A Facile Synthetic Route towards Substituted Thieno[3,2-*e*]indoles

Wim Van Snick, Wienand Nulens, Sarah Jambon, Wim Dehaen*

Department of Chemistry, K. U. Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium
Fax +32(16)327990; E-mail: wim.dehaen@chem.kuleuven.be

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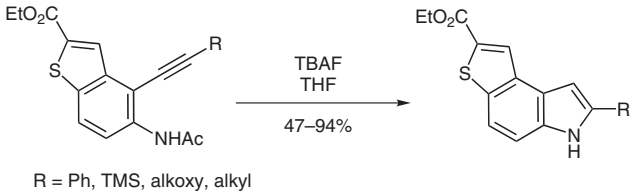
Abstract: A number of substituted thieno[3,2-*e*]indoles have been prepared in high yields via a tetrabutylammonium fluoride mediated cyclization of 5-acetamido-4-ethynylbenzothiophenes, which, in turn, are easily accessible from the corresponding 4-iodobenzothiophenes. This method presents a viable alternative to the traditionally used Fischer indolization procedures.

Key words: thienoindoles, palladium, cyclizations, fused-ring systems, tetrabutylammonium fluoride

Few versatile methods exist for the synthesis of thieno[3,2-*e*]indoles. Among these, the Fischer indolization of a 5-substituted benzothiophene hydrazone,[1] the photochemical cyclization of 2-[2-(2-thienyl)vinyl]-1*H*-pyrroles,[2] and the cyclocondensation of a 3-oxoindole with 2-thienylacetonitrile to give a thienocarbazole[3] are the most important. These procedures have significant drawbacks, however, such as vigorous reaction conditions, which lead to low yields and restrict the number of possible substituents. Hence, in general, they are of limited applicability.

In this manuscript, we will discuss a new, high-yielding procedure for the synthesis of thieno[3,2-*e*]indoles using readily available starting materials. The key step is the synthesis of 5-amino-4-ethynylbenzothiophenes by a Sonogashira coupling reaction of 5-amino-4-iodobenzothiophene with external acetylenes. Based on the available literature of indolization reactions,[4] the 5-amino-4-ethynylbenzothiophene should easily be cyclized to the thienoindole. Cyclizing agents such as copper(I) iodide in *N*,*N*-dimethylformamide,[5] copper(II) salts,[6] and potassium hydride or potassium *tert*-butoxide in *N*-methylpyrrolidin-2-one,[7] among others, have been employed with varying success. The use of tetrabutylammonium fluoride in tetrahydrofuran, however, proved to be a very successful method (Scheme 1). Moreover, it seems to be a particularly soft and easy method, as there is no need for dry conditions.[8]

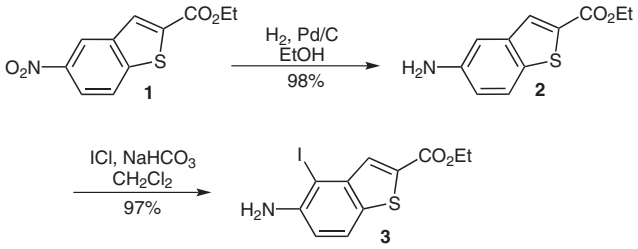
Hence, thienoindoles are easily synthesized in three steps, requiring little or no purification. The first step involves the iodination of 5-aminobenzothiophene **2** (Scheme 2). The second step is the Sonogashira coupling reaction of this 4-iodobenzothiophene derivative. Finally, the indolization can proceed with tetrabutylammonium fluoride as the cyclizing agent (Scheme 1).



R = Ph, TMS, alkoxy, alkyl

Scheme 1

Ethyl 5-nitrobenzo[*b*]thiophene-2-carboxylate (**1**) was conveniently prepared by the condensation of 2-chloro-4-nitrobenzaldehyde with ethyl 2-sulfanylacetate.[9] After reduction of the nitro group using hydrogen and palladium on carbon,[10] the iodination reaction of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate (**2**) proceeded selectively in the 4-position using iodine monochloride and sodium hydrogen carbonate as a base giving ethyl 5-amino-4-iodobenzo[*b*]thiophene-2-carboxylate (**3**) (Scheme 2).[11] All of these reactions proceeded in nearly quantitative yield.



Scheme 2

In the second step, a number of 5-amino-4-ethynylbenzothiophenes **4a–d** were prepared in high yields (89–97%) using a general Sonogashira approach (Scheme 3, equation 1 and Table 1).

In order to perform the ring closure using tetrabutylammonium fluoride as a cyclizing agent, conversion of the free amine function **4** into an amide was required. Acetylation turned out to be the easiest method, using either acetyl chloride or acetic anhydride in dichloromethane, the latter requiring slightly longer reaction times (Scheme 3, equation 1). Even though this procedure worked well for the phenylethynyl- and (trimethylsilyl)ethynyl-substituted benzothiophenes **4a**,**b** (98% and 94% yields, respectively), problems were encountered with those acetylenes containing alcohol functional groups **4c**,**d** (Table 2). As could be expected, the propargyl alcohol group in **4c** was acetylated together with the amine, leading to the doubly acetylated product **5cc**

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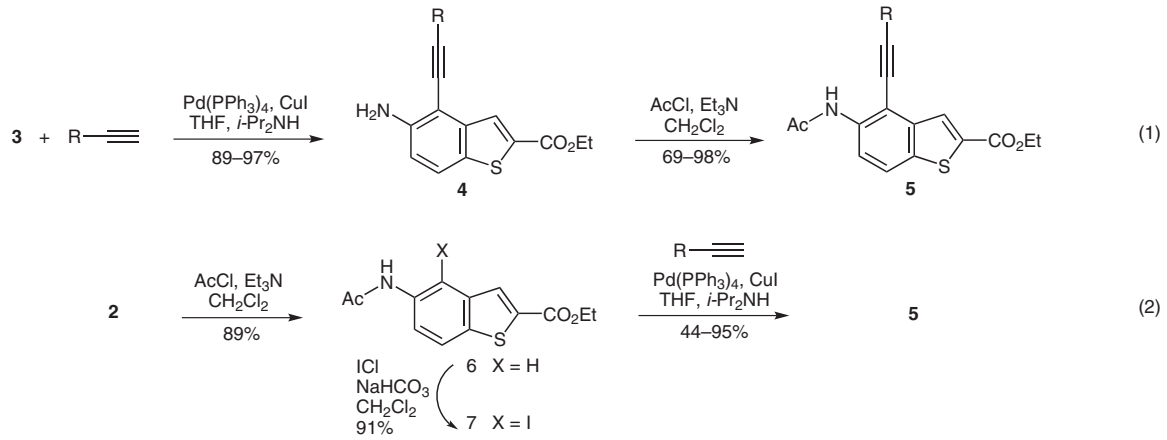
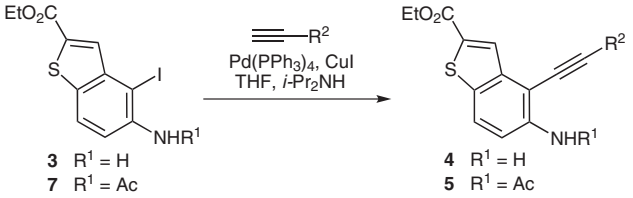


Scheme 3

(Figure 1). This was not observed with the 1-hydroxy-1-methylethyl group (CMe_2OH) in **4d**, probably due to steric effects. An alternative approach to the direct acetylation of the propargyl alcohol derivative **4c** was also considered, using sodium bisulfate supported on silica gel catalyst.[12] In this case, an N-monoacetylated product **5c** was acquired in 69% yield.

Table 1 Sonogashira Cross-Coupling Reaction



Entry	Aryl iodide	R^2	Product	Yield[a] (%)
1	**3**	Ph	**4a**	97
2	**3**	TMS	**4b**	94
3	**3**	CH_2OH	**4c**	89
4	**3**	CMe_2OH	**4d**	95
5	**3**	CO_2Et	**4e**	–
6	**7**	Ph	**5a**	94, 97[b]
7	**7**	TMS	**5b**	86, 91[b]
8	**7**	CH_2OH	**5c**	44
9	**7**	CMe_2OH	**5d**	86
10	**7**	$(CH_2)_2OH$	**5e**	90
11	**7**	CH_2OTHP	**5f**	81
12	**7**	CMe_2OTHP	**5g**	95
13	**7**	$(CH_2)_2OTHP$	**5h**	73
14	**7**	Bu	**5i**	82

[a] All yields refer to isolated products.
[b] 1 mol% of $PdCl_2(PPh_3)_2$ was used as a catalyst.

To obtain the propargyl alcohol derivative, we then decided to reverse our protocol and introduce the acetyl group before the Sonogashira coupling reaction (Scheme 3, equation 2). Fearing that the iodination reaction might proceed too slowly on an acetanilide, we first tried to acetylate the 4-iodo derivative **3**. This reaction turned out to be difficult to control, however, leading to a mixture of products containing a doubly acetylated product **8**, next to the desired acetanilide **7** (Figure 1). We then tried to iodinate the acetanilide derivative **6**, which was easily prepared by acetylation of **2**. While considerably slower than the iodination reaction with the free amine, this reaction afforded the N-protected iodobenzothiophene **7** in high yield (91%) (Scheme 3, equation 2). The subsequent Sonogashira coupling reactions proceeded uneventfully towards the acetylene substituted benzothiophenes **5**. For ease of work, we decided to use this protocol as a general method for the synthesis of all other acetylenes **5a–i** (Table 1, entries 6–14).

Table 2 Acetylation of 5-Amino-4-ethynylbenzothiophenes **4**

Entry	Substrate	R	Conditions[a]	Product	Yield[b] (%)
1	**4a**	Ph	A	**5a**	98
2	**4b**	TMS	A	**5b**	94
3	**4c**	CH_2OH	B	**5cc**	85[c]
4	**4c**	CH_2OH	C	**5c**	69
5	**4d**	CMe_2OH	B	**5d**	69
6	**4d**	CMe_2OH	C	**5d**	69

[a] Conditions A: AcCl, Et_3N, CH_2Cl_2; B: Ac_2O, pyridine, CH_2Cl_2; C: Ac_2O, $NaHSO_4$–silica gel, CH_2Cl_2.
[a] All yields refer to isolated products.
[c] Doubly acetylated product **5cc**.

When using ethyl propynoate in the Sonogashira coupling with 5-amino-4-iodobenzothiophene **3**, no coupled product could be detected, despite complete consumption of the starting materials (Table 1, entry 5). Other attempts to create the Sonogashira coupled product by varying the

temperature and the amount of catalyst used also failed. We then decided to try a Negishi cross-coupling on the *N*-acetyl-protected iodobenzothiophene **7**, but to our surprise a Michael-type adduct **9** was acquired in 45% yield (Figure 1). In an ultimate effort we used the *N*-mesyl-protected iodobenzothiophene **10**, which has been reported to yield better results in this type of reaction,[13] but this also was to no avail. Based on mass spectrometry, the product seemed to be present in the reaction mixture, but turned out to be unstable during purification.

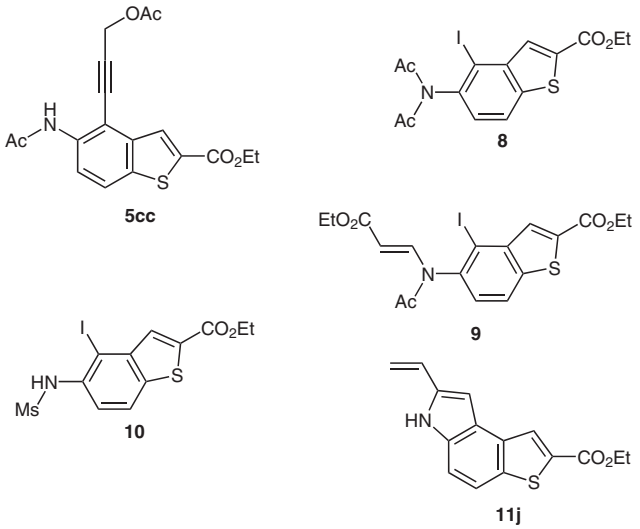


Figure 1

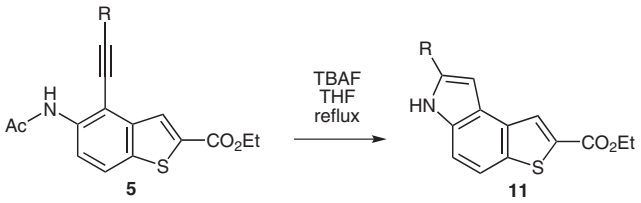
Finally, ring closure of acetylenes **4a** and **4b** to the indoles was first attempted with the classical Castro reaction, using an excess of copper(I) iodide in refluxing *N*,*N*-dimethylformamide. The 2-phenylthienoindole **11a** was thus prepared in 70% yield, but in the case of the trimethylsilyl-protected acetylene **4b** we could only note the complete decomposition of the starting material. We then tried Knochel's method,[7] first using potassium *tert*-butoxide in *N*-methylpyrrolidin-2-one, but in this case even the phenylethynyl derivative **4a** failed to produce any indole, though some starting material was recovered. Moreover, when using potassium hydride we had to witness the complete decomposition of the starting compound. Most probably the ester function is too sensitive to survive these reaction conditions.

At this stage, ring closure of the 5-acetamido-4-ethynylbenzothiophenes **5** was investigated using tetrabutylammonium fluoride as the cyclizing agent (Table 3).[8] A first attempt using phenylacetylene **5a** and 2.5 equivalents of tetrabutylammonium fluoride led to an incomplete reaction. Increasing the amount of tetrabutylammonium fluoride to three equivalents, however, resulted in the formation of the desired thienoindole **11a** in a satisfying 89% yield. Similar results were obtained with most other compounds.

Again, the propargylic alcohol groups proved to be problematic. In both cases **5c**,**d**, only decomposition of the starting materials could be noted. While ring closure of butynol derivative **5e** was successful, the yield was considerably lower compared to the hex-1-yne compound **5i** (53% vs 88%). However, about 40% (based on ^{1}H NMR) of ethyl 7-vinyl-6*H*-thieno[3,2-*e*]indole-2-carboxylate (**11j**) had also been formed (Figure 1). This dehydration reaction has been reported before under conditions similar to ours, and has been attributed to the electron-withdrawing properties of an *N*-sulfonyl substituent.[14] In another case, using analogous products and reaction conditions but without tetrabutylammonium fluoride, no dehydration was observed.[15] This leads us to conclude that the formation of vinylindoles is mediated by tetrabutylammonium fluoride, regardless of the nature of the other substituents. When protecting the alcohol groups as the tetrahydro-2*H*-pyran-2-yl ethers **5f**–**h**, treatment with tetrabutylammonium fluoride gave the corresponding indoles in moderate to high yields. In the case of **5h**, again about 40% of a 7-vinylindole derivative **11j** was obtained. The tetrahydro-2*H*-pyran-2-yl-protected thienoindole **11g** seemed to degrade during column chromatography purification, leading to a lower yield (57%). Moreover, compound **11g** could not be fully characterized, due to its instability.

In conclusion, an easy and versatile procedure for the synthesis of thieno[3,2-*e*]indoles has been developed, with most reaction steps requiring little or no purification.

Table 3 Tetrabutylammonium Fluoride Mediated Cyclization



Entry	Substrate	R	Equiv TBAF	Time (h)	Product	Yield[a] (%)
1	**5a**	Ph	2.5	18	**11a**	60[b]
2	**5a**	Ph	3	18	**11a**	89
3	**5b**	TMS	3	2	**11b**	94[c]
4	**5c**	CH_2OH	3	18	–	–
5	**5d**	CMe_2OH	3	18	–	–
6	**5e**	$(CH_2)_2OH$	3	18	**11e** + **11j**	53[d]
7	**5f**	CH_2OTHP	3	18	**11f**	91
8	**5g**	CMe_2OTHP	3	18	**11g**	57
9	**5h**	$(CH_2)_2OTHP$	3	18	**11h** + **11j**	47[d]
10	**5i**	Bu	3	18	**11i**	88

[a] All yields refer to isolated products.
[b] 20% of starting product was recovered.
[c] Product is ethyl 6*H*-thieno[3,2-*e*]indole-2-carboxylate (R = H).
[d] In addition to the yield of isolated product (**11e** or **11h**), about 40% of ethyl 7-vinyl-6*H*-thieno[3,2-*e*]indole-2-carboxylate (**11j**, R = $CH{=}CH_2$) was obtained (as estimated by ^{1}H NMR).

These procedures can easily be scaled up (up to 20 mmol with only marginally lower yields). Research to convert the Sonogashira coupling–tetrabutylammonium fluoride cyclization into a one-pot procedure is currently ongoing. Due to the general applicability of the method devised, a number of substituted thienoindoles are currently being investigated in a structure–activity relationship study.

Melting points (not corrected) were determined using a Reichert Thermovar apparatus. IR spectra were recorded using a Bruker ALPHA-P spectrophotometer. NMR spectroscopy was performed on commercial instruments (Bruker Avance 300 MHz, Bruker AMX 400 MHz or Bruker Avance II$^+$ 600 MHz) and referenced to TMS (^{1}H) or the carbon signal of deuterated solvents (^{13}C). Mass spectra were run using a HP5989A apparatus (CI and EI, 70 eV ionization energy) with Apollo 300 data system, and a Kratos MS50TC instrument for exact mass measurements (performed in the EI mode at a resolution of 10000). For column chromatography 70–230 mesh silica 60 (E. M. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. The following products were prepared according to the literature: ethyl 5-nitrobenzo[*b*]thiophene-2-carboxylate (**1**),[9] and ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate (**2**).[10]

Ethyl 5-Amino-4-iodobenzo[*b*]thiophene-2-carboxylate (3)

To a stirred soln of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate (**2**, 10.4 g, 46.8 mmol) and $NaHCO_3$ (7.9 g, 93.7 mmol) in CH_2Cl_2 (350 mL) was added dropwise a soln of ICl (8.4 g, 51.5 mmol) in CH_2Cl_2 (70 mL). The mixture was stirred at r.t. for 2 h. The resulting mixture was washed with sat. $Na_2S_2O_3$ (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with sat. $NaHCO_3$ and brine (both 200 mL) and dried ($MgSO_4$). The mixture was filtered and evaporated to dryness to afford **3** as a brownish solid; yield: 15.8 g (97%); mp 157 °C. The product was used without further purification.

IR: 3400, 3300, 3180, 2990, 1710 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 4.26 (s, 2 H, NH_2), 4.41 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 6.90 (d, *J* = 9.1 Hz, 1 H), 7.56 (d, *J* = 9.1 Hz, 1 H), 7.98 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 61.7, 78.4, 116.5, 123.1, 131.7, 133.6, 134.5, 142.7, 144.9, 162.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{10}INO_2S$: 346.9477; found: 346.9479.

5-Amino-4-ethynylbenzo[*b*]thiophenes 4a–d and 5-Acetamido-4-ethynylbenzo[*b*]thiophenes 5a–i; General Procedure for the Sonogashira Reaction

A suspension of $Pd(PPh_3)_4$ (1 mol%) and CuI (2 mol%) in THF–*i*-Pr_2NH (1:1, 10 mL) was purged with N_2. 4-Iodobenzo[*b*]thiophene **3** or **7** (1 mmol) and acetylene (1.5 mmol) were added, and the mixture was stirred overnight at 45 °C. After cooling, EtOAc (20 mL) and sat. NH_4Cl soln (20 mL) were added. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography (silica gel, CH_2Cl_2–EtOAc) to afford **4** or **5**.

Ethyl 5-Amino-4-(phenylethynyl)benzo[*b*]thiophene-2-carboxylate (4a)

Yield: 97%.

IR: 3450, 3360, 2990, 2190, 1710 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 4.41 (m, 4 H, NH_2, CO_2CH_2), 6.93 (d, *J* = 8.2 Hz, 1 H), 7.38 (m, 3 H), 7.59 (m, 3 H), 8.16 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 61.6, 83.6, 102.2, 106.0, 116.6, 123.1, 123.5, 128.5, 129.3, 131.6, 132.4, 134.8, 140.2, 142.2, 146.2, 162.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{19}H_{15}NO_2S$: 321.0823; found: 321.0813.

Ethyl 5-Amino-4-[(trimethylsilyl)ethynyl]benzo[*b*]thiophene-2-carboxylate (4b)

Yield: 94%; mp 104 °C.

IR: 3480, 3390, 2980, 2140, 1710 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.32 (s, 9 H, $SiCH_3$), 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 4.40 (m, *J* = 7.3 Hz, 4 H, NH_2, CO_2CH_2), 6.88 (d, *J* = 9.1 Hz, 1 H), 7.55 (d, *J* = 9.1 Hz, 1 H), 8.07 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.0, 14.1, 61.4, 99.0, 102.8, 104.6, 116.2, 123.4, 129.1, 132.0, 134.4, 140.2, 146.6, 162.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{19}NO_2SSi$: 317.0906; found: 317.0876.

Ethyl 5-Amino-4-(3-hydroxyprop-1-ynyl)benzo[*b*]thiophene-2-carboxylate (4c)

Yield: 89%; mp 151 °C.

IR: 3450, 3410, 3320, 2920, 2220, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.89 (s, 1 H, OH), 4.35 (s, 2 H, NH_2), 4.40 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 4.67 (s, 2 H, CH_2OH), 6.88 (d, *J* = 9.1 Hz, 1 H), 7.57 (d, *J* = 9.1 Hz, 1 H), 8.07 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 51.9, 61.6, 80.1, 97.2, 116.6, 123.7, 128.5, 129.1, 132.3, 134.9, 140.6, 146.6, 162.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{13}NO_3S$: 275.0616; found: 275.0621.

Ethyl 5-Amino-4-(3-hydroxy-3-methylbut-1-ynyl)benzo[*b*]thiophene-2-carboxylate (4d)

Yield: 95%; mp 103 °C.

IR: 3440, 3320, 3190, 2980, 2220, 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.72 [s, 6 H, $C(CH_3)_2$], 2.15 (s, 1 H, OH), 4.30 (s, 2 H, NH_2), 4.40 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 6.89 (d, *J* = 8.2 Hz, 1 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 8.03 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 32.0, 61.7, 66.2, 75.7, 101.6, 104.2, 116.7, 123.6, 129.2, 132.0, 134.9, 140.6, 146.6, 162.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{17}NO_3S$: 303.0929; found: 303.0932.

Ethyl 5-Acetamido-4-(phenylethynyl)benzo[*b*]thiophene-2-carboxylate (5a)

Yield: 94%; mp 157 °C.

IR: 3400, 3350, 2900, 2200, 1720, 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.29 (s, 3 H, CH_3CO), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.45 (m, 3 H, Ph), 7.61 (m, 2 H, Ph), 7.79 (d, *J* = 9.1 Hz, 1 H), 8.03 (s, 1 H, NH), 8.23 (s, 1 H), 8.57 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 25.1, 61.9, 82.2, 101.2, 122.2, 123.6, 128.9, 129.5, 129.6, 131.8, 135.6, 137.2, 137.4, 139.5, 162.7, 168.4.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{21}H_{17}NO_3S$: 363.0929; found: 363.0922.

Ethyl 5-Acetamido-4-[(trimethylsilyl)ethynyl]benzo[*b*]thiophene-2-carboxylate (5b)
Yield: 86%; mp 152 °C.

IR: 3380, 2960, 2140, 1700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.37 [s, 9 H, $Si(CH_3)_3$], 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.26 (s, 3 H, CH_3CO), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.78 (d, *J* = 9.1 Hz, 1 H), 8.05 (s, 1 H, NH), 8.15 (s, 1 H), 8.57 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.0, 14.3, 24.9, 61.8, 97.8, 107.2, 107.5, 119.1, 123.7, 129.5, 135.4, 136.8, 138.1, 139.2, 162.6, 168.2.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{21}NO_3SSi$: 359.1011; found: 359.1016.

Ethyl 5-Acetamido-4-(3-hydroxyprop-1-ynyl)benzo[*b*]thiophene-2-carboxylate (5c)
Yield: 44%; mp 190–191 °C.

IR: 3280, 2920, 1700, 1665 cm^{-1}.

^1H NMR (300 MHz, CD_3OD–$CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.60 (br s, 1 H, OH), 2.27 (s, 3 H, CH_3CO), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 4.62 (s, 2 H, CH_2O), 7.81 (d, *J* = 9.1 Hz, 1 H), 8.09 (s, 1 H), 8.18 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD–$CDCl_3$): δ = 13.1, 22.5, 49.8, 61.2, 71.3, 98.2, 109.9, 122.2, 128.2, 131.2, 134.4, 136.3, 137.4, 139.3, 162.2, 170.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{15}NO_4S$: 317.0722; found: 317.0706.

Ethyl 5-Acetamido-4-(3-hydroxy-3-methylbut-1-ynyl)benzo[*b*]thiophene-2-carboxylate (5d)
Yield: 86%; mp 122–123 °C.

IR: 3240, 2920, 1710, 1670 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.75 [s, 6 H, $C(CH_3)_2$], 2.26 (s, 3 H, CH_3CO), 2.67 (br s, 1 H, OH), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.73 (d, *J* = 9.1 Hz, 1 H), 7.97 (s, 1 H, NH), 8.07 (s, 1 H), 8.46 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 24.8, 31.7, 62.0, 65.9, 75.4, 106.3, 107.7, 120.0, 123.3, 129.4, 135.3, 137.2, 137.3, 139.2, 162.7, 168.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{19}NO_4S$: 345.1035; found: 345.1039.

Ethyl 5-Acetamido-4-(4-hydroxybut-1-ynyl)benzo[*b*]thiophene-2-carboxylate (5e)
Yield: 90%; mp 131 °C.

IR: 3490, 3390, 3340, 2900, 2230, 1700, 1680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.92 (s, 1 H, OH), 2.26 (s, 3 H, CH_3CO), 2.89 (t, *J* = 6.4 Hz, 2 H, $C{\equiv}CCH_2$), 3.96 (m, 2 H, CH_2OH), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.75 (d, *J* = 9.1 Hz, 1 H), 8.15 (s, 1 H), 8.21 (s, 1 H, NH), 8.55 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 24.2, 25.0, 61.1, 61.9, 99.5, 108.0, 119.7, 123.0, 129.7, 135.0, 135.3, 137.9, 139.5, 162.8, 168.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{17}NO_4S$: 331.0878; found: 331.0879.

Ethyl 5-Acetamido-4-[3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-ynyl]benzo[*b*]thiophene-2-carboxylate (5f)
Yield: 81%; mp 130 °C.

IR: 3300, 2930, 2220, 1710, 1670 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.84–1.59 (m, 6 H, THP), 2.27 (s, 3 H, CH_3CO), 3.62 (m, 1 H, THP), 3.96 (m, 1 H, THP), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 4.69 (s, 2 H, $C{\equiv}CCH_2$), 4.98 (m, 1 H, THP), 7.78 (d, *J* = 9.1 Hz, 1 H), 8.12 (s, 1 H, NH), 8.16 (s, 1 H), 8.57 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 19.2, 25.0, 25.5, 30.6, 55.6, 61.9, 62.4, 79.2, 97.6, 98.1, 107.0, 119.7, 123.7, 129.6, 135.6, 137.0, 138.2, 139.7, 162.7, 168.7.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{23}NO_5S$: 401.1297; found: 401.1308.

Ethyl 5-Acetamido-4-[3-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)but-1-ynyl]benzo[*b*]thiophene-2-carboxylate (5g)
Yield: 95%; mp 96 °C.

IR: 3300, 2940, 1710, 1690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.67 (m, 12 H, $C(CH_3)_2$, THP), 2.27 (s, 3 H, CH_3CO), 3.56 (m, 1 H, THP), 4.05 (m, 1 H, THP), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 5.29 (m, 1 H, THP), 7.75 (d, *J* = 9.1 Hz, 1 H), 8.10 (s, 1 H), 8.55 (d, *J* = 9.1 Hz, 1 H), 8.69 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 19.5, 24.4, 25.6, 29.3, 31.1, 32.0, 61.9, 62.2, 70.6, 95.2, 103.8, 107.4, 120.3, 123.2, 129.6, 135.2, 136.9, 138.4, 139.3, 162.7, 169.3.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{23}H_{27}NO_5S$: 429.1610; found: 429.1616.

Ethyl 5-Acetamido-4-[4-(tetrahydro-2*H*-pyran-2-yloxy)but-1-ynyl]benzo[*b*]thiophene-2-carboxylate (5h)
Yield: 73%; mp 130 °C.

IR: 3280, 2940, 2230, 1710, 1660 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.9–1.5 (m, 6 H, THP), 2.26 (s, 3 H, CH_3CO), 2.93 (t, *J* = 7.3 Hz, 2 H, $C{\equiv}CCH_2$), 3.55 (m, 1 H, THP), 3.79 (m, 1 H, CH_2O), 3.93 (m, 1 H, CH_2O), 4.02 (m, 1 H, THP), 4.41 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 4.73 (m, 1 H, THP), 7.73 (d, *J* = 9.1 Hz, 1 H), 8.09 (s, 1 H, NH), 8.15 (s, 1 H), 8.52 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 19.7, 21.6, 25.0, 25.5, 30.8, 61.8, 62.8, 65.8, 74.9, 99.2, 100.0, 108.2, 119.6, 122.9, 129.8, 135.2, 137.0, 137.6, 139.7, 162.7, 168.6.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{25}NO_5S$: 415.1453; found: 415.1454.

Ethyl 5-Acetamido-4-(hex-1-ynyl)benzo[*b*]thiophene-2-carboxylate (5i)
Yield: 82%; mp 116–118 °C.

IR: 3380, 2960, 2230, 1710, 1650 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.42 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.59 (m, 2 H, CH_2), 1.73 (m, 2 H, CH_2), 2.26 (s, 3 H, CH_3CO), 2.64 (t, *J* = 7.3 Hz, 2 H, $C{\equiv}CCH_2$), 4.41 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.72 (d, *J* = 9.1 Hz, 1 H), 7.99 (s, 1 H, NH), 8.14 (s, 1 H), 8.55 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 14.3, 19.6, 22.2, 24.9, 30.8, 61.7, 73.9, 102.9, 108.4, 119.4, 122.5, 129.8, 134.9, 136.9, 137.1, 139.6, 162.6, 168.2.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{21}NO_3S$: 343.1242; found: 343.1242.

Ethyl 5-Acetamido-4-(phenylethynyl)benzo[*b*]thiophene-2-carboxylate (5a); Typical Procedure by Acetylation of 4a
To a stirred soln of **4a** (404 mg, 1.24 mmol) and Et_3N (0.19 mL, 1.37 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added AcCl (106 mg, 1.37 mmol). The mixture was allowed to warm to r.t., stirred for 2.5

h and then poured into H_2O (15 mL). The product was extracted, the combined organic layers were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL) and dried ($MgSO_4$). The mixture was filtered and evaporated to afford **5a**; yield: 443 mg (98%).

Ethyl 5-Acetamido-4-[(trimethylsilyl)ethynyl]benzo[*b*]thiophene-2-carboxylate (5b)

Following the typical procedure for **5a** using **4b** (140 mg, 0.441 mmol). The crude product was purified by column chromatography (silica gel, CH_2Cl_2–EtOAc, 95:5) to afford **5b**; yield: 149 mg (94%).

Ethyl 5-Acetamido-4-(3-acetoxyprop-1-ynyl)benzo[*b*]thiophene-2-carboxylate (5cc); Acetylation of 4c

To a stirred soln of **4c** (50.0 mg, 182 μmol) and pyridine (32.3 μL, 399 μmol) in CH_2Cl_2 (4 mL) at 0 °C was added Ac_2O (37.7 μL, 399 μmol). The mixture was allowed to warm to r.t., stirred overnight and then poured into H_2O (10 mL). The product was extracted, the combined organic layers were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL) and dried ($MgSO_4$). The mixture was filtered and evaporated to dryness. The residue was purified by column chromatography (silica gel, CH_2Cl_2–EtOAc, 95:5) to afford **5cc**; yield: 56.0 mg (85%); mp 126 °C.

IR: 3290, 2990, 2230, 1740, 1700, 1670 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.18 (s, 3 H, CH_3CON), 2.33 (s, 3 H, CH_3CO_2), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 5.01 (s, 2 H, $C{\equiv}CCH_2$), 7.79 (d, *J* = 9.1 Hz, 1 H), 8.14 (s, 2 H, NH, Ar), 8.60 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 21.0, 24.9, 53.2, 61.9, 80.0, 95.2, 106.1, 119.6, 124.2, 129.4, 135.8, 136.9, 139.1, 139.6, 162.6, 169.2, 170.9.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{17}NO_5S$: 359.0827; found: 359.0835.

Ethyl 5-Acetamido-4-(3-hydroxyprop-1-ynyl)benzo[*b*]thiophene-2-carboxylate (5c); Acetylation of 4c Using $NaHSO_4$–Silica Gel

To a stirred soln of **4c** (50.0 mg, 182 μmol) and $NaHSO_4$–silica gel (18 mg) in CH_2Cl_2 (4 mL) at 0 °C was added Ac_2O (20.5 μL, 218 μmol). The mixture was allowed to warm to r.t. and stirred for 30 min. The mixture was filtered and the filtrate evaporated to dryness. The residue was purified by column chromatography (silica gel, EtOAc–petroleum ether, 90:10) to afford **5c**; yield: 49.3 mg (69%).

Ethyl 5-Acetamidobenzo[*b*]thiophene-2-carboxylate (6)

To a soln of ethyl 5-aminobenzo[*b*]thiophene-2-carboxylate (**2**, 10.6 g, 48.5 mmol) and Et_3N (8.1 mL, 93.7 mmol) in CH_2Cl_2 (400 mL) at 0 °C was added AcCl (4.2 mL, 58.2 mmol). The mixture was allowed to warm to r.t., stirred for 2.5 h and then poured into H_2O (400 mL). The product was extracted; the combined organic layers were washed with brine (400 mL), and dried ($MgSO_4$). The mixture was filtered and evaporated to afford **6** as an off-white solid; yield: 11.4 g (89%); mp 172–174 °C. The product was used without further purification.

IR: 3290, 2980, 1715, 1650 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.22 (s, 3 H, CH_3CO), 4.40 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.34 (s, 1 H, NH), 7.43 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 8.2 Hz, 1 H), 8.00 (s, 1 H), 8.21 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 24.8, 61.8, 116.1, 120.4, 123.2, 130.4, 135.3, 135.4, 138.1, 139.5, 162.6, 168.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{13}NO_3S$: 263.0616; found: 263.0613.

Ethyl 5-Acetamido-4-iodobenzo[*b*]thiophene-2-carboxylate (7)

To a stirred soln of **6** (11.4 g, 43.4 mmol) and $NaHCO_3$ (7.28 g, 86.7 mmol) in CH_2Cl_2 (320 mL) was added dropwise a soln of ICl (7.74g, 47.7 mmol) in CH_2Cl_2 (70 mL). The mixture was stirred at r.t. for 18 h. The resulting soln was washed with sat. $Na_2S_2O_3$ (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with sat. $NaHCO_3$ (200 mL) and brine (200 mL) and dried ($MgSO_4$). The mixture was filtered and evaporated to dryness to afford **7** as a brownish solid; yield: 15.4 g (91%); mp 188 °C. The product was used without further purification.

IR: 3270, 2980, 1700, 1660 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.30 (s, 3 H, CH_3CO), 4.43 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.51 (s, 1 H, NH), 7.78 (d, *J* = 8.2 Hz, 1 H), 8.08 (s, 1 H), 8.24 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 24.8, 62.0, 122.0, 122.3, 123.2, 134.5, 135.3, 136.7, 137.4, 142.3, 162.4, 168.6.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}INO_3S$: 388.9583; found: 388.9568.

Ethyl 5-(*N*-Acetylacetamido)-4-iodobenzo[*b*]thiophene-2-carboxylate (8)

Following the typical procedure for **5a** using **2** (2.08 g, 6.0 mmol). The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to afford ethyl 5-acetamido-4-iodobenzo[*b*]thiophene-2-carboxylate (**7**) (1.66 g, 71%) and the doubly acetylated product ethyl 5-(*N*-acetylacetamido)-4-iodobenzo[*b*]thiophene-2-carboxylate (**8**) (677 mg, 26%); mp 168–169 °C.

IR: 2990, 1710, 1690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.32 (s, 6 H, Ac_2N), 4.44 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.27 (d, *J* = 9.1 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 8.15 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 27.3, 62.4, 99.2, 124.5, 127.6, 134.9, 136.6, 140.3, 141.2, 144.0, 162.3, 172.6.

Ethyl (*E*)-5-[*N*-(3-Ethoxy-3-oxoprop-1-enyl)acetamido]-4-iodobenzo[*b*]thiophene-2-carboxylate (9)

A mixture of **7** (389 mg, 1 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), and $ZnBr_2$ (270 mg, 1.20 mmol) in THF (4 mL) was purged with N_2. Et_3N (670 μL, 4.80 mmol) and ethyl propynoate (486 μL, 4.8 mmol) were added. The mixture was stirred at 45 °C for 18 h. After evaporation of the solvent, EtOAc (50 mL) and H_2O (50 mL) were added. The mixture was extracted (2 × 50 mL), the combined organic layers were washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL) and dried ($MgSO_4$). The mixture was filtered and evaporated to dryness and the residue was purified by column chromatography (silica gel, CH_2Cl_2–EtOAc, 80:20 to afford **9**; yield: 219 mg (45%); mp 170–171 °C.

IR: 3000, 2920, 1700, 1690, 1630 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.46 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.93 (s, 3 H, AcN), 4.15 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 4.46 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.27 (m, 2 H), 7.96 (d, *J* = 8.2 Hz, 1 H). 8.18 (s, 1 H), 8.69 (d, *J* = 14.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 23.6, 60.4, 62.4, 98.1, 102.7, 125.0, 126.9, 134.7, 137.0, 138.7, 140.4, 141.4, 144.2, 162.0, 167.2, 169.0.

Ethyl 4-Iodo-5-(methylsulfonamido)benzo[*b*]thiophene-2-carboxylate (10)

To a soln of **2** (5.0 g, 14.4 mmol) and Et_3N (6.0 mL, 43.2 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added dropwise a soln of MsCl (2.9 mL, 37.5 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 0 °C

for 30 min and then poured into H_2O (200 mL). The product was extracted and the organic layer was washed with brine (200 mL) and dried ($MgSO_4$). The mixture was filtered and evaporated to dryness to afford ethyl 4-iodo-5-[*N*-(methylsulfonyl)methylsulfonamido]benzo[*b*]thiophene-2-carboxylate (7.0 g). Without purification, this product (7.0 g, 13.9 mmol) was refluxed together with K_2CO_3 (2.6 g, 18.7 mmol) in MeCN (100 mL). The mixture was stirred overnight, then poured into H_2O (200 mL), and extracted with EtOAc (5 × 150 mL). The combined organic layers were washed with brine (200 mL) and dried ($MgSO_4$). The mixture was filtered and evaporated to dryness to afford **10** as a brownish solid; yield: 4.5 g (76%); mp 192 °C. The product was used without further purification.

IR: 3250, 2930, 1700, 1370, 1330, 1300, 1280, 1160 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 3.02 (s, 3 H, CH_3SO_2), 4.43 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 6.75 (s, 1 H, NH), 7.75 (d, *J* = 8.2 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 8.08 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 40.5, 62.2, 90.2, 122.5, 124.0, 134.4, 135.9, 136.2, 138.7, 142.8, 162.2.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}INO_4S_2$: 424.9252; found: 424.9243.

7-Substituted Thienoindoles 11; General Procedure for TBAF-Mediated Indolization

5-Acetamido-4-ethynylbenzo[*b*]thiophene **5** (0.25 mmol) was dissolved in THF (5 mL). 1 M TBAF in THF (3 equiv) was added, and the resulting mixture was heated at reflux for 18 h. After completion of the reaction, THF was evaporated and H_2O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted using EtOAc (3 × 10 mL) and the combined organic layers were washed with brine. The mixture was filtered and evaporated and the residue was purified by column chromatography (silica gel, CH_2Cl_2–EtOAc) to afford **11**.

Ethyl 7-Phenyl-6*H*-thieno[3,2-*e*]indole-2-carboxylate (11a)

Yield: 89%; mp 199–201 °C.

IR: 3350, 2900, 1670 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.3 Hz, 3 H, CH_3), 4.43 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 7.15 (s, 1 H), 7.35 (t, *J* = 7.3 Hz, 1 H, Ph), 7.47 (t, *J* = 7.3 Hz, 2 H, Ph), 7.53 (d, *J* = 9.1 Hz, 1 H), 7.60 (d, *J* = 9.1 Hz, 1 H), 7.71 (d, *J* = 7.3 Hz, 2 H, Ph), 8.40 (s, 1 H), 8.72 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 61.5, 99.1, 112.5, 116.5, 125.0, 125.3, 128.0, 128.6, 129.3, 131.9, 132.1, 132.9, 133.9, 136.6, 137.8, 163.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{15}NO_2S$: 321.0823; found: 321.0824.

Ethyl 6*H*-Thieno[3,2-*e*]indole-2-carboxylate (11b)

Yield: 94%; mp 151 °C.

IR: 3290, 2920, 1690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.3 Hz, 3 H, CH_3), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 6.88 (s, 1 H), 7.31 (s, 1 H), 7.52 (d, *J* = 9.1 Hz, 1 H), 7.61 (d, *J* = 9.1 Hz, 1 H), 8.38 (s, 1 H), 8.55 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 61.5, 101.8, 112.8, 116.2, 123.5, 124.0, 128.6, 132.1, 132.8, 132.9, 136.3, 163.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{11}NO_2S$: 245.0510; found: 245.0511.

Ethyl 7-(2-Hydroxyethyl)-6*H*-thieno[3,2-*e*]indole-2-carboxylate (11e)

Yield: 53%; mp 69–70 °C.

IR: 3410, 3250, 2900, 1670 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.84 (s, 1 H, OH), 3.09 (m, 2 H, C=CCH_2), 4.03 (m, 2 H, CH_2O), 4.42 (q, 2 H, CO_2CH_2), 6.62 (s, 1 H), 7.44 (d, *J* = 9.1 Hz, 1 H), 7.54 (d, *J* = 9.1 Hz, 1 H), 8.30 (s, 1 H), 8.89 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 31.2, 61.5, 62.5, 99.6, 112.4, 115.3, 124.0, 128.6, 131.5, 132.4, 133.0, 136.1, 137.3, 163.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{15}NO_3S$: 289.0773; found: 289.0777.

Ethyl 7-[(Tetrahydro-2*H*-pyran-2-yloxy)methyl]-6*H*-thieno[3,2-*e*]indole-2-carboxylate (11f)

Yield: 91%; mp 145 °C.

IR: 3280, 2920, 1690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, ^1J = 5.3 Hz, 3 H, CH_3), 1.61 (m, 6 H, THP), 3.60 (m, 1 H, THP), 3.97 (m, 1 H, THP), 4.42 (q, *J* = 5.3 Hz, 2 H, CO_2CH_2), 4.72 (m, 1 H, THP), 4.87 (dd, *J* = 9.8, 26.4 Hz, 2 H, OCH_2), 6.76 (s, 1 H), 7.48 (d, *J* = 7.1 Hz, 1 H), 7.57 (d, *J* = 6.4 Hz, 1 H), 8.33 (s, 1 H), 8.90 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 20.0, 25.4, 30.8, 61.5, 63.1, 63.3, 99.1, 100.7, 112.7, 116.2, 123.8, 128.6, 132.0, 132.8, 133.4, 135.3, 136.2, 163.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{21}NO_4S$: 359.1191; found: 359.1190.

Ethyl 7-[1-Methyl-1-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-6*H*-thieno[3,2-*e*]indole-2-carboxylate (11g)

Yield: 57%.

IR: 3340, 2920, 1680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.69 [m, 12 H, $C(CH_3)_2$, THP], 3.40 (m, 1 H, THP), 3.97 (m, 1 H, THP), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 4.55 (m, 1 H, THP), 6.71 (s, 1 H), 7.48 (d, *J* = 9.1 Hz, 1 H), 7.57 (d, *J* = 9.1 Hz, 1 H), 8.35 (s, 1 H), 9.01 (s, 1 H, NH).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{25}NO_4S$: 387.1504; found: 387.1497.

No further characterization was possible due to the instability of this product.

Ethyl 7-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]-6*H*-thieno[3,2-*e*]indole-2-carboxylate (11h)

Yield: 47%.

IR: 3330, 2920, 2850, 1700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.70 (m, 6 H, THP), 3.13 (m, 2 H, C=CCH_2), 3.52 (m, 1 H, THP), 3.81 (m, 2 H, THP, OCH_2), 4.11 (m, 1 H, OCH_2), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 4.66 (m, 1 H, THP), 6.59 (s, 1 H), 7.45 (d, *J* = 9.1 Hz, 1 H), 7.53 (d, *J* = 9.1 Hz, 1 H), 8.33 (s, 1 H), 9.00 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 20.1, 25.4, 28.8, 31.0, 61.4, 63.1, 67.4, 99.3, 99.7, 112.4, 115.1, 124.0, 128.7, 131.5, 132.3, 132.9, 136.0, 137.8, 163.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{23}NO_4S$: 373.1348; found: 373.1343.

Ethyl 7-Butyl-6*H*-thieno[3,2-*e*]indole-2-carboxylate (11i)

Yield: 88%; mp 138 °C.

IR: 3360, 3330, 2960, 2930, 1670 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 3.6 Hz, 3 H, CH_3), 1.43 (t, *J* = 3.6 Hz, 3 H, CH_3), 1.44 (m, *J* = 3.6 Hz, 2 H, CH_2), 1.75 (m, *J* = 3.6 Hz, 2 H, CH_2), 2.83 (t, *J* = 3.6 Hz, 2 H, CH_2), 4.41 (q, *J* = 3.6 Hz, 2 H, CO_2CH_2), 6.58 (s, 1 H), 7.43 (d, *J* = 4.4 Hz, 1 H), 7.52 (d, *J* = 4.4 Hz, 1 H), 8.19 (s, 1 H, NH), 8.32 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 14.6, 22.5, 28.2, 31.6, 61.4, 99.0, 112.2, 115.0, 124.5, 128.7, 131.5, 132.4, 132.6, 136.1, 140.1, 163.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{19}NO_2S$: 301.1136; found: 301.1128.

Ethyl 7-Vinyl-6*H*-thieno[3,2-*e*]indole-2-carboxylate (11j)
Yield: 40%; mp 138 °C.

IR: 3360, 3330, 2920, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 3 H, CH_3), 4.42 (q, *J* = 7.3 Hz, 2 H, CO_2CH_2), 5.32 (d, *J* = 11.0 Hz, 1 H, CH_2=C), 5.63 (d, *J* = 17.4 Hz, 1 H, CH_2=C), 6.79 (dd, *J* = 17.4 Hz, 11.0 Hz, 1 H, CH=C), 6.83 (s, 1 H), 7.46 (d, *J* = 9.1 Hz, 1 H), 7.59 (d, *J* = 9.1 Hz, 1 H), 8.33 (s, 1 H), 8.48 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 61.6, 102.0, 112.3, 112.8, 117.0, 124.5, 127.5, 128.5, 132.0, 133.0, 133.6, 136.1, 136.4, 163.3.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{13}NO_2S$: 271.0667; found: 271.0675.

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