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The Synthesis of Three 4-Substituted Benzo[*b*]thiophene-2-Carboxamidines as Potent and Selective Inhibitors of Urokinase

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Abstract—Efficient syntheses of structurally novel 4-substituted benzo[*b*]thiophene-2-carboxamidines **1–3**, which selectively inhibit urokinase-type plasminogen activator (uPA) with IC_{50} values of 70–320 nM, are described. The key intermediate, methyl 4-iodobenzo[*b*]thiophene-2-carboxylate (**7**), is prepared from 3-fluoroiodobenzene in two steps in 70% overall yield via fluorine-directed metalation/formylation and subsequent thiophene annulation. Amidination of ester **7** gives the 320 nM inhibitor **1**. Palladium-catalyzed arylacetylene and vinyl stannane couplings with ester **7** or 4-iodobenzo[*b*]thiophene-2-carbonitrile (**16**, derived from **7**), respectively, followed by amidination leads to the more potent inhibitors **2** (IC_{50} = 133 nM) and **3** (IC_{50} = 70 nM). These compounds represent an important new class of synthetic uPA inhibitors, with carboxamidine **3** being the most potent selective inhibitor currently described in the literature.

Introduction

The ability of cells to penetrate and move through physical barriers such as extracellular matrix (ECM) and basement membrane (BM) is known as cellular invasiveness. This process, driven by highly regulated extracellular proteolysis, is a key component of many normal and disease-state physiological processes such as wound healing, angiogenesis and neovascularization, ovulation and trophoblast implantation, embryonic development, breast, uterine, and prostatic involution, arthritis and inflammation, and tumor metastasis and invasion.[1] Urokinase-type plasminogen activator (uPA) is a key initiator of the extracellular proteolytic cascades driving cellular invasiveness.[2–4] This enzyme is a serine protease which is highly specific for the zymogen plasminogen, and activates the latter to the potent but relatively non-specific serine protease plasmin.[2–4] In turn, plasmin proteolytically degrades ECM and BM proteins such as fibronectin and laminin. In addition, plasmin proteolytically activates latent collagenases thereby triggering degradation of ECM and BM collagen.[5–7] Thus, uPA associated with invasive cells (via binding to high affinity cell surface uPA receptors[8,9]) initiates a multi-component proteolytic cascade which results in destruction of ECM and BM, and consequently in removal of the physical barriers to cellular movement. This central role of uPA as an initiator of cellular invasiveness suggests that appropriately selective synthetic uPA inhibitors could be important therapeutic agents for the treatment of a variety of disorders. Indeed, the validity of this concept has been demonstrated in experiments showing that anti-catalytic anti-uPA antibodies can block metastasis and invasion *in vivo*.[10–14]

Tissue-type plasminogen activator (tPA), the primary mediator of blood clot dissolution or fibrinolysis, shares an identical specificity with uPA for plasminogen. Accordingly, clinically-useful uPA inhibitors must be free of significant inhibitory effects against either tPA or plasmin to avoid anti-fibrinolytic side effects. This requirement for high uPA selectivity relative to tPA and plasmin eliminates most of the known synthetic uPA inhibitors. Those that remain, including *p*-aminobenzamidine,[15–17] amiloride,[18] and several 4-substituted phenylguanidines,[19] have only moderate anti-uPA potency. Thus there is a need to develop selective, low molecular weight uPA inhibitors with increased potency.

Here we present the syntheses and *in vitro* activities of three 4-substituted benzo[*b*]thiophene-2-carboxamidines, **1–3** (Figure 1). These three compounds represent an important new series of potent and selective synthetic uPA inhibitors.[20]

Synthesis

Our initial investigation of mono-, bi-, and tricyclic aromatic amidines as urokinase inhibitors[21] revealed that benzo[*b*]thiophene-2-carboxamidine possessed reasonably good inhibitory activity (IC_{50} = 4 μM). Accordingly, we developed a general synthesis of B-ring substituted benzo[*b*]thiophene-2-carboxamidines (Scheme I). The amidination of esters and other carboxylic acid derivatives with the reagent derived from NH_4Cl/Me_3Al[22] proceeds smoothly, and our synthetic scheme was simplified to the production of substituted benzo[*b*]thiophene-2-carboxy-

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lates. These compounds were prepared from substituted aryl fluorides via fluorine-directed metalation/formylation and subsequent thiophene annulation as previously reported.[23,24] By using a fluorine atom as the basis for annulation of the thiophene ring, one can exploit the considerable variety of commercially available aryl fluorides in the preparation of C4–C7 substituted benzo[*b*]thiophenes. One of our first synthetic goals was to produce benzothiophenes with an iodine atom at each of the four B-ring positions (R^1 = I),[24] since it was believed that these aryl iodides would be useful substrates for C–C bond formation via palladium-catalyzed coupling reactions.[25] In subsequent SAR studies it became apparent that 4-substitution was the most beneficial for producing potent benzothiophene-based uPA inhibitors, and amidines **1**–**3** are three of the more interesting compounds in this series.

Amidine **1** was synthesized following the general pathway illustrated in Scheme I. Lithiation of 3-fluoroiodobenzene (**4**; Figure 2) was carried out with lithium diisopropylamide (LDA, THF, -78 °C),[23] and quenching of the intermediate lithiospecies **5** with DMF yielded benzaldehyde **6** in 92% crude yield. This crude material was treated directly with methyl thioglycolate and triethylamine in DMSO at 80 °C, followed by an ice–water quench, filtration, and methanol wash, to afford methyl 4-iodobenzo[*b*]thiophene-2-carboxylate (**7**) in 77% yield.[24] Treatment of ester **7** with excess NH_4Cl/Me_3Al,[22] followed by chromatographic purification, provided amidine **1** in 73% yield.

Ester **7** served as the starting point for the preparation of amidine **2** (Scheme II). Piperonal was subjected to Corey/Fuchs ethynylation[26] (PPh_3/CBr_4 followed by 2 equiv. *n*-BuLi, -78 to 0 °C) providing acetylene **8**[27] in 76% distilled yield. Coupling of acetylene **8** with iodoester **7** ($PdCl_2(PPh_3)_2/CuI/Et_3N$)[23] went smoothly at 25 °C to give diarylalkyne **9** in 65% purified yield. This ester was also amidinated (Me_3Al/NH_4Cl) to afford amidine **2** in 54% yield after chromatographic purification.

The initial synthesis of amidine **3** began with the lithiation/formylation of 2-(3-fluorophenyl)-1,3-dioxolane (**10**, Scheme III) followed by thiophene annulation to give the protected 4-formylbenzothiophene derivative **11** in good yield.[23,24] Acetal hydrolysis and subsequent diborane reduction of the aldehyde afforded alcohol **12**. Bromination of **12** with PPh_3/CBr_4,[29] and conversion to the corresponding phosphonium salt **13** (PPh_3, $PhCH_3$, 110 °C) was followed by reaction of **13** with potassium *t*-butoxide and piperonal to provide the styrene **14** in low yield (28%) as an *E*/*Z*-mixture. Subsequent amidination of **14** with Me_3Al/NH_4Cl worked well on a small scale (≤ 50 mg) to give the desired amidine **3** (>90% *E*).[30]

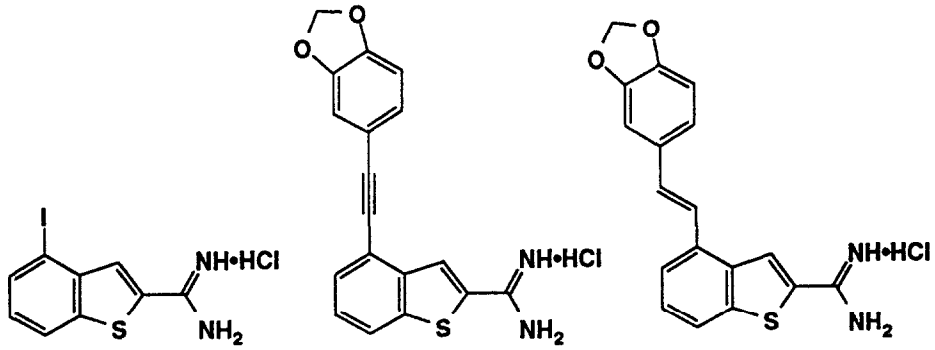
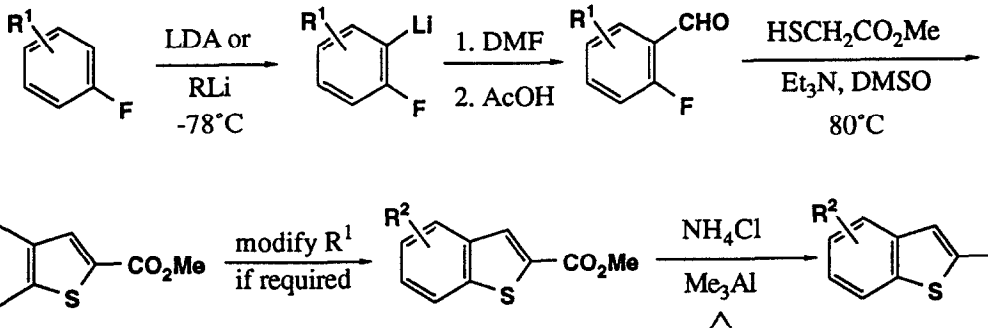


Figure 1.



Scheme I. General synthesis of benzo[*b*]thiophene-2-carboxamidines from fluorobenzenes.

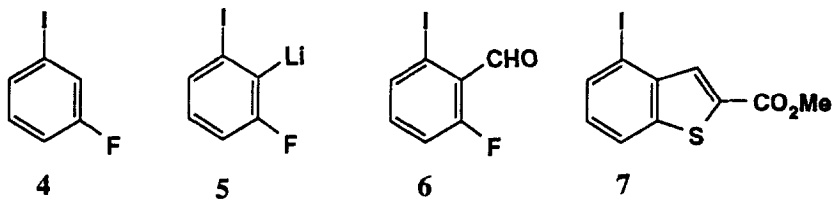
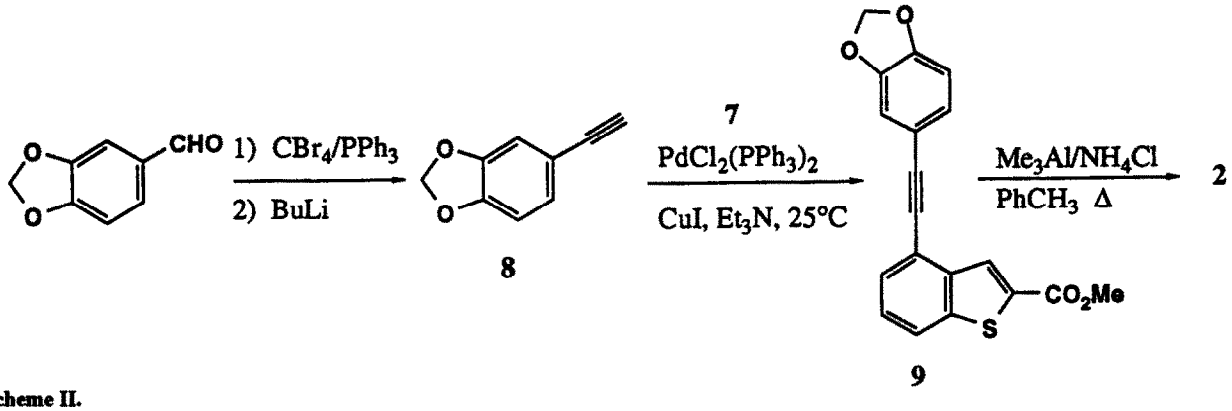


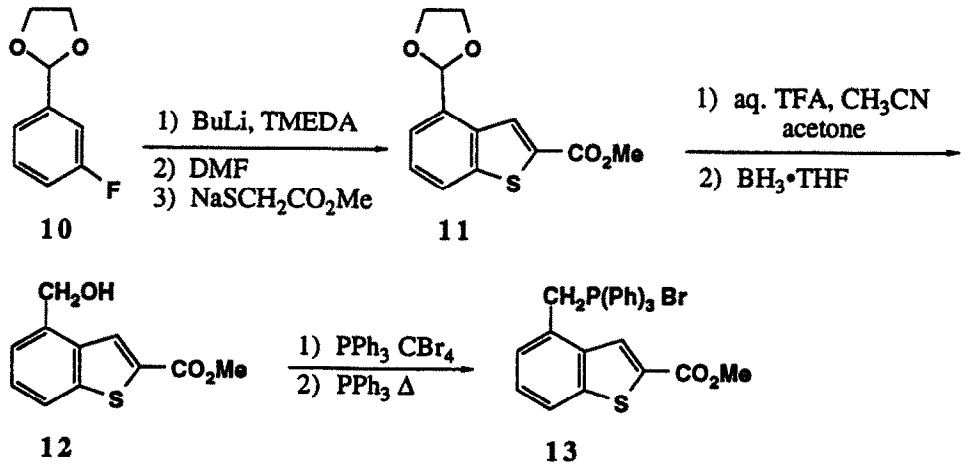
Figure 2.

Although Wittig condensations with **13** were very useful for making a wide variety of aralkenyl substituted analogs, they were not suitable for larger scale synthesis of **3**; yields for the Wittig reaction remained low, with production of somewhat variable isomeric mixtures, under a variety of conditions. Moreover, scaling up the amidination of **14** led to destruction of the methylenedioxy substituent by the aluminum reagent, at a rate similar to amidine formation. We therefore examined a different route to amidine **3** based on a stereospecific palladium-catalyzed vinyl stannane coupling with 4-iodobenzothiophene-2-carbonitrile, followed by amidination under basic conditions.

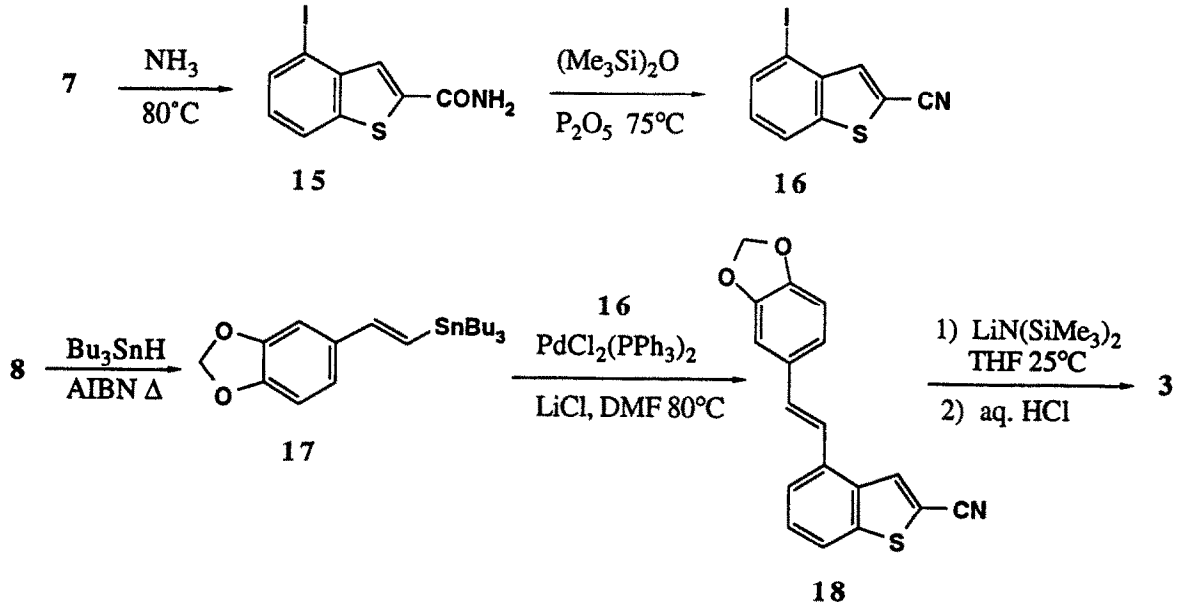
Accordingly, ester **7** was converted into the corresponding carboxamide **15** (Scheme IV) in quantitative yield by treatment with ammonia at 80 °C, and the amide was dehydrated to nitrile **16** with hexamethyldisiloxane/-P_2O_5[31] (dichloroethane, 75 °C) in 92% yield. Reaction of acetylene **8** with a slight excess of tri-*n*-butyltin hydride and catalytic AIBN (toluene, 90 °C) gave the corresponding *E*-vinyl stannane **17** in 91% purified yield. Coupling of stannane **17** with iodonitrile **16** (DMF, 3 equiv. LiCl, 0.03 equiv. $PdCl_2(PPh_3)_2$, 80 °C)[32] went smoothly to give the highly crystalline nitrile **18** in 77% yield. Reaction of nitrile **17** with $LiN(SiMe_3)_2$[33] in THF followed by acid hydrolysis afforded amidine **3**. This compound was cleanly obtained in 83% yield by filtration of the acidified reaction mixture, rinsing the solids with cold ethanol, and vacuum drying. This reaction sequence is rapid and efficient, and allows for the convenient preparation of **3** on a multi-gram scale.



Scheme II.



Scheme III.



Scheme IV.

Table 1. Inhibitory potencies of benzo[*b*]thiophene-2-carboxamidines and amiloride against plasminogen system enzymes[a]

Compound	uPA IC_{50} (μM)[b]	n	tPA IC_{50} (μM)[b]	n	Plasmin IC_{50} (μM)[b]	n
amiloride	7.2 ± 0.9	10	>1000	2	>1000	2
1	0.32 ± 0.02	14	107 ± 22	3	352 ± 30	2
2	0.13 ± 28	6	8	1	500	1
3	0.07 ± 0.01	18	24 ± 2	5	>250	4

[a]Details of the chromogenic assays are presented in Ref. 20.
[b]Mean ±SEM for $n \geq 3$; for n =1 or 2, values are given as a range.

In Vitro Activities

The inhibitory activities of amidines **1–3** against uPA, tPA, and plasmin are summarized in Table 1. Data for amiloride, a known selective uPA inhibitor of moderate potency,[18] are also presented for comparative purposes. As shown, compounds **1–3** are potent inhibitors of uPA with little activity against tPA or plasmin. The most potent of these inhibitors, benzothiophene **3**, is approximately 100-fold more potent than amiloride, with 350- and >3500-fold selectivities for uPA relative to tPA and plasmin inhibition, respectively. Further details of the inhibitory activities of **1** and **3** are reported elsewhere.[20]

In summary, this paper describes novel and efficient preparations of three 4-substituted benzo[*b*]thiophene-2-carboxamidines, **1–3**, all of which are potent and selective inhibitors of the plasminogen activator urokinase. To our knowledge, carboxamidine **3** is the most potent selective uPA inhibitor currently described in the literature. These compounds and related analogs should prove to be important biological probes of uPA-mediated cellular invasive processes, and should also have great interest as potential pharmaceutical agents.

Experimental

General

Compounds were purchased from Lancaster Synthesis or Aldrich Chemical Co., and were used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Toluene, dimethylsulfoxide (DMSO), and *N*,*N*-dimethylformamide (DMF) were anhydrous grade obtained in Sure/Seal™ bottles from

Aldrich. Silica gel was E. M. Merck 70–230 mesh, and preparative chromatography plates were Analtech 20 x 20 cm silica gel plates of 0.1 or 0.2 cm thickness. ^{1}H NMR spectra were performed at 400 MHz on a JEOL GSX400 or a Bruker AMX-400 spectrometer and ^{13}C spectra on the same instruments at 100 MHz (NMR abbreviations: s = singlet, d = doublet, t = triplet, br = broad). IR spectra were performed on a Nicolet FT-IR Spectrometer. Melting points were taken on an Electrothermal IA9100 and are uncorrected. Microanalyses were carried out by Atlantic Microlab Inc., Norcross, GA.

6-Fluoro-2-iodobenzaldehyde (6)

Lithium diisopropylamide solution (prepared at 0 °C under N_2 from *n*-butyl lithium (2.5 M in hexanes, 105 mL, 0.263 mol) and *N,N*-diisopropylamine (27.8 g, 0.275 mol)) in THF (200 mL) was added dropwise via cannula over 100 min to a solution of 3-fluoroiodobenzene (55.5 g, 0.25 mol) in THF (250 mL) stirred mechanically under N_2 at -78 °C. After 15 min, DMF (23.2 mL, 0.30 mol) was added dropwise over 15 min, producing a thick precipitate by the end of the addition. After 10 min the reaction was quenched at -78 °C by rapid sequential addition of glacial acetic acid (60 mL) and water (500 mL). The phases were separated, and the aqueous phase was extracted with ether (2 x 250 mL). The combined organic extracts were washed with dilute hydrochloric acid (0.5 M, 250 mL), water (2 x 250 mL), saturated brine (200 mL), and dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure to give **6** (57.63 g, 92%) as a yellow–brown oil which crystallized upon standing. An analytical sample was recrystallized from hexanes at -20 °C as light yellow needles, m.p. 37.5–38 °C: Calc. for C_7H_4FIO: C, 33.63%, H, 1.61%; Found C, 33.61%, H, 1.62%; IR ν 1696, 1653, 1590, 1576, 1560, 1539, 1265, 1200, 1182, 878, 789 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.14 (1H, d, J = 0.9 Hz), 7.81 (1H, dt, J = 7.3, 1.2 Hz), 7.23 (1H, ddd, J = 8.2, 7.3, 5.8 Hz), 7.18 (1H, ddd, J = 8.2, 9.5, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 190.46, 163.06 (d, J = 265.2 Hz), 137.19 (d, J = 2.9 Hz), 135.75 (d, J = 10.3 Hz), 124.2, 117.18 (d, J = 20.5 Hz), 96.81.

*Methyl 4-iodobenzo[*b*]thiophene-2-carboxylate (7)*

Methyl thioglycolate (23.2 mL, 0.253 mol) was added over 1 min to a solution of 6-fluoro-2-iodobenzaldehyde (**6**, 57.63 g, 0.23 mol) in DMSO (200 mL) stirred under N_2 at 25 °C. A moderate exotherm was noted. Triethylamine (70.0 mL, 0.5 mol) was added, and the mixture was heated to 60 °C for ~2 h. The reaction mixture was poured slowly onto vigorously stirred ice–water (2 L). After 30 min of stirring, the light yellow precipitate was collected by suction filtration, rinsed with water (2 x 250 mL), and air dried to give the crude benzothiophene (71.2 g). This was stirred as a suspension in refluxing MeOH (400 mL) for 10 min, and the mixture was cooled to 0 °C, the solid collected by suction filtration, rinsed with cold MeOH (2 x 50 mL), and dried *in vacuo* to give **7** (56.76 g, 77%) as a very pale yellow crystalline solid, m.p. 120–121 °C. An analytical sample was recrystallized from toluene/hexanes as pale yellow needles m.p. 119–120 °C: Calc. for $C_{10}H_7IO_2S$: C, 37.75%; H, 2.22%; I, 39.89%; S, 10.08%; Found: C, 37.76%; H, 2.20%; I, 39.98%; S, 10.00%; IR ν 1719, 1523, 1249, 1195, 1180, 783, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.12 (1H, s), 7.82 (2H, d, J = 8 Hz), 7.15 (1H, t, J = 7.9 Hz), 3.97 (3H, s); ^{13}C NMR ($CDCl_3$) δ 162.75, 141.79, 141.27, 135.02, 134.26, 133.58, 127.88, 122.67, 92.10, 52.65.

*4-Iodobenzo[*b*]thiophene-2-carboxamidine hydrochloride (1)*

[**Caution!** Trimethylaluminum is extremely reactive, and large amounts of gas evolve during this experiment. Reactions should be carried out in flasks no more than 30% filled, and heating should be carried out slowly, under careful scrutiny even on the scale described here.]

Trimethylaluminum (2.0 M in toluene, 50 mL, 100 mmol) was added dropwise over 30 min to a suspension of ammonium chloride (5.35 g, 100 mmol) in toluene (50 mL), stirred under N_2 at 0 °C. *Vigorous gas evolution!* When gas evolution moderated, the mixture was stirred at 25 °C for 30 min, when most of the solid had dissolved. Methyl 4-iodobenzo[*b*]thiophene-2-carboxylate (**7**, 8.66 g, 27.2 mmol) was added in one portion to form a clear yellow solution. *This solution was heated to reflux in stages over 1 h, vigorous gas evolution being seen in the 60–100 °C range.* After 2.5 h of reflux, the reaction mixture was allowed to cool to 25 °C, and was poured onto a vigorously stirred slurry of silica gel (50 g) in $CHCl_3$ (500 mL). A mild exotherm and gas evolution was observed. After 20 min the solids were collected by suction filtration, and washed with MeOH (3 x 250 mL). The combined filtrates were evaporated to dryness, and the residual yellow solid (10.75 g) was purified by flash chromatography on silica gel (800 g), eluting with 10%, 20%, and finally 25% MeOH/$CHCl_3$. After solvent removal the yellow residue was dissolved in refluxing MeOH (100 mL), treated with activated charcoal (2 g), and filtered through a pad of Celite. The solvent was removed under reduced pressure at 65 °C to give **1** (6.79 g, 74%) as a pale yellow crystalline solid. An analytical sample was recrystallized from MeOH (-20 °C), m.p. 270–271 °C: Calc. for $C_9H_7IN_2S{\cdot}HCl{\cdot}0.5\ CH_3OH$: C, 32.17%; H, 2.84%; N, 7.90%; S, 9.04%; Found: C, 32.27%; H, 2.83%; N, 7.86%; S, 8.95%; IR ν 3200, 3060, 1670, 1559, 1534, 762 cm^{-1}; ^{1}H NMR (DMSO d_6) δ 9.67 (4H, br s), 8.40 (1H, s), 8.22 (1H, d, J = 8.2 Hz), 7.96 (1H, d, J = 7.6 Hz), 7.32 (1H, t, J = 7.9 Hz); ^{13}C NMR (DMSO d_6) δ 159.24, 140.92, 139.93, 135.64, 134.00, 129.51, 129.03, 123.17, 93.02.

5-Ethynylbenzo-1,3-dioxolane (8)

A solution of triphenylphosphine (69.90 g, 0.26 mol) in CH_2Cl_2 (80 mL) was added via cannula to a stirred 0 °C solution of carbon tetrabromide (44.04 g, 0.13 mol) in CH_2Cl_2 (80 mL) under N_2. After stirring for 5 min, a solution of piperonal (10.00 g, 0.67 mol) in CH_2Cl_2 (40 mL) was added dropwise via cannula, and the reaction was

stirred for 30 min. The mixture was transferred to an Erlenmeyer flask and hexane (400 mL) was added with vigorous stirring. The solids were removed by filtration, washed with hexane, and the combined organics were evaporated. Hexane (400 mL) was added to the residue, the solids were filtered and washed with hexane, and the solvent was rigorously removed under reduced pressure. The residue was dissolved in THF (200 mL), cooled to -78 °C under N_2, and *n*-BuLi (72 mL, 2.13 M) was added dropwise via cannula. The dark-colored reaction mixture was stirred at -78 °C for 1 h, stirred at 0 °C for 1 h, and quenched with aqueous NH_4Cl solution. The mixture was diluted with Et_2O, washed with water (3x), saturated brine, and dried ($MgSO_4$). Filtration and solvent removal gave an oil which was purified by bulb-to-bulb distillation to afford **8** (6.89 g, 71%) as a clear, colorless oil. Spectral data matched that provided in Ref. 27.

*Methyl 4-[(benzo-1,3-dioxolan-5-yl)ethynyl]benzo[*b*]thiophene-2-carboxylate (**9**)*

A slurry of alkyne **8** (156.1 mg, 1.06 mmol), methyl 4-iodobenzo[*b*]thiophene-2-carboxylate (**7**, 301.4 mg, 0.95 mmol), bis(triphenylphosphine)palladium(II) chloride (24.0 mg, 0.03 mmol), and CuI (8.8 mg, 0.04 mmol) in Et_3N (3 mL) was stirred under N_2 at 25 °C for 2 h. The reaction mixture was diluted with EtOAc, washed with water (2x), brine, and dried ($MgSO_4$). After filtration and solvent removal, the residue was purified by flash chromatography (10% EtOAc/hexane) to afford **9** (208.4 mg, 65%) as a light yellow solid, m.p. 117.3–117.7 °C: Calc. for $C_{19}H_{12}O_4S$: C, 67.84%; H, 3.59%; S, 9.53%; Found: C, 67.09%; H, 3.57%; S, 9.33%; IR ν 3024, 2223, 1746, 1644, 1268, 1054, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (1H, d, J = 0.6 Hz), 7.79 (1H, d, J = 8.2 Hz), 7.55 (1H, dd, J = 7.4, 0.6 Hz), 7.41 (1H, t, J = 7.8 Hz), 7.15 (1H, dd, J = 8.2, 1.6 Hz), 7.06 (1H, d, J = 8.0 Hz), 6.83 (1H, d, J = 8.0 Hz), 6.02 (2H, s), 3.97 (3H, s); ^{13}C NMR ($CDCl_3$) δ 162.93, 148.19, 147.45, 141.88, 139.51, 133.48, 129.91, 128.21, 126.58, 126.47, 122.40, 120.36, 115.97, 111.49, 108.48, 101.38, 94.12, 85.27, 52.49.

*4-[(Benzo-1,3-dioxolan-5-yl)ethynyl]benzo[*b*]thiophene-2-carboxamidine hydrochloride (**2**)*

Treatment of ester **9** (208.4 mg, 0.62 mmol) with 5.1 equiv. of Me_3Al/NH_4Cl (toluene, 130 °C, 5.5 h) gave, after workup and chromatographic purification (15% MeOH/$CHCl_3$), amidine **2** (119.4 mg, 54%) as a bright yellow solid, m.p. 240.5–242.2 °C: Calc. for $C_{18}H_{13}ClN_2O_2S$: C, 60.58%; H, 3.67%; Cl, 9.93%; N, 7.85%; S, 8.98%; Found: C, 58.47%; H, 3.85%; Cl, 9.41%; N, 7.61%; S, 8.52%; IR ν 3344, 3059, 2130, 1666, 1489, 1245, 1039 cm^{-1}; ^1H NMR (CD_3OD) δ 8.54 (1H, s), 8.02 (1H, d, J = 8.0 Hz), 7.67 (1H, d, J = 7.4 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.20 (1H, dd, J = 8.0, 1.5 Hz), 7.12 (1H, d, J = 1.5 Hz), 6.89 (1H, d, J = 8.1 Hz), 6.05 (2H, s), 4.85 (4H, br s); ^{13}C NMR (CD_3OD) δ 162.43, 150.84, 149.92, 143.48, 141.22, 132.08, 131.22, 130.89, 129.92, 128.59, 124.45, 122.86, 117.78, 113.20, 110.39, 103.82, 96.80, 86.35.

*4-Iodobenzo[*b*]thiophene-2-carboxamide (**15**)*

[**Caution!** High pressure reaction. Bomb should never be more than 40% filled by reaction mixture, and heater should have a safety cut-off system.] Methyl 4-iodobenzo[*b*]thiophene-2-carboxylate (**3**, 31.81 g, 0.10 mol) was heated to 80 °C for 10 h in a stainless steel bomb with liquid ammonia (50 mL). The bomb was cooled on a dry ice/*i*-PrOH bath, opened, and the ammonia allowed to evaporate at 25 °C. The residue was scraped out and dried *in vacuo* at 60 °C to give **15** (30.3 g, 100%) as a cream colored solid, m.p. 186–187.5 °C: Calc. for C_9H_6IONS: C, 35.56%; H, 2.00%; N, 4.62%; Found: C, 35.73%; H, 1.99%; N, 4.57%; IR ν 3350, 1651, 1614, 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (1H, d, J = 8 Hz), 7.82 (1H, s), 7.81 (1H, d, J = 7.6 Hz), 7.12 (1H, t, J = 7.8 Hz), 6.2–5.8 (br d).

*4-Iodobenzo[*b*]thiophene-2-carbonitrile (**16**)*

A slurry of phosphorus pentoxide (40.0 g, 282 mmol) and hexamethyldisiloxane (100 mL, 470 mmol) in 1,2-dichloroethane (200 mL) was heated to 90 °C with stirring under N_2 for 2 h, forming a clear solution. This was allowed to cool to 40 °C, and 4-iodobenzo[*b*]thiophene-2-carboxamide (**15**, 30.0 g, 99 mmol) was added in one portion. The reaction mixture was heated to 75 °C under N_2 with stirring for 4 h (all solid dissolved within ~1 h), cooled to 25 °C, and stirred with aq. NaCl (6 M, 1 L) for 10 min. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (2 x 250 mL). The combined organic phases were washed with aq. NaCl (6 M, 250 mL), dilute aqueous Na_2CO_3 (0.1 M, 250 mL), brine (250 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give nitrile **16** (27.6 g, 98%) as a light yellow solid, >98% pure by ^1H NMR analysis. This material was recrystallized from EtOH at 0 °C to give **16** as lemon yellow needles, m.p. 125–126 °C, 1st crop (24.3 g, 86%), 2nd crop (1.6 g, 6%): Calc. for C_9H_4INS: C, 37.91%; H, 1.41%; N, 4.93%; I, 44.51%; S, 11.25%; Found: C, 37.81%; H, 1.36%; N, 4.88%; I, 44.56%; S, 11.36%; IR ν 1670, 1559, 1539, 1195, 855, 767 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (1H, s), 7.88 (1H, d, J = 7.4 Hz), 7.82 (1H, d, J = 8.4 Hz), 7.23 (1H, t, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 140.68, 140.35, 138.84, 135.83, 128.83, 122.26, 113.83, 109.96, 91.58.

*5-[E-(2-tri-*n*-Butylstannyl)ethenyl]benzo-1,3-dioxolane (**17**)*

A solution of 5-ethynylbenzo-1,3-dioxolane (**8**, 6.89 g, 47.2 mmol), tri-*n*-butyltin hydride (13.8 mL, 51 mmol) and AIBN (133 mg, 0.81 mmol) in toluene (200 mL) was heated to 95 °C under N_2 for 5.5 h. The reaction mixture was allowed to cool, and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (1% Et_3N/7% EtOAc/92% hexanes), and the solvent was removed under reduced pressure to give **17** (18.80 g, 91%) as a colorless oil: IR ν 2999, 2942, 1511, 1451, 1266, 1060, 778 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (1H, d, J = 1.5 Hz), 6.82 (1H, dd, J = 8.0,

1.5 Hz), 6.76 (1H, d, J = 19.4 Hz), 6.75 (1H, d, J = 8.0 Hz), 6.62 (1H, d, J = 19.4 Hz), 5.95 (2H, s), 1.60–1.44 (6H, m), 1.38–1.25 (6H, m), 1.04–0.79 (12H, m); ^{13}C NMR ($CDCl_3$) δ 148.11, 147.22, 145.40, 133.81, 127.05, 120.89, 108.19, 105.29, 101.06, 29.22, 27.41, 13.84, 9.67.

4-[E-2-(Benzo-1,3-dioxolan-5-yl)ethenyl]benzo[b]thiophene-2-carbonitrile (18)

4-Iodobenzo[*b*]thiophene-2-carbonitrile (**16**, 4.02 g, 14.10 mmol), bis(triphenylphosphine)palladium dichloride (400.9 mg, 0.57 mmol) and anhydrous lithium chloride (1.82 g, 42.9 mmol) were purged under N_2 in a dry flask. Dry DMF (100 mL) was added, followed by dropwise addition via cannula of 5-(*E*-(2-tri-*n*-butylstannyl)ethenyl)benzo-1,3-dioxolane (**17**, 6.82 g, 15.5 mmol) in DMF (10 mL). The mixture was heated to 80 °C under N_2 for 3.5 h, cooled to 25 °C, and diluted with EtOAc (300 mL). The reaction mixture was washed with water (5 x 100 mL), brine (100 mL), and dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure, and the solid yellow residue was stirred with ether (200 mL) for 1 h at reflux. The slurry was cooled to -20 °C, the solid was collected by suction filtration, rinsed with cold ether, and dried *in vacuo* to give **18** (3.31 g, 77%) as a bright yellow solid, m.p. 173.1–173.5 °C: Calc. for $C_{18}H_{11}NO_2S$: C, 70.80%; H, 3.63%; N, 4.58%; S, 10.50%; Found: C, 70.77%; H, 3.65%; N, 4.56%; S, 10.42%; IR ν 2211, 1502, 1446, 1260, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.19 (1H, d, J = 0.7 Hz), 7.74 (1H, d, J = 8.0 Hz), 7.67 (1H, d, J = 7.4 Hz), 7.53 (1H, t, J = 7.8 Hz), 7.34 (1H, d, J = 16.1 Hz), 7.14 (1H, d, J = 16.1 Hz), 7.13 (1H, s), 7.00 (1H, dd, J = 8.1, 1.7 Hz), 6.84 (1H, d, J = 8.0 Hz), 6.02 (2H, s); ^{13}C NMR ($CDCl_3$) δ 148.42, 148.12, 142.12, 135.79, 135.00, 133.11, 132.33, 131.23, 128.18, 122.53, 122.23, 121.88, 121.01, 114.62, 109.43, 108.64, 105.74, 101.41.

4-[E-2-(Benzo-1,3-dioxolan-5-yl)ethenyl]benzo[b]thiophene-2-carboxamidine hydrochloride (3)

Lithium hexamethyldisilazide (13.0 mL, 1.0 M in hexane) was added dropwise to a 0 °C solution of 4-[*E*-2-(benzo-1,3-dioxolan-5-yl)ethenyl]benzo[*b*]thiophene-2-carbonitrile (**18**, 3.31 g, 10.83 mmol) in THF (50 mL). After 5 min the ice-bath was removed and the red–brown solution was stirred for an additional 8 h. Aqueous 10% HCl (50 mL) was added to the reaction mixture with vigorous stirring, with immediate formation of a bright yellow precipitate. The thick slurry was stirred at room temperature for 15 h, the solids were filtered, rinsed with cold ethanol, and dried in a vacuum oven (45 °C) to afford **3** (3.3 g, 85%) as a bright yellow solid, m.p. 204.3 °C (dec): Calc. for $C_{18}H_{15}ClN_2O_2S$: C, 60.42%; H, 4.21%; Cl, 9.88%; N, 7.81%; S, 8.93%; Found: C, 60.18%; H, 4.19%; Cl, 9.97%; N, 7.83%; S, 8.85%; IR ν 3440, 3020, 1694, 1511, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.74 (1H, s), 7.89 (1H, d, J = 8.2 Hz), 7.82 (1H, d, J = 7.6 Hz), 7.59 (1H, d, J = 15.9 Hz), 7.58 (1H, t, J = 7.8 Hz), 7.31 (1H, d, J = 15.9 Hz), 7.29 (1H, s), 7.09 (1H, dd, J = 8.0, 1.5 Hz), 6.84 (1H, d, J = 8.0 Hz), 5.99 (2H, s), 4.91 (4H, br s); ^{13}C NMR ($CDCl_3$) δ 162.32, 150.49, 150.11, 144.23, 138.75, 137.50, 133.88, 133.68, 131.89, 130.52, 129.99, 124.56, 124.39, 123.40, 123.29, 110.34, 107.57, 103.52.

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