 3-hydroxythiophenes **13a,b** (0.3 mmol) in CH_2Cl_2 (5.0 mL) was added iodine (114 mg, 0.45 mmol) and K_2CO_3 (83 mg, 0.6 mmol), and the reaction mixture was further stirred at room temperature for 6 h (monitored by TLC). It was then concentrated under reduced pressure and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with water and brine, dried, and concentrated to give crude **14a,b**, which were purified by column chromatography on silica gel.

*5-(4-(Dimethylamino)phenyl)-6-(4-methoxyphenyl)-2-phenylthieno[3,2-b]furan (**14a**):* yellow solid (79 mg, 62%); mp 187−189 °C; R_f 0.21 (4:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.73 (d, J = 9.2 Hz, 2H), 7.66−7.64 (m, 2H), 7.62−7.58 (m, 1H), 7.49−7.45 (m, 2H), 7.36 (d, J = 9.2 Hz, 2H), 6.77 (d, J = 9.2 Hz, 2H), 6.70 (d, J = 9.2 Hz, 2H), 3.77 (s, 3H), 3.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 149.6, 144.2, 132.7, 132.6, 132.3, 131.8, 128.6, 128.4, 127.1, 126.9, 119.5, 115.9, 114.2, 112.9, 109.4, 108.6, 55.5, 40.6; IR (neat, cm^{-1}) 1654, 1589, 1473, 1281, 1108, 746; HRMS (ESI) m/z calcd for $C_{27}H_{24}NO_2S$ $[M + H]^+$ 426.1528, found 426.1521.

*6-(1-Methyl-1H-indole-3-yl)-2-phenyl-5-(4-(piperidin-1-yl)-phenyl)thieno[3,2-b]furan (**14b**):* brown solid (99 mg, 68%); mp 183−185 °C; R_f 0.1 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 9.2 Hz, 2H), 7.67−7.66 (m, 3H), 7.64−7.55 (m, 2H), 7.48−7.44 (m, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.29−7.26 (m, 1H), 7.19−7.15 (m, 1H), 7.07 (s, 1H), 6.77 (d, J = 9.2 Hz, 2H), 3.77 (s, 3H), 3.36−3.35 (m, 4H), 1.68−1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 139.2, 137.2, 134.5, 132.1, 131.4, 130.7, 139.9, 129.5, 129.2, 127.7, 127.4, 127.1, 127.0, 122.5, 119.8, 118.4, 118.3, 112.9, 112.2, 109.7, 103.1, 48.6, 32.9, 25.4, 19.9; IR (neat, cm^{-1}) 1591, 1448, 1251, 1109, 750; HRMS (ESI) m/z calcd for $C_{32}H_{29}N_2OS$ $[M + H]^+$ 489.2001, found 489.1993.

General Procedure for the Acetylation of 3-Amino-2-(2-bromophenyl)thiophenes 16a−c. To a solution of 3-aminothiophenes **16a−c** (0.3 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.18 mL, 1.2 mmol) and acetyl chloride (0.02 mL, 0.33 mmol) followed by stirring at room temperature for 3−4 h (monitored by TLC). The reaction mixture was concentrated in vacuo, diluted with water, and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with 10% aq $NaHCO_3$ solution, water, and brine, dried, and concentrated under reduced pressure to give crude products, which were purified by column chromatography using hexane/ethyl acetate as eluents.

*N-(2-(2-Bromophenyl)-4-(3,4-dimethoxyphenyl)-5-(4-fluorophenyl)thiophen-3-yl)acetamide (**17a**):* off-white solid (148 mg, 94%); mp 123−125 °C; R_f 0.53 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.40−7.36 (m, 2H), 7.24−7.19 (m, 2H), 6.97−6.91 (m, 2H),

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6.85−6.77 (m, 3H), 6.63 (br s, 1H), 3.90 (s, 3H), 3.73 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 163.1, 160.7, 149.8, 148.4, 140.4, 138.1, 133.1, 133.0, 132.8, 129.8, 129.5, 129.0, 128.5, 124.3, 123.5, 120.0, 117.4, 117.2, 116.9, 116.6, 114.9, 112.8, 112.6, 101.2, 56.2, 55.1, 24.6; IR (neat, cm^{-1}) 3418−2620 (br), 1613, 1510, 1237, 1109, 750; HRMS (ESI) m/z calcd for $C_{26}H_{22}BrFNO_3S$ $[M + H]^+$ 526.0488 and 528.0467, found 526.0475 and 528.0457.

*N-(5-(2-Bromophenyl)-3-(pyridin-3-yl)-2-(2-(5-dimethylamino)-thienyl)thiophen-4-yl)acetamide (**17b**):* off-white solid (142 mg, 95%); mp 163−165 °C; R_f 0.18 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.4 Hz, 1H), 8.54−8.52 (m, 1H), 7.87−7.81 (m, 3H), 7.66 (d, J = 4.4 Hz, 1H), 7.62 (dd, J = 8.0, 1.2 Hz, 1H), 7.22−7.18 (m, 2H), 7.01−6.97 (m, 1H), 5.98 (d, J = 4.4 Hz, 1H), 3.09 (s, 6H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 151.1, 147.9, 139.2, 138.7, 132.0, 131.3, 131.2, 130.8, 130.7, 129.9, 129.4, 127.7, 127.05, 126.98, 124.9, 121.0, 112.2, 105.3, 42.0, 30.8; IR (KBr, cm^{-1}) 3345−2571 (br), 1599, 1437, 1257, 1189, 1019, 750; HRMS (ESI) m/z calcd for $C_{23}H_{21}BrN_3OS_2$ $[M + H]^+$ 498.0309 and 500.0289, found 498.0305 and 500.0286.

*N-(5-(2-Bromophenyl)-2-thienylthiophen-4-yl)acetamide(**17c**):* off-white solid (103 mg, 92%); mp 121−123 °C; R_f 0.36 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, 1H), 7.49 (d J = 7.6 Hz, 2H), 7.40 (s, 1H), 7.30 (t, J = 8.0 Hz, 2H), 7.22 (dd, J = 5.6, 1.2 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.04 (dd, J = 1.2, 3.6 Hz, 1H), 6.86 (dd, J = 3.6, 5.6 Hz, 1H), 2.15 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 153.0, 146.5, 144.2, 132.6, 129.9, 128.4, 127.7, 127.1, 119.4, 117.3, 115.8, 112.3, 109.4, 26.1; IR (neat, cm^{-1}) 3367−2587 (br), 1589, 1425, 1211, 1125, 854; HRMS (ESI) m/z calcd for $C_{16}H_{13}BrNOS_2$ $[M + H]^+$ 377.9622 and 379.9601, found 377.9621 and 379.9598.

General Procedure for the Synthesis of Thieno[3,2-*b*]indoles 18a−c from 3-(*N*-Acylamino)thiophenes 17a−c. To a solution of 3-(*N*-acylamino)thiophenes **17a−c** (0.1 mmol) in toluene (5 mL) were added CuI (3.8 mg, 0.02 mmol), DMEDA (0.004 mL, 0.04 mmol), and Cs_2CO_3 (65 mg, 0.2 mmol), and the reaction mixture was refluxed with stirring at 90 °C, under nitrogen for 6−9 h (monitored by TLC). It was then diluted with water and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with water, dried, and concentrated in vacuo to give crude products, which were purified by column chromatography over silica gel, using hexane/ethyl acetate as eluents.

*1-(3-(3,4-Dimethoxyphenyl)-2-(4-fluorophenyl)-4H-thieno[3,2-b]-indol-4-yl)ethanone (**18a**):* white solid (33 mg, 76%); mp 137−139 °C; R_f 0.3 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 8.0, 1.6 Hz, 1H), 7.46−7.40 (m, 3H), 7.37 (dd, J = 8.0, 1.6 Hz, 1H), 7.33 (td, J = 7.2, 1.6 Hz, 1H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H), 6.98−6.92 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.2, 160.7, 153.0, 149.9, 148.5, 146.5, 140.4, 133.1, 133.0, 132.9, 129.5, 128.5, 123.5, 117.4, 117.3, 117.2, 116.7, 116.6, 114.9, 113.2, 112.8, 112.7, 112.3, 56.2, 56.1, 26.1; IR (neat, cm^{-1}) 1601, 1542, 1481, 1429, 1101, 1053, 751; HRMS (ESI) m/z calcd for $C_{26}H_{21}FNO_3S$ $[M + H]^+$ 446.1226, found 446.1223.

*1-(2-(5-(Dimethylamino)thiophen-2-yl)-3-(pyridin-3-yl)-4H-thieno[3,2-b]indol-4-yl)ethanone (**18b**):* brown solid (29 mg, 71%); mp 171−173 °C; R_f 0.2 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.53 (d, J = 4.8 Hz, 1H), 7.82 (dt, J = 8.0, 1.2 Hz, 1H), 7.66 (dd, J = 4.4, 1.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.43−7.37 (m, 2H), 7.34−7.30 (m, 1H), 7.20 (dd, J = 8.0, 4.8 Hz, 1H), 5.98 (d, J = 4.8 Hz, 1H), 3.09 (s, 6H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 151.2, 148.0, 139.3, 138.8, 132.1, 131.4, 131.2, 130.8, 130.0, 127.8, 127.1, 127.0, 126.0, 124.9, 121.1, 112.3, 112.1, 105.4, 42.1, 30.8; IR (neat, cm^{-1}) 1605, 1585, 1423, 1109, 1023, 749; HRMS (ESI) m/z calcd for $C_{23}H_{20}N_3OS_2$ $[M + H]^+$ 419.1048, found 419.1045.

*1-(2-(Thiophen-2-yl)-4H-thieno[3,2-b]indol-4-yl)ethanone (**18c**):* off-white solid (21 mg, 73%); mp 143−145 °C; R_f 0.17 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 4.8 Hz, 2H), 7.94−7.93 (m, 3H), 7.73 (dd, 8.0, 1.2 Hz, 1H), 7.33 (td, J = 8.0, 1.6 Hz, 1H), 7.24 (dd, J = 4.8, 4.0 Hz, 1H), 7.13 (td, J = 8.0, 1.2 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 146.5, 132.7, 129.9, 128.4, 127.7, 127.1, 127.0, 119.5, 117.3, 115.9, 112.3, 112.2, 109.4, 26.1; IR (neat, cm^{-1}) 2925, 2865, 1604, 1519, 1457, 1106, 748; HRMS (ESI) m/z calcd for $C_{16}H_{12}NOS_2$ $[M + H]^+$ 298.0360, found 298.0357.

*Deacylation of **18a**. Synthesis of 4-NH-Thieno[3,2-b]indole **19a**.* A solution of **18a** (44 mg, 0.1 mmol) in MeOH (5 mL) and TFA (0.02 mL, 0.3 mmol) was stirred at room temperature for 5 h (monitored by TLC). It was then concentrated under reduced pressure, and the residue was diluted with water, neutralized with 20% aq $NaHCO_3$ solution, and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography using hexane/EtOAc as eluents.

*3-(3,4-Dimethoxyphenyl)-2-(4-fluorophenyl)-4H-thieno[3,2-b]-indole (**19a**):* off-white solid (20 mg, 71%); mp 151−153 °C; R_f 0.43 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.2, 1.6 Hz, 1H), 7.47−7.32 (m, 5H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H), 6.98−6.93 (m, 3H), 6.73 (d, J = 9.2 Hz, 1H), 6.37 (br s, 1H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 148.5, 145.4, 144.2, 133.1, 133.0, 132.7, 129.9, 128.4, 127.7, 127.1, 126.8, 123.5, 119.5, 117.4, 117.2, 116.6, 115.8, 115.0, 112.9, 112.7, 112.4, 112.2, 109.4, 156.2, 56.1; IR (neat, cm^{-1}) 3436−2698 (br), 1592, 1471, 1211, 1051, 750; HRMS (ESI) m/z calcd for $C_{24}H_{19}FNO_2S$ $[M + H]^+$ 404.1121, found 404.1118.

General Procedure for the Synthesis of Thieno[3,2-*b*]-benzofuran 21a,b from 3-Hydroxythiophene 20a,b. A suspension of 3-hydroxythiophenes **20a,b** (0.3 mmol) (3 mL), CuO (4.8 mg, 0.06 mmol), and K_2CO_3 (83 mg, 0.6 mmol) in dry deoxygenated pyridine was refluxed at 100 °C under nitrogen for 3−5 h (monitored by TLC). The reaction mixture was then diluted with 20% aq HCl solution (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was washed with 10% aq NaOH, dried, and concentrated in vacuo. The solid residue was purified by column chromatography with hexane/ethyl acetate as eluents.

*2,3-Bis(4-methoxyphenyl)thieno[3,2-b]benzofuran (**21a**):* white solid (96 mg, 83%); mp 187−189 °C; R_f 0.2 (4:1 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 6.0, 3.2 Hz, 1H), 7.47 (dd, J = 6.0, 3.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.21 (dd, J = 6.0, 3.2 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 159.0, 158.2, 157.9, 140.1, 130.7, 130.5, 127.5, 125.1, 124.1, 123.1, 121.9, 119.0, 116.5, 114.2, 114.1, 112.4, 55.29, 55.26; IR (neat, cm^{-1}) 1509, 1246, 1174, 1032, 746; HRMS (ESI) m/z calcd for $C_{24}H_{19}O_3S$ $[M + H]^+$ 387.1055, found 387.1053.

*1-Methyl-3-(2-(thiophen-2-yl)thieno[3,2-b]benzofuran-3-yl)-1H-indole (**21b**):* brown solid (84 mg, 73%); mp 198−200 °C; R_f 0.2 (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93−7.91 (m, 1H), 7.72 (s, 1H), 7.67−7.65 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 4.8, 0.8 Hz, 1H), 7.39−7.36 (m, 2H), 7.22−7.18 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.02−6.95 (m, 2H), 7.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, 157.7, 136.8, 133.2, 130.1, 127.4, 126.1, 126.1, 124.9, 123.6, 123.2, 121.6, 119.6, 119.5, 119.4, 116.5, 112.4, 110.2, 104.2, 32.7; IR (neat, cm^{-1}) 2922, 1567, 1428, 1260, 1011, 739; HRMS (ESI) m/z calcd for $C_{23}H_{16}NOS_2$ $[M + H]^+$ 386.0673, found 386.0671.

General Procedure for the Domino One-Pot Synthesis of Thieno[3,2-*b*]pyridin5-ones 24a−c and Thieno[3,2-*c*]-isoquinolin-5-ones 27a,b. To a stirring solution of LDA (2.2 mmol) in THF (3 mL) at 0 °C was added corresponding (het)arylacetonitriles (1.0 mmol) in THF (3 mL), and the reaction mixture was further stirred for 10 min, followed by a dropwise addition of a solution of (het)aryl dithioester (1.0 mmol) in THF (3 mL). The stirring was continued further for 0.5 h, while maintaining the temperature at 0 °C (monitored by TLC). To this reaction mixture was added, dropwise at 0 °C, a solution of the methyl 4-bromocrotonate (179 g, 1.0 mmol)/ethyl 2-(bromomethyl)benzoate (243 mg, 1.0 mmol) in THF (2 mL), and stirring was continued for 0.5 h at 0 °C and then at room temperature for 8 h (monitored by TLC). The reaction mixture was then diluted with a saturated NH_4Cl

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solution (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water (3 × 25 mL) and brine, dried over Na_2SO_4, and evaporated under vacuum to give the crude products, which were purified by column chromatography using hexane/ethyl acetate as eluents.

*2-(5-(Dimethylamino)thiophen-2-yl)-3-(thiophen-3-yl)thieno[3,2-b]pyridin-5(4H)-one (**24a**):* black solid (293 mg, 82%); mp 195−197 °C; R_f 0.48 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 9.2 Hz, 1H), 7.52 (dd, J = 4.8, 1.2 Hz, 1H), 7.39 (dd, J = 2.8, 1.2 Hz, 1H), 7.06 (dd, J = 4.8, 1.2 Hz, 1H), 6.85 (d, J = 4.0 Hz, 1H), 6.41 (d, J = 9.6 Hz, 1H), 5.70 (d, J = 4.0 Hz, 1H), 2.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 161.5, 142.3, 141.0, 134.8, 131.5, 129.0, 128.4, 127.8, 126.6, 118.4, 117.3, 116.0, 114.0, 102.2, 42.5; IR (neat, cm^{-1}) 3239−2499 (br), 2923, 1716, 1621, 1416, 751; HRMS (ESI) m/z calcd for $C_{17}H_{15}N_2OS_3$ $[M + H]^+$ 359.0347, found 359.0339.

*2-(4-(Dimethylamino)phenyl)-3-(pyridin-3-yl)thieno[3,2-b]-pyridin-5(4H)-one (**24b**):* brown solid (274 mg, 79%); mp 198−200 °C; R_f 0.28 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (br d, J = 3.2 Hz, 1H), 8.58 (br s, 1H), 8.55 (br s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.39 (dd, J = 7.2, 5.2 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 9.2 Hz, 1H), 6.50 (d, J = 8.8 Hz, 2H), 2.95 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 151.1, 149.6, 148.0, 138.7, 134.8, 132.6, 131.7, 130.8, 128.6, 128.3, 127.0, 124.9, 121.3, 114.2, 108.5, 40.6; IR (KBr, cm^{-1}) 3205−2660 (br), 1629, 1603, 1275, 750; HRMS (ESI) m/z calcd for $C_{20}H_{18}N_3OS$ $[M + H]^+$ 348.1171, found 348.1169.

*1-(2-(Thiophen-2-yl)-4H-thieno[3,2-b]indol-4-yl)ethanone (**24c**):* brown solid (213 mg, 79%); R_f 0.35 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 3.2 Hz, 1H), 6.69 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 3.2 Hz, 1H), 3.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 150.0, 131.8, 130.8, 130.0, 128.4, 127.8, 127.1, 114.2, 112.3, 108.6, 40.7; IR (neat, cm^{-1}) 3467−2517 (br), 1603, 1577, 1435, 1289, 1109, 750; HRMS (ESI) m/z calcd for $C_{15}H_{15}N_2OS$ $[M + H]^+$ 271.0905, found 271.0897.

*3-(3,4-Dimethoxyphenyl)-2-(4-(piperidin-1-yl)phenyl)thieno[3,2-c]isoquinolin-5(4H)-one (**27a**):* brown solid (391 mg, 79%); mp 216−218 °C; R_f 0.52 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 9.2 Hz, 2H), 7.85 (br s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 4.4 Hz, 2H), 7.36−7.31 (m, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 8.4, 2.4 Hz, 1H), 6.92−6.89 (m, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.41−3.40 (m, 4H), 1.59−1.57 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 154.1, 149.7, 148.3, 139.3, 132.8, 132.6, 130.6, 130.3, 128.9, 128.5, 128.4, 128.2, 127.4, 123.0, 118.6, 114.8, 113.4, 112.3, 111.8, 111.1, 55.8, 55.6, 47.6, 24.9, 19.2; IR (neat, cm^{-1}) 3381−2651 (br), 1610, 1521, 1437, 1158, 756; HRMS (ESI) m/z calcd for $C_{30}H_{29}N_2O_3S$ $[M + H]^+$ 497.1899, found 497.1894.

*2-(4-(Dimethylamino)phenyl)-3-(1-methyl-1H-indol-3-yl)thieno-[3,2-c]isoquinolin-5(4H)-one (**27b**):* brown solid (323 mg, 72%); mp 225−227 °C; R_f 0.31 (3:2 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (br s, 1H), 7.52, (t, J = 8.8 Hz, 2H), 7.58 (br s, 1H), 7.43−7.41 (m, 2H), 7.35−7.27 (m, 4H), 7.22 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 6.64 (d, J = 9.2 Hz, 2H), 3.76 (s, 3H), 2.86 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 149.5, 139.3, 136.7, 135.4, 132.7, 131.3, 130.6, 129.9, 128.5, 128.1, 127.8, 127.4, 126.3, 121.7, 119.3, 119.0, 118.6, 118.2, 114.2, 109.9, 107.1, 102.9, 47.2, 32.4; IR (neat, cm^{-1}) 3214−2598 (br), 1608, 1523, 1451, 1213, 761; HRMS (ESI) m/z calcd for $C_{28}H_{23}N_3OS$ $[M + H]^+$ 450.1640, found 450.1635.

General Procedure for the Synthesis of Thieno[3,2-*b*]pyran-5-ones 29a,b from 3-Hydroxythiophene 28a,b. To a solution of 3-hydroxythiophenes **29a,b** (0.3 mmol) in MeOH (5 mL) in a sealed tube was added P(n-Bu)$_3$ (25% solution in EtOAc) (121 mg, 0.6 mmol), and the reaction mixture was heated to 75 °C for 10 h (monitored by TLC). It was then cooled to room temperature and evaporated under reduced pressure, and the residue was diluted with water and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo, and the crude products were purified by column chromatography using hexane/ethyl acetate as eluents.

*2-(4-(Dimethylamino)phenyl)-3-(4-methoxyphenyl)-5H-thieno-[3,2-b]pyran-5-one (**29a**):* black solid (56 mg, 50%); mp 217−219 °C; R_f 0.4 (7:3 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 3.2 Hz, 1H), 7.72 (d, J = 3.2 Hz, 1H), 7.44 (J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.65 (J = 8.8 Hz, 2H), 3.75 (s, 3H), 2.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.8, 149.7, 132.4, 131.8, 130.8, 130.0, 128.4, 127.8, 127.1, 115.9, 114.2, 112.9, 112.3, 108.6, 55.5, 40.7; IR (neat, cm^{-1}) 1694, 1524, 1456, 1108, 1029, 748; HRMS (ESI) m/z calcd for $C_{22}H_{20}NO_3S$ $[M + H]^+$ 378.1164, found 378.1159.

*2-(5-(Dimethylamino)thiophen-2-yl)-3-(1-methyl-1H-indol-3-yl)-5H-thieno[3,2-b]pyran-5-one (**29b**):* black solid (67 mg, 55%); mp 231−233 °C; R_f 0.3 (4:1 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, J = 3.6 Hz, 1H), 7.71 (s, J = 3.6 Hz, 1H), 7.70 (d, J = 4.8 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.34 (s, 1H), 7.21 (td, J = 7.2, 0.8 Hz, 1H), 7.12−7.08 (m, 1H), 6.26 (d, J = 5.2 Hz, 1H), 3.77 (s, 3H), 3.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 137.2, 131.2, 130.8, 129.9, 128.3, 127.7, 127.4, 127.1, 122.5, 119.8, 118.3, 112.2, 109.7, 105.4, 103.0, 42.0, 32.9; IR (neat, cm^{-1}) 1700, 1602, 1448, 1259, 743; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O_2S_2$ $[M + H]^+$ 407.0888, found 407.0885.

General Procedure for the Synthesis of Thieno[3,2-*c*]-isochromen-5-one 31a,b from 3-Hydroxythiophene 30a,b. To a solution of 3-hydroxythiophenes **31a,b** (0.3 mmol) in MeOH (5 mL) was added H_2SO_4 (0.08 mL, 0.15 mmol), and the reaction mixture was refluxed at 55 °C for 9−10 h (monitored by TLC). It was then concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give crude products, which were purified by column chromatography using hexane/ethyl acetate as eluents.

*2-(5-(Dimethylamino)thiophen-2-yl)-3-(4-methoxyphenyl)-5H-thieno[3,2-c]isochromen-5-one (**31a**):* black solid (89 mg, 69%); mp 219−221 °C; R_f 0.4 (7:3 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (dd, J = 7.6, 1.2 Hz, 1H), 7.66 (d, J = 4.8 Hz, 1H), 7.62 (dd, J = 8.0, 1.2 Hz, 1H), 7.36 (d, J = 9.2 Hz, 2H), 7.20 (td, J = 7.6, 1.2 Hz, 1H), 6.99 (td, J = 7.6, 1.6 Hz, 1H), 6.77 (d, J = 9.2 Hz, 2H), 5.98 (d, J = 4.8 Hz, 1H), 3.78 (s, 3H), 3.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 158.9, 140.5, 132.9, 132.4, 132.2, 130.0, 129.6, 128.5, 127.8, 127.1, 125.0, 115.9, 113.0, 112.3, 105.4, 101.3, 55.6, 42.1; IR (neat, cm^{-1}) 1712, 1697, 1583, 1431, 1106, 750; HRMS (ESI) m/z calcd for $C_{24}H_{20}NO_3S_2$ $[M + H]^+$ 434.0885, found 434.0881.

*2-(4-(Dimethylamino)phenyl)-3-(1-methyl-1H-indol-3-yl)-5H-thieno[3,2-c]isochromen-5-one (**31b**):* black solid (97 mg, 72%); mp 235−237 °C; R_f 0.2 (4:1 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (dd, J = 7.6, 1.2 Hz, 1H), 7.72 (dd, J = 8.0, 1.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.34−7.27 (m, 4H), 7.21 (t, J = 8.0 Hz, 1H) 7.15−7.08 (m, 2H), 6.65 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 2.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 149.6, 132.64, 132.58131.7, 128.6, 128.4, 127.4, 127.1, 126.5, 122.5, 119.8, 119.4, 118.3, 115.8, 114.2, 109.7, 109.4, 108.5, 103.1, 40.6, 32.9; IR (neat, cm^{-1}) 1701, 1654, 4583, 1251, 1023, 750; HRMS (ESI) m/z calcd for $C_{28}H_{23}N_2O_2S$ $[M + H]^+$ 451.1480, found 451.1480.

General Procedure for the Acetylation of 3-Amino-2-(2-chloroenzoyl)thiophenes 33a,b. To a solution of 3-amino-thiophenes **33a,b** (0.3 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.18 mL, 1.2 mmol) and acetyl chloride (0.02 mL, 0.33 mmol), and the reaction mixture was stirred at room temperature for 3−4 h (monitored by TLC). It was then evaporated under vacuum, diluted with water, and extracted with ethyl acetate (3 × 25 mL), and the combined organic layer was washed with 10% aq $NaHCO_3$ solution, water, and brine, dried, and concentrated under reduced pressure. The crude products were purified by column chromatography using hexane/ethyl acetate as eluents.

*N-(2-(2-Chlorobenzoyl)-4,5-bis(4-methoxyphenyl)thiophen-3-yl)-acetamide (**34a**):* yellow solid (138 mg, 94%); R_f 0.18 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.53 (m, 1H), 7.43−7.30 (m, 5H), 7.01 (br s, 1H), 6.79−6.73 (m, 4H), 6.64 (d, J = 8.8 Hz,

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2H), 3.78 (s, 3H), 3.74 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 163.6, 152.9, 140.4, 140.1, 132.8, 130.7, 130.5, 129.9, 129.8, 128.5, 127.7, 127.1, 116.5, 114.9, 113.8, 112.2, 101.3, 55.8, 55.5, 26.4; IR (neat, cm^{-1}) 3341, 1705, 1605, 1435, 1247, 750; HRMS (ESI) m/z calcd for $C_{27}H_{23}ClNO_4S$ $[M + H]^+$ 492.1036 and 494.1007, found 492.1033 and 494.1005.

*N-(2-(2-Chlorobenzoyl)-4-(1-methyl-1H-indol-3-yl)-5-(pyridin-3-yl)thiophen-3-yl)acetamide (**34b**):* brown solid (134 mg, 92%); R_f 0.13 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.0 Hz, 1H), 8.52 (dd, J = 4.8, 1.2 Hz, 1H), 7.82–7.79 (m, 1H), 7.57–7.53 (m, 2H), 7.42–7.37 (m, 2H), 7.33–7.29 (m, 2H), 7.29–7.25 (m, 1H), 7.20–7.15 (m, 2H), 7.07 (s, 1H), 3.76 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 151.1, 147.9, 139.2, 138.7, 137.2, 132.0, 131.3, 130.7, 129.9, 129.4, 127.7, 127.4, 127.04, 126.97, 126.5, 124.9, 122.5, 121.0, 119.8, 118.3, 118.2, 112.2, 109.7, 103.0, 32.8; IR (neat, cm^{-1}) 3249, 1715, 1638, 1275, 749; HRMS (ESI) m/z calcd for $C_{27}H_{21}ClN_3O_2S$ $[M + H]^+$ 489.1043 and 488.1014, found 489.1042 and 488.1012.

General Procedure for the Synthesis of Thieno[3,2-*b*]-quinolin-9-ones 35a,b from 3-(*N*-Acylaminothiophenes 34a,b. To a solution of 3-(*N*-acylamino)thiophenes **34a,b** (0.1 mmol) in DMF (8 mL) were added CuI (3.8 mg, 0.02 mmol), L-proline (4.6 mg, 0.04 mmol), and K_2CO_3 (28 mg, 0.2 mmol), and the reaction mixture was heated at 90 °C under nitrogen for 4–5 h (monitored by TLC). It was then diluted with water and extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed with water, dried, and concentrated in vacuo. The crude products were purified by column chromatography with hexane/ethyl acetate as eluents.

*2,3-Bis(4-methoxyphenyl)thieno[3,2-b]quinolin-9(4H)-one (**35a**):* off-white solid (33 mg, 81%); mp 183–185 °C; R_f 0.21 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 811.23 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.65 (td, J = 7.2, 1.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 158.7, 152.9, 152.8, 146.4, 144.2, 140.1, 132.6, 132.2, 128.4, 119.3, 117.3, 116.4, 115.8, 114.9, 112.8, 112.3, 109.3, 55.8, 55.4; IR (neat, cm^{-1}) 3244–2650 (br), 2938, 1620, 1606, 1513, 1173, 760; HRMS (ESI) m/z calcd for $C_{25}H_{20}NO_3S$ $[M + H]^+$ 414.1164, found 414.1160.

*3-(1-Methyl-1H-indol-3-yl)-2-(pyridin-3-yl)thieno[3,2-b]quinolin-9(4H)-one (**35b**):* yellow-brown solid (31 mg, 76%); mp 191–193 °C; R_f 0.23 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 2.4 Hz, 1H), 8.57 (dd, J = 1.2, 4.8 Hz, 1H), 8.06 (ddd, J = 1.6, 2.4, 8.0 Hz, 1H), 7.84 (br s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.42–7.38 (m, 3H), 7.35–7.31 (m, 2H), 7.23–7.19 (m, 1H), 7.12–7.08 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 151.1, 147.9, 144.6, 140.4, 138.7, 137.2, 133.8, 132.8, 132.5, 129.8, 128.5, 127.4, 126.5, 124.9, 122.5, 121.0, 119.8, 118.3, 118.2, 109.7, 103.0, 32.9; IR (neat, cm^{-1}) 3256–2667 (br), 2927, 1620, 1565, 1470, 1156, 748; HRMS (ESI) m/z calcd for $C_{25}H_{18}N_3OS$ $[M + H]^+$ 408.1171, found 408.1169.

General Procedure for the Synthesis of Thieno[3,2-*b*]-chromen-9-one 37a,b from 3-Hydroxy-2-(2-chlorobenzoyl)-thiophenes 36a,b. To a solution of 3-hydroxythiophenes **36a,b** (0.3 mmol) in DMSO (2 mL) was added K_2CO_3 (83 mg, 0.6 mmol), and the reaction mixture was heated to 130 °C for 2 h (monitored by TLC). It was then cooled to room temperature, diluted with saturated NH_4Cl solution, and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give solids, which were washed with diethyl ether to provide the pure thieno[3,2-*b*]chromen-9-ones **37a,b**.

*2-(Benzo[d][1,3]dioxol-5-yl)-3-(3-methoxyphenyl)-9H-thieno[3,2-b]chromen-9-one (**37a**):* off-white solid (102 mg, 82%); mp 105–107 °C; R_f 0.8 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, J = 8.0, 1.6 Hz, 1H), 7.62–7.58 (m, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.29–7.51 (m, 1H), 6.90–6.87 (m, 3H), 6.84 (dd, J = 8.0, 2.0 Hz, 1H), 6.71–6.68 (m, 2H), 5.90 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 159.9, 156.9, 156.4, 148.7, 148.11, 148.07, 133.7, 133.3, 129.9, 127.5, 127.1, 126.1, 124.8, 123.7, 122.8, 122.5, 120.0, 118.3, 115.9, 114.0, 109.5, 108.8, 101.6, 55.4; IR (KBr, cm^{-1}) 1647, 1466, 1246, 1036, 750; HRMS (ESI) m/z calcd for $C_{25}H_{17}O_5S$ $[M + H]^+$ 429.0797, found 429.0793.

*3-(1-Methyl-1H-indol-3-yl)-2-(pyridin-3-yl)-9H-thieno[3,2-b]-chromen-9-one (**37b**):* brown solid (104 mg, 85%); mp 134–136 °C; R_f 0.9 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (br s, 1H), 8.49 (br s, 1H), 8.39–8.37 (m, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.69–7.64 (m, 1H), 7.46–7.38 (m, 3H), 7.25–7.18 (m, 4H), 7.02–6.98 (m, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 157.5, 156.4, 149.7, 149.2, 142.4, 137.2, 136.0, 133.9, 130.6, 129.3, 126.5, 126.2, 124.9, 123.5, 122.5, 122.5, 122.4, 121.1, 120.3, 120.2, 118.3, 109.8, 105.2, 33.3; IR (neat, cm^{-1}) 1640, 1433, 1415, 882, 737; HRMS (ESI) m/z calcd for $C_{25}H_{17}N_2O_2S$ $[M + H]^+$ 409.1011, found 409.1008.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01153.

Figures showing scanned copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **9a–c**, **10a–c**, **11a–c**, **12a**, **13a,b**, **14a,b**, **16a–d**, **17a–c**, **18a–c**, **19a**, **20a,b**, **21a,b**, **23a–c**, **24a–c**, **26a,b**, **27a,b**, **28a,b**, **29a,b**, **30a,b**, **31a,b**, **33a,b**, **34a–b**, **35a,b**, **36a,b** and **37a,b** (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Miguel Yus on the occasion of his 70th Birthday.

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