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Efficient synthesis of substituted thieno[3,2-*e*]indoles

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ABSTRACT

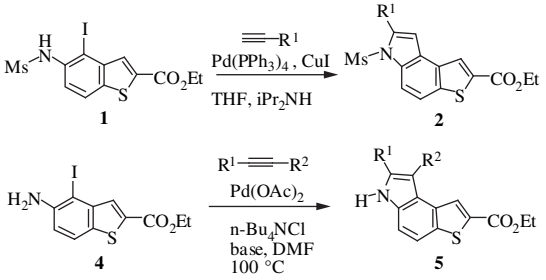
Efficient cyclization reactions of 5-aminobenzothiophene derivatives with internal and terminal acetylenes, giving 7- and 8-substituted thieno[3,2-*e*]indoles, are described. The reaction of 4-iodo-5-(methylsulfonamido)benzothiophene with terminal alkynes gave 7-substituted thienoindoles using general Sonogashira reaction conditions. Reaction of 5-amino-4-iodobenzothiophene with internal acetylenes, using Larock's heterocyclization reaction conditions, gave 7,8-disubstituted thieno[3,2-*e*]indoles.

1. Introduction

Few versatile methods exist for the synthesis of thieno[3,2-*e*]indoles. The Fischer indolization of 5-substituted benzothiophene hydrazone,[1] the photochemical cyclization of 2-[2-(2-thienyl)vinyl]-1*H*-pyrroles,[2] and the cyclocondensation of 3-oxoindole with 2-thienylacetonitrile resulting in thienocarbazole[3] are the most important methods for the synthesis of thieno[3,2-*e*]indoles. The need for harsh reaction conditions in these procedures is an important drawback and leads to low yields and a restricted number of possible substituents.

In our preceding work we have reported the synthesis of 7-substituted thieno[3,2-*e*]indoles via the tetrabutylammonium fluoride (TBAF) mediated cyclization of 5-acetamido-4-alkynylbenzothiophenes.[4] This indole cyclization procedure requires two steps, (a) coupling of terminal alkynes onto the benzothiophene ring system via Sonogashira coupling and (b) the subsequent TBAF cyclization reaction. Recently, Sakamoto and his co-workers have reported a one-pot indole synthesis from 2-iodoanilines and terminal alkynes using a palladium catalyst in the presence of TBAF.[5] Also, the one-pot synthesis of methylsulfonyl-protected iodoanilines with terminal acetylenes was reported.[6–8] This reaction involves a general Sonogashira coupling followed by ring formation to the desired indole in one step, by addition of NH to the triple bond.[7–9]

In order to provide an efficient method for the synthesis of 7-substituted thienoindoles, we herein wish to report a one-pot procedure for the synthesis of 7-substituted thieno[3,2-*e*]indoles from 4-iodo-5-(methylsulfonamido)benzothiophene (**1**) and terminal alkynes using a palladium catalyst under typical Sonogashira reaction conditions[7,8] (Scheme 1). We also wish to report that there is no specific requirement for TBAF as cyclizing agent in this reaction.



R^1, R^2 = aryl, TMS, alkyl, alkoxy,...

Scheme 1. Synthesis of substituted thieno[3,2-*e*]indoles **2** and **5**.

A convenient way of preparing 2,3-disubstituted indoles from 2-iodoanilines and internal acetylenes has been reported by Larock and co-workers.[8,10] As a second part in this manuscript, we wish to report the synthesis of 7,8-disubstituted thieno[3,2-*e*]indoles in high yields via general Larock heterocyclization reaction conditions from 5-amino-4-iodobenzothiophene (**4**) and internal alkynes. The use of a specific base is crucial in this cyclization procedure.

2. Results and discussion

In our preceding work we synthesized 7-substituted thieno[3,2-*e*]-indoles through cyclization of 5-acetamido-4-alkynylbenzothiophenes in the presence of 3 equiv of tetrabutylammonium fluoride (TBAF).[4] The synthetic procedures for the preparation of ethyl-5-acetamido-4-iodobenzothiophene-2-carboxylate (**1a**) and ethyl-4-iodo-5-(methylsulfonamido)benzothiophene-2-carboxylate (**1b**) (Table 1) were described therein.[4]

The reaction conditions for the alternative one-pot indole synthesis from these amino-protected 4-iodobenzothiophenes (**1a**,**b**) with phenylacetylene were examined as shown in Table 1. When a mixture of benzothiophene (**1a**) and phenylacetylene is refluxed

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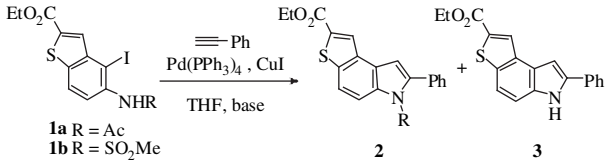
Table 1
One-pot indole cyclization reaction of benzothiophenes **1** with phenylacetylene



1a R = Ac
1b R = SO_2Me
2 **3**

Entry	Aryl iodide	Base conditions[a]	Yield[b] (%)
1	**1a**	A	**3** (48)
2	**1a**	B	**3** (62)
3	**1b**	A	**3** (82)
4	**1b**	B	**3** (86)
5	**1b**	C	**2** (68)

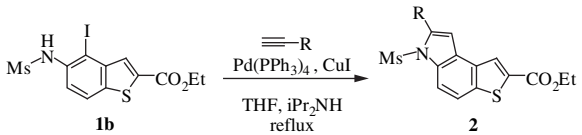
[a] Base conditions: (A) *i*-Pr_2NH and TBAF (3 equiv) in one-pot, (B) *i*-Pr_2NH/THF was evaporated and TBAF (3 equiv)/THF was added, (C) *i*-Pr_2NH (no TBAF).
[b] All yields refer to isolated products.

in the presence of a palladium catalyst and 3 equiv of TBAF, ethyl-7-phenyl-6*H*-thieno[3,2-*e*]indole-2-carboxylate **3** was obtained in 48% yield. The reaction of benzothiophene (**1b**) with phenylacetylene in the presence of TBAF resulted in the same demesylated compound **3** in 82% yield. Addition of TBAF to the evaporated reaction mixture after completion of the Sonogashira coupling reaction (Table 1, entries 2 and 4) gave in both cases thienoindole **3** with only slightly improved yields (62 and 86%, respectively). After performing the reaction with benzothiophene (**1b**) under general Sonogashira conditions without the use of TBAF as the cyclizing agent (Table 1, entry 5), we obtained the methylsulfonyl-protected thienoindole **2** in 68% yield.

Based on the above results, we next examined this thienoindole synthesis from (**1b**) with different terminal acetylenes, as shown in Table 2. We previously reported that cyclization of ethyl-5-acetamido-4-(4-hydroxybut-1-ynyl)benzothiophene-2-carboxylate (and analogous products) under TBAF reaction conditions resulted in the formation of 7-vinylthienoindoles as byproducts.[4] In contrast, the Sonogashira coupling reaction of (**1b**) with 2-(but-3-ynyloxy)tetrahydro-2*H*-pyran or but-3-yn-1-ol (Table 2, entries 2 and 3) resulted in the formation of 7-substituted thienoindoles **2b** and **2c** in excellent yields (91% and 86%, respectively). The reaction with propargyl alcohol (entry 4) gave a rather disappointing result (31% yield), next to an excellent yield of 88% for the 7-(2-hydroxy-2-propyl)thienoindole **2e**. The indole synthesis using trimethylsilylacetylene gave only 11% of the expected thienoindole **2f1**, accompanied by the formation of the open Sonogashira product, ethyl-5-(methylsulfonamido)-4-(trimethylsilylethynyl)benzothiophene-2-carboxylate **2f2** in 61% yield. Finally, the cyclization reaction of (**1b**) with electron deficient acetylenes, such as 2-ethynylpyridine, gave no product under normal Sonogashira reaction conditions. In accordance to literature we tried to use $ZnBr_2$ under Negishi reaction conditions.[11] We found that only on addition of a large excess of Hünig's base the expected product 7-(pyridin-2-yl)thienoindole **2g** could be synthesized in an acceptable yield of 66%.

Next to the synthesis of 7-substituted thienoindoles, we explored the synthesis of 7,8-disubstituted thienoindoles. Using Larock's method for the synthesis of indoles, we tried different bases (K_2CO_3, KOAc, Na_2CO_3, NaOAc) with or without PPh_3 for the coupling of 5-amino-4-iodobenzothiophene (**4**) with internal alkynes. The coupling with *tert*-butyldimethyl(4-(tetrahydro-2*H*-pyran-2-yloxy)-but-1-ynyl)silane (Table 3, entry 1) gave an excellent result, when using Na_2CO_3 with 5 mol % of PPh_3. It is important to note that the yield highly depends on the choice of base. Different alkynes were coupled as shown in Table 3. The cyclization with 4-(pyridin-2-yl)but-3-yn-1-ol (entry 3) gave only one isomer **5c** in 85% yield. The coordination of the pyridine ring in the palladium-complex intermediate resulting in one product has recently been reported.[12] In contrast, the coupling with 2-(phenylethynyl)pyridine (entry 4) gave a mixture of both isomers (**5d1**, **5d2**). The cyclization with 2-(3-fluorophenyl)ethynyltrimethylsilane (entry 5) using NaOAc gave next to the desired compound **5e1** the desilylated product ethyl-8-(3-fluorophenyl)-6*H*-thieno[3,2-*e*]indole-2-carboxylate **5e2** in 34% yield. The use of electron deficient alkynes, such as ethyl phenylpropiolate (entry 7), resulted in a complex mixture of products, from which it was not possible to isolate the desired thienoindole. Analysis of the structure of different isomers **5** has been established by 2D NMR spectroscopy.

Table 2
Thienoindole synthesis from ethyl-5-(methylsulfonamido)-4-iodobenzothiophene-2-carboxylate **1b**

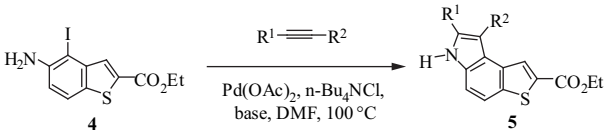


1b **2**

Entry	Acetylene R=	Time (h)	Yield[a] (%)
1	Phenyl	24	**2a**, 68[b]
2	CH_2CH_2OTHP	18	**2b**, 91
3	CH_2CH_2OH	19	**2c**, 86
4	CH_2OH	18	**2d**, 31
5	CMe_2OH	20	**2e**, 88
6	TMS	22	**2f1**, 11[c]
7	2-Pyridinyl	17	**2g**, 66[d]

[a] All yields refer to isolated products.
[b] $Pd(PPh_3)_4$ (5 mol %) and CuI (10 mol %) were used.
[c] Ethyl-5-(methylsulfonamido)-4-((trimethylsilyl)ethynyl)benzo[*b*]thiophene-2-carboxylate **2f2** (61%) obtained.
[d] $Pd(PPh_3)_4$ (10 mol %), $ZnBr_2$ (3 equiv), and Hünig's base were used.

Table 3
Thienoindole synthesis from ethyl-5-amino-4-iodobenzothiophene-2-carboxylate **4**



4 **5**

Entry	R^1	R^2	Base[a]	Time (h)	Thienoindole **5**, yield[b] (%)
1	TBDMS	CH_2CH_2OTHP	Na_2CO_3(+)	18	**5a**, 91
2	Phenyl	CH_2CH_2OH	Na_2CO_3 (+)	18	**5b1**, 48 and **5b2**,[c] 40
3	2-Pyridinyl	CH_2CH_2OH	Na_2CO_3 (+)	16	**5c**, 85
4	2-Pyridinyl	Phenyl	KOAc (−)	48	**5d1**, 36 and **5d2**,[c] 38
5	TMS	3-Fluorophenyl	NaOAc (−)	2	**5e1**, 43[d]
6	TMS	CH_2CH_2OH	Na_2CO_3 (+)	17	**5f**, 71
7	Phenyl	CO_2Et	—	—	**5g**, —[e]

[a] All yields refer to isolated products.
[b] (+): 5 mol % of PPh_3 is used; (−): no PPh_3 used.
[c] R^1 and R^2 interchanged.
[d] Desilylated product (34%) formed, ethyl-8-(3-fluorophenyl)-6*H*-thieno[3,2-*e*]indole-2-carboxylate **5e2**.
[e] Different base conditions were tried; no product obtained.

In conclusion, we have synthesized 7-substituted and 7,8-disubstituted thieno[3,2-*e*]indoles by different procedures. One is the one-pot cyclization of 5-(methylsulfonamido)-4-iodobenzothiophene with terminal acetylenes, using general Sonogashira reaction conditions. 7,8-Disubstituted thieno[3,2-*e*]indoles were synthesized by Larock's heteroannulation reaction.

3. Experimental section

3.1. General

Melting points (not corrected) were determined using a Reichert Thermovar apparatus, using the product obtained from purification by column chromatography. IR spectra were recorded using a Bruker ALPHA-P spectrometer. NMR spectroscopy was performed on commercial instruments (Bruker Avance 300 MHz and Bruker AMX 400 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (^{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 10,000). 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 synthetic procedures for the preparation of ethyl-5-(acetamido)-4-iodobenzothiophene-2-carboxylate (**1a**), ethyl-4-iodo-5-(methylsulfonamido)benzothiophene-2-carboxylate (**1b**), ethyl-5-amino-4-iodobenzothiophene-2-carboxylate (**4**), and ethyl-5-amino-4-(phenylethynyl)benzo[*b*]thiophene-2-carboxylate were described in our previous work.[4]

3.2. Ethyl-7-phenyl-6*H*-thieno[3,2-*e*]indole-2-carboxylate (3) (Table 1, entry 1)[4]

To a suspension of tetrakis(triphenylphosphine)palladium(0) (11.6 mg, 1 mol %) and CuI (3.8 mg, 2 mol %) in 12 mL of THF/*i*-Pr_2NH 1:1 were added ethyl-4-iodo-5-acetamidobenzothiophene-2-carboxylate (**1a**) (389 mg, 1 mmol), phenylacetylene (153 mg, 1.5 mmol), and TBAF (3 mL, 1 M solution in THF). The mixture was stirred for 18 h at 60 °C. After cooling, water (20 mL) was added. The mixture was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to afford 154 mg of ethyl-7-phenyl-6*H*-thieno[3,2-*e*]indole-2-carboxylate (**3**). Obtained as a yellow solid; mp 199–201 °C; IR: 3350, 2900, 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, 3H, J=7.3 Hz), 4.43 (q, 2H, J=7.3 Hz), 7.15 (s, 1H), 7.35 (t, 1H, J=7.3 Hz), 7.47 (t, 2H, J=7.3 Hz), 7.53 (d, 1H, J=9.1 Hz), 7.60 (d, 1H, J=9.1 Hz), 7.71 (d, 2H, J=7.3 Hz), 8.40 (s, 1H), 8.72 (br s, 1H); ^{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 calcd for $C_{19}H_{15}O_2NS$ (M^+): 321.0823; found 321.0824.

3.3. Preparation of 7-substituted thieno[3,2-*e*]indoles 2: typical procedure for the one-pot reaction of 4-iodo-5-(methylsulfonamido)benzothiophene (1b) with external acetylene

To a suspension of tetrakis(triphenylphosphine)palladium(0) (1 mol %) and CuI (2 mol %) in 10 mL of THF/*i*-Pr_2NH 1:1 were added ethyl-4-iodo-5-(methylsulfonamido)benzothiophene-2-carboxylate (**1b**) (1 mmol) and acetylene (1.5 mmol). The mixture was refluxed for the appropriate time indicated in Table 2. After cooling, EtOAc and water (both 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 over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography to afford **2** (silica, eluent: CH_2Cl_2/EtOAc mixtures).

*3.3.1. Ethyl-6-(methylsulfonyl)-7-phenyl-6H-thieno[3,2-e]indole-2-carboxylate (**2a**).* Obtained as a yellow solid; mp 206–208 °C; IR: 2980, 1705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H, J=7.3 Hz), 2.80 (s, 3H), 4.43 (q, 2H, J=7.3 Hz), 7.04 (s, 1H), 7.47 (m, 3H), 7.60 (m, 2H), 7.80 (d, 1H, J=9.1 Hz), 8.28 (d, 1H, J=9.1 Hz), 8.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 40.4, 61.8, 111.3, 115.8, 119.2, 126.3, 127.9, 129.3, 130.5, 131.7, 134.8, 135.3, 139.4, 142.4, 162.8; HRMS (EI): m/z calcd for $C_{20}H_{17}O_4NS_2$ (M^+): 399.0599; found: 399.0609.

*3.3.2. Ethyl-6-(methylsulfonyl)-7-(2-(tetrahydro-2H-pyran-2-yloxy)-ethyl)-6H-thieno[3,2-e]indole-2-carboxylate (**2b**).* Obtained as a yellow solid; mp 44 °C; IR: 2940, 1705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H, J=7.3 Hz), 1.70 (m, 6H), 3.11 (s, 3H), 3.38 (t, 2H, J=6.4 Hz), 3.53 (m, 1H), 3.82 (m, 2H), 4.15 (m, 1H), 4.43 (q, 2H, J=7.3 Hz), 4.66 (m, 1H), 6.90 (s, 1H), 7.68 (d, 1H, J=9.1 Hz), 8.15 (d, 1H, J=9.1 Hz), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 19.7, 25.4, 29.4, 30.7, 41.3, 61.7, 62.6, 66.2, 99.1, 107.9, 114.3, 118.0, 125.6, 127.9, 131.2, 133.7, 134.2, 138.6, 139.3, 162.8; HRMS (EI): m/z calcd for $C_{21}H_{25}O_6NS_2$ (M^+): 451.1123; found: 451.1120.

*3.3.3. Ethyl-7-(2-hydroxyethyl)-6-(methylsulfonyl)-6H-thieno[3,2-e]indole-2-carboxylate (**2c**).* Obtained as a solid; mp 155–156 °C; IR: 3460, 2930, 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, 3H, J=7.3 Hz), 2.32 (br s, 1H), 3.09 (s, 3H), 3.32 (t, 2H, J=6.4 Hz), 4.04 (t, 2H, J=6.4 Hz), 4.40 (q, 2H, J=7.3 Hz), 6.89 (s, 1H), 7.68 (d, 1H, J=9.1 Hz), 8.15 (d, 1H, J=9.1 Hz), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 32.3, 41.3, 61.8, 61.9, 108.7, 114.4, 118.3, 125.6, 127.9, 131.3, 133.9, 134.4, 139.0, 162.8; HRMS (EI): m/z calcd for $C_{15}H_{15}O_5NS_2$ (M^+): 353.0392; found: 353.0397.

*3.3.4. Ethyl-7-(hydroxymethyl)-6-(methylsulfonyl)-6H-thieno[3,2-e]indole-2-carboxylate (**2d**).* Obtained as a yellow-white solid; mp 165–166 °C; IR: 3550, 2930, 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H, J=7.3 Hz), 2.83 (t, 1H, J=6.4 Hz), 3.24 (s, 3H), 4.43 (q, 2H, J=7.3 Hz), 4.97 (d, 2H, J=6.4 Hz), 7.01 (s, 1H), 7.78 (d, 1H, J=9.1 Hz), 8.16 (d, 1H, J=9.1 Hz), 8.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 41.6, 58.3, 61.9, 109.6, 114.0, 119.5, 127.8, 131.9, 135.0, 138.9, 139.9, 162.8; HRMS (EI): m/z calcd for $C_{16}H_{17}O_5NS_2$ (M^+): 367.0548; found: 367.0540.

*3.3.5. Ethyl-7-(2-hydroxypropan-2-yl)-6-(methylsulfonyl)-6H-thieno[3,2-e]indole-2-carboxylate (**2e**).* Obtained as a yellow-white solid; mp 110–112 °C; IR: 3530, 2980, 2930, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H, J=7.3 Hz), 1.84 (s, 6H), 3.16 (s, 3H), 4.43 (q, 2H, J=7.3 Hz), 4.52 (s, 1H), 7.03 (s, 1H), 7.74 (d, 1H, J=9.1 Hz), 8.23 (d, 1H, J=9.1 Hz), 8.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 31.3, 40.8, 61.7, 69.7, 108.4, 115.0, 119.3, 125.0, 127.6, 131.8, 134.9, 135.3, 139.0, 148.2, 162.7; HRMS (EI): m/z calcd for $C_{17}H_{19}O_5NS_2$ (M^+): 381.0705; found: 381.0708.

*3.3.6. Ethyl-6-(methylsulfonyl)-7-(trimethylsilyl)-6H-thieno[3,2-e]indole-2-carboxylate (**2f1**).* Obtained as an off-white to gray solid; mp 54–56 °C; IR: 2955, 1705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.46 (s, 9H), 1.45 (t, 3H, J=7.3 Hz), 3.07 (s, 3H), 4.43 (q, 2H, J=7.3 Hz), 7.26 (s, 1H), 7.77 (d, 1H, J=9.1 Hz), 8.16 (d, 1H, J=9.1 Hz), 8.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.4, 14.5, 40.9, 61.8, 113.8, 119.3, 119.4, 126.6, 127.9, 131.8, 134.9, 136.1, 138.6, 142.8, 162.8; HRMS (EI): m/z calcd for $C_{17}H_{21}O_4NS_2Si$ (M^+): 395.0681; found: 395.0701.

*3.3.7. Ethyl-5-(methylsulfonamido)-4-((trimethylsilyl)ethynyl)benzo-[b]thiophene-2-carboxylate (**2f2**).* A white solid; mp 145–146 °C; IR: 3250, 2930, 2165, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.36 (s, 9H), 1.44 (t, 3H, J=7.3 Hz), 3.01 (s, 3H), 4.43 (q, 2H, J=7.3 Hz), 7.04 (br s, 1H), 7.74 (d, 1H, J=9.1 Hz), 7.82 (d, 1H, J=9.1 Hz), 8.15 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 0.03, 14.4, 40.0, 62.1, 97.4, 108.0, 110.9, 120.5, 124.2, 129.5, 136.3, 136.4, 138.8, 140.1, 162.4; HRMS (EI): *m*/*z* calcd for $C_{17}H_{21}O_4NS_2Si$ (M^+): 395.0681; found: 395.0671.

3.4. Ethyl-6-(methylsulfonyl)-7-(pyridin-2-yl)-6*H*-thieno[3,2-*e*]indole-2-carboxylate (2g)

To a solution of $ZnBr_2$ (168 mg, 0.75 mmol) in THF (3 mL) under nitrogen atmosphere were added *i*-Pr_2NEt (1 mL), ethyl-4-iodo-5-(methylsulfonamido)benzo[*b*]thiophene-2-carboxylate (**1b**) (106 mg, 0.25 mmol), 2-ethynylpyridine (77.3 mg, 0.75 mmol), and tetrakis (triphenylphosphine)palladium(0) (29 mg, 10 mol %). The mixture was stirred for 17 h at 60 °C. After cooling, water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (2×30 mL) and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (90:10) as eluent to afford 65.8 mg of ethyl-6-(methylsulfonyl)-7-(pyridin-2-yl)-6*H*-thieno[3,2-*e*]-indole-2-carboxylate **4g** as a yellow-white solid; mp 208–209 °C; IR: 3020, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H, *J*=7.3 Hz), 3.67 (s, 3H), 4.43 (q, 2H, *J*=7.3 Hz), 7.16 (s, 1H), 7.34 (dd, 1H, *J*=7.3, 5.0 Hz), 7.66 (d, 1H, *J*=7.3 Hz), 7.82 (m, 2H), 8.24 (d, 1H, *J*=9.1 Hz), 8.33 (s, 1H), 8.67 (d, 1H, *J*=4.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 43.3, 61.7, 110.4, 115.0, 119.3, 123.2, 124.5, 124.9, 127.8, 131.8, 134.6, 135.0, 136.8, 138.6, 139.8, 148.6, 151.2, 162.8; HRMS (EI): *m*/*z* calcd for $C_{19}H_{16}O_4N_2S_2$ (M^+): 400.0551; found: 400.0570.

3.5. Preparation of 7,8-disubstituted thieno[3,2-*e*]indoles 5: typical procedure for the Larock heteroannulation reaction of 5-amino-4-iodobenzothiophene (4) with internal acetylene

A mixture of $Pd(OAc)_2$ (5 mol %), *n*-Bu_4NCl (0.5 mmol), PPh_3 (5 mol %), the appropriate base (see Table 3, 2.5 mmol), aryl iodide (**4**) (174 mg, 0.5 mmol) and alkyne (2.5 mmol) in DMF (10 mL) was purged with nitrogen and stirred for the appropriate time (as indicated in Table 3) at 100 °C. After cooling, water (40 mL) was added and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The mixture was filtered, evaporated to dryness, and the residue was purified by column chromatography to afford **5** (silica, eluent: CH_2Cl_2/EtOAc mixtures).

*3.5.1. Ethyl-7-(tert-butyldimethylsilyl)-8-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-6H-thieno[3,2-e]indole-2-carboxylate (**5a**).* Obtained as an off-white solid; mp 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.44 (s, 6H), 0.94 (s, 9H), 1.42 (t, 3H, *J*=7.3 Hz), 1.68 (m, 6H), 3.45 (m, 3H), 3.69 (m, 1H), 3.96 (m, 2H), 4.41 (q, 2H, *J*=7.3 Hz), 4.69 (m, 1H), 7.48 (d, 1H, *J*=9.1 Hz), 7.55 (d, 1H, *J*=9.1 Hz), 8.40 (br s, 1H), 8.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, 14.5, 17.9, 19.5, 25.6, 26.7, 28.5, 30.7, 61.4, 62.0, 68.5, 99.0, 112.7, 116.5, 122.8, 123.6, 128.8, 131.5, 132.1, 132.7, 136.0, 136.6, 163.4; HRMS (EI): *m*/*z* calcd for $C_{26}H_{37}O_4NSSi$ (M^+): 487.2213; found: 487.2213.

*3.5.2. Ethyl-8-(2-hydroxyethyl)-7-phenyl-6H-thieno[3,2-e]indole-2-carboxylate (**5b1**).* Obtained as a yellow-white solid; mp 87–91 °C; IR: 3360, 2925, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, 3H, *J*=7.1 Hz), 1.67 (br s, 1H), 3.38 (t, 2H, *J*=7.0 Hz), 4.02 (t, 2H, *J*=6.8 Hz), 4.41 (q, 2H, *J*=7.1 Hz), 7.38 (m, 1H), 7.47 (m, 3H), 7.62 (m, 3H), 8.48 (s, 1H), 8.49 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 29.1, 61.6, 62.9, 110.4, 112.6, 116.6, 123.9, 128.2, 128.3, 128.6, 129.1, 131.7, 132.8, 133.0, 133.2, 136.0, 137.2, 163.4.

*3.5.3. Ethyl-7-(2-hydroxyethyl)-8-phenyl-6H-thieno[3,2-e]indole-2-carboxylate (**5b2**).* Obtained as a yellow solid; mp 76–78 °C; IR: 3320, 2925, 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, 2H, *J*=7.3 Hz), 2.15 (br s, 1H), 2.99 (t, 2H, *J*=5.5 Hz), 3.92 (t, 2H, *J*=5.5 Hz), 4.31 (q, 2H, *J*=7.3 Hz), 7.44 (m, 6H), 7.54 (d, 1H, *J*=8.2 Hz), 7.95 (s, 1H), 9.27 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 28.8, 61.3, 62.6, 112.6, 115.6, 116.0, 122.5, 127.1, 128.6, 128.9, 130.8, 131.2, 131.7, 132.1, 134.2, 134.3, 136.9, 163.4.

*3.5.4. Ethyl-8-(2-hydroxyethyl)-7-(pyridin-2-yl)-6H-thieno[3,2-e]indole-2-carboxylate (**5c**).* Obtained as a white solid; mp 194–196 °C; IR: 3135, 2850, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (t, 3H, *J*=7.3 Hz), 3.42 (t, 2H, *J*=5.5 Hz), 4.34 (t, 2H, *J* 5.5 Hz), 4.47 (q, 2H, *J*=7.3 Hz), 6.61 (br s, 1H), 6.88 (d, 1H, *J*=8.2 Hz), 6.97 (d, 1H, *J*=8.2 Hz), 7.02 (m, 1H), 7.51 (d, 1H, *J*=8.2 Hz), 7.66 (t, 1H, *J*=8.2 Hz), 8.17 (d, 1H, *J*=4.6 Hz), 8.32 (s, 1H), 10.02 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 27.8, 61.6, 63.1, 112.8, 113.7, 116.4, 121.8, 122.4, 122.8, 127.6, 131.5, 132.6, 133.7, 134.2, 137.0, 137.1, 148.3, 150.3, 163.5; HRMS (EI): *m*/*z* calcd $C_{20}H_{18}O_3N_2S$ for (M^+): 366.1038; found: 366.1057.

*3.5.5. Ethyl-8-phenyl-7-(pyridin-2-yl)-6H-thieno[3,2-e]indole-2-carboxylate (**5d1**).* Obtained as a yellow solid; mp 167–170 °C; IR: 3370, 2920, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, 3H, *J*=7.0 Hz), 4.30 (t, 2H, *J*=7.0 Hz), 7.08 (m, 1H), 7.13 (d, 1H, *J*=8.2 Hz), 7.41 (dt, 1H, *J*=8.2, 1.8 Hz), 7.55 (m, 7H), 7.64 (d, 1H, *J*=8.2 Hz), 8.57 (d, 1H, *J*=4.8 Hz), 10.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 61.3, 112.8, 117.7, 117.8, 121.1, 122.0, 124.8, 128.2, 128.4, 129.4, 130.9, 131.9, 132.1, 132.3, 132.6, 136.1, 136.4, 137.2, 149.3, 150.3, 163.1; HRMS (EI): *m*/*z* calcd for $C_{24}H_{18}O_2N_2S$ (M^+): 398.1089; found: 398.1095.

*3.5.6. Ethyl-7-phenyl-8-(pyridin-2-yl)-6H-thieno[3,2-e]indole-2-carboxylate (**5d2**).* Obtained as a yellow solid; mp 235–236 °C; IR: 2950, 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, 3H, *J*=7.0 Hz), 4.34 (t, 2H, *J*=7.0 Hz), 7.24 (m, 7H), 7.32 (d, 1H, *J*=7.8 Hz), 7.41 (d, 1H, *J*=8.8 Hz), 7.58 (d, 1H, *J*=8.8 Hz), 7.67 (dt, 1H, *J*=7.8, 1.8 Hz), 8.08 (s, 1H), 8.82 (d, 1H, *J*=4.5 Hz), 9.07 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 61.3, 112.5, 115.8, 117.0, 122.2, 123.4, 126.4, 128.1, 128.4, 128.9, 129.9, 131.6, 131.9, 132.2, 133.1, 135.8, 136.5, 137.7, 149.9, 155.5, 163.3; HRMS (EI): *m*/*z* calcd for $C_{24}H_{18}O_2N_2S$ (M^+): 398.1089; found: 398.1086.

*3.5.7. Ethyl-8-(3-fluorophenyl)-7-(trimethylsilyl)-6H-thieno[3,2-e]indole-2-carboxylate (**5e1**).* Obtained as a yellow solid; mp 163–167 °C; IR: 3400, 2925, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.21 (s, 9H), 1.36 (t, 3H, *J*=7.3 Hz), 4.32 (q, 2H, *J*=7.3 Hz), 7.17 (m, 2H), 7.27 (m, 1H), 7.44 (m, 1H), 7.55 (d, 1H, *J*=9.1 Hz), 7.63 (d, 1H, *J*=9.1 Hz), 7.74 (s, 1H), 8.54 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −0.5, 14.4, 53.6, 61.4, 112.6, 114.3, 114.6, 117.0, 117.8, 118.1, 123.3, 126.7, 126.9, 128.3, 129.7, 129.9, 131.4, 132.5, 134.7, 134.9, 137.0, 139.4, 139.5, 161.1, 163.2, 164.4.

*3.5.8. Ethyl-8-(3-fluorophenyl)-6H-thieno[3,2-e]indole-2-carboxylate (**5e2**).* Obtained as a yellow solid; mp 222–223 °C; IR: 3365, 2985, 1680 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ 1.41 (t, 3H, *J*=7.0 Hz), 4.40 (q, 2H, *J*=7.3 Hz), 7.10 (dt, 1H, *J*=8.3, 2.0 Hz), 7.51 (m, 2H), 7.67 (m, 3H), 7.76 (d, 1H, *J*=7.8 Hz), 8.45 (s, 1H), 11.19 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 14.7, 61.9, 100.2, 100.3, 112.4, 112.6, 114.0, 114.1, 114.8, 115.0, 117.2, 121.8, 121.9, 125.5, 129.2, 131.8, 131.9, 132.7, 133.6, 135.4, 135.6, 135.7, 136.8, 137.3, 163.1, 163.3, 165.5; HRMS (EI): *m*/*z* calcd for $C_{19}H_{14}O_2NSF$ (M^+): 339.0729; found: 339.0731.

*3.5.9. Ethyl-8-(2-hydroxyethyl)-7-(trimethylsilyl)-6H-thieno[3,2-e]indole-2-carboxylate (**5f**).* Obtained as a white solid; mp 155–157 °C; IR: 3500, 3290, 2950, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.42 (s, 9H), 1.41 (t, 3H, *J*=7.3 Hz), 2.40 (br s, 1H), 3.35 (t, 2H, *J*=7.3 Hz), 3.93 (t, 2H, *J*=7.3 Hz), 4.40 (q, 2H, *J*=7.3 Hz), 7.49 (d, 1H, *J*=9.1), 7.55 (d, 1H, *J*=9.1 Hz), 8.50 (s, 1H), 8.62 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −0.3, 14.5, 30.9, 61.6, 63.1, 112.9, 116.6,

121.4, 123.5, 128.5, 131.4, 132.6, 134.8, 135.9, 136.8, 163.5; HRMS (EI): m/z calcd for $C_{18}H_{23}O_3NSSi$ (M^+): 361.1168; found: 361.1179.

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