

A Facile Synthesis of 3-Substituted-2-aminothiophenes and 1,3-Disubstituted-2-methylthiopyrroles

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Received July 31, 2000

Electron-rich 3-functionalized-2-aminothiophenes **6** and 1,3-disubstituted-2-methylthiopyrroles **10** were synthesized from substituted allyl benzotriazoles **2** and isothiocyanates **3** via condensation and subsequent heterocyclization.

Introduction

Cycloadditions are powerful synthetic tools.¹ Recently, novel routes to important heterocycles, including 2-aminothiophenes and 2-alkylthiopyrroles, were developed on the basis of cyclizations of intermediates formed from unsaturated carbanions and isothiocyanates.²

Since the first reported preparation of 2-aminothiophene,³ the synthesis of functionalized aminothiophenes has been studied extensively.⁴ Four main synthetic approaches have been applied, three of which utilize preexisting thiophene rings: (i) reduction of nitro-⁵ or nitroso-thiophenes,⁶ (ii) Beckmann, Schmidt,⁷ or Curtius rearrangements⁸ of thiophenecarboxylic acid derivatives, and (iii) nucleophilic displacements in mercapto-⁹ or iodo-thiophenes¹⁰ with amines. Route (iv), ring closure reactions from non thiophene starting materials, is less developed for the preparation of simple 2-aminothiophenes. To the best of our knowledge, the only described examples reported are based on the use of (a) methyl *N*-phenyl-2-alkenimidothioates,¹¹ (b) metalated ynamines or allenic amines,^{12a,b} and (c) lithiated 1-alkynes or allenes.¹³

Approaches to 3-substituted-2-(alkylthio)pyrroles, especially those with an electron-donating 3-substituent, are rather limited. The two main routes are (i) cyclizations of [3 + 2] products from acyl- or nitro-ketene *S,N*-acetals and bromoacetaldehyde acetal,^{14a,b} a highly regioselective reaction which is limited to products containing an electron-withdrawing substituent (acyl or nitro) at the

C(3) position; (ii) cyclizations of [3 + 2] products from 1-lithiomethoxyallene and *c*-hexyl isothiocyanate or methyl isothiocyanate, these gave 2-ethylthio-3-methoxy-*N*-cyclohexylpyrrole or 2-methylthio-3-methoxy-*N*-methylpyrrole in 11% or 54% yield, respectively.^{15a,b}

Following our use of benzotriazole-stabilized carbanions for the preparation of pyrroles¹⁶ and furans,¹⁷ we now report the synthesis of 3-functionalized-2-aminothiophenes and 1,3-disubstituted-2-methylthiopyrroles via [3 + 2] component cyclizations.

Results and Discussion

1. Synthesis of 3-Substituted-2-aminothiophenes.

1-Allylbenzotriazole (**1**) (Scheme 1) was functionalized by the sequential addition of a solution of *n*-BuLi and quenching the resulting anion with various electrophiles¹⁸ which gave 1-(1-alkylprop-2-enyl)benzotriazoles **2a–f** (Scheme 1) in excellent yields. The use of *n*-BuLi at a low-temperature prevents the isomerization of the compound **1**.¹⁸

Intermediate **2g** (Scheme 2) was obtained by one-step condensation of acrolein diethyl acetal with benzotriazole in refluxing hexanes for 18 h,¹⁹ followed by purification of the crude product by flash column chromatography which allowed for the separation of the Bt¹ and Bt² isomers (for the structures of Bt¹ and Bt², see Scheme 1).

Treatment of intermediates **2a–e,g** with *n*-BuLi and subsequent condensation reactions with various isothiocyanates **3u–x** (see Table 1) followed by the addition of saturated aqueous ammonium chloride at –78 °C gave the expected thioamides **4** (accompanied by the regioisomers **5**, Scheme 1). Isolation of derivative **4au** (Table

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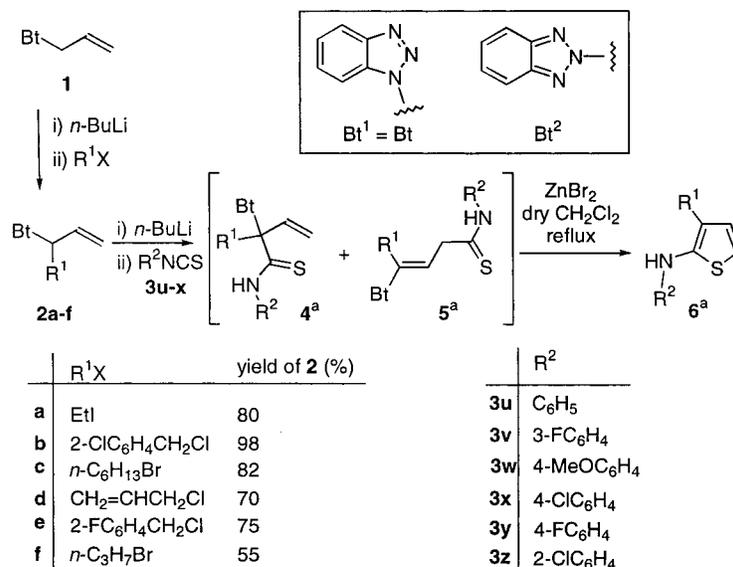
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Scheme 1



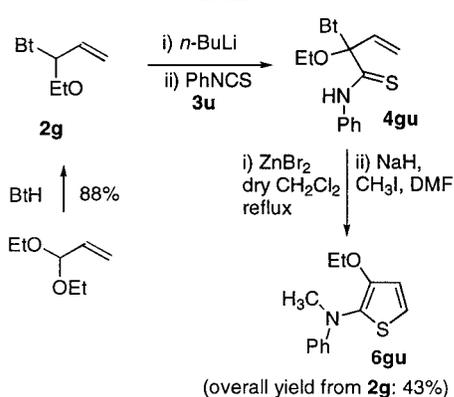
^a For the significance of 4, 5, and 6, see Table 1.

Table 1. Preparation of 3-Substituted-2-aminothiophenes 6

entry ^a	R ¹	R ²	crude 4 + 5		isolated 6 yield (%) ^b	starting materials
			yield (%)	ratio 4:5		
au	Et	C ₆ H ₅	106	1.6:1	50	2a, 3u
bu	2-ClC ₆ H ₄ CH ₂	C ₆ H ₅	112	6:1	80	2b, 3u
bv	2-ClC ₆ H ₄ CH ₂	3-FC ₆ H ₄	102	5.8:1	69	2b, 3v
cu	<i>n</i> -C ₆ H ₁₃	C ₆ H ₅	111	1.7:1	41	2c, 3u
dx	CH ₂ =CHCH ₂	4-ClC ₆ H ₄	102	1.3:1	25	2d, 3x
ew	2-FC ₆ H ₄ CH ₂	4-MeOC ₆ H ₄	99	4:1	54	2e, 3w

^a The lettering system for 4, 5, and 6 follows that the first letter is the same as in the starting material 2, the second letter is the same as in the starting material 3, eg, 2a + 3u → [4au + 5au] → 6au. ^b Isolated yields of compounds 6 based on starting materials 2.

Scheme 2



1) by recrystallization from Et₂O and identification of two ethylenic hydrogens [4.61 ppm (d, 1H) and 5.29 ppm (d, 1H)] and an acidic proton (9.8–10.1 ppm, 1H) by ¹H NMR demonstrated the occurrence of an α -substitution reaction at 1-(1-ethylprop-2-enyl)benzotriazole 2a. In addition to the characteristic peaks for 4au from crude ¹H NMR, the observation of a doublet (3.9 ppm, 2H), a triplet (6.3 ppm, 1H), and another broad singlet (10.1–10.2 ppm, 1H), demonstrated the presence of the corresponding γ -regioisomer 5au (Scheme 1). Similarly, intermediates 5bu, bv, cu, dx, ew were also observed in the crude ¹H NMR spectra. The ratios of 4 vs 5 deduced from the crude ¹H NMR spectra are reported in Table 1. For those with simple R¹ substituents such as alkyl groups (4au, cu) or allyl group (4dx), the regioselectivities were relatively

low. However, with benzyl groups as the substituents R¹ (4bu, bv, ew), the regioselectivities were higher. Particularly, with ethoxy as R¹ group, only α -isomer 4gu (Scheme 2) was observed from crude ¹H and ¹³C NMR spectra. This is presumably due to the electron-withdrawing ability of the oxygen atom upon the stabilization of α -carbanion generated. Intermediates 5 (Scheme 1) were not isolated due to their instability on silica gel during column chromatography purification.

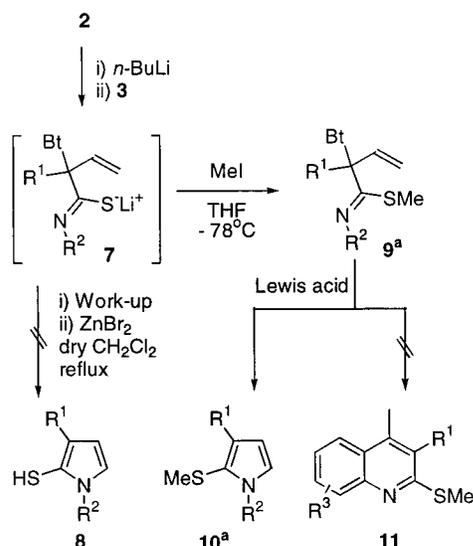
Although compounds 4 can be isolated as described above, thioamides 4 undergo partial decomposition (similar to 5) upon flash column chromatography on silica gel and therefore were conveniently directly converted without purification into the desired 3-substituted-2-aminothiophenes 6 by anhydrous ZnBr₂-promoted cyclization. It is noteworthy that only the α isomers 4 were cyclized, while the γ isomers 5 were unchanged. This simplified significantly the purification procedure for the final products, since 5 (ca *R_f*: 0.01 with ethyl ether: pentane = 1:10) are far more polar than 6 (ca *R_f*: 0.5 with ethyl ether: pentane = 1:10). After removal of the benzotriazole generated in situ with sodium hydroxide solution, the expected products 6 (Table 1) were obtained as oils in 25–80% overall yields after quick flash column chromatography. Due to the relative instability of thienylamines,¹⁴ we encountered problems for elemental CHN analyses for the compounds 6dx, ew.

A variety of substituents was investigated for 6. Simple alkyl (6au, cu), benzyl (6bu, bv, ew), allyl (6dx), and ethoxy (6gu) groups were successfully utilized as sub-

Table 2. Synthesis of Intermediates **9** and Products **10**

entry ^a	R ¹	R ²	9			10	
			yield (%) ^b	mp (°C)	method ^c	yield (%) ^d	yield (%) ^e
gu	EtO	Ph	71	112.5–112.8	A	65	85
gv	EtO	3-FC ₆ H ₄	60	113–115	A	59	79
gw	EtO	4-MeOC ₆ H ₄	80	104–106	A	<i>f</i>	<i>f</i>
gx	EtO	4-ClC ₆ H ₄	63	78–79	A	33	76
gy	EtO	4-FC ₆ H ₄	59	78–81	A	38	94
gz	EtO	2-ClC ₆ H ₄	75	93–94	A	21	75
du	CH ₂ =CHCH ₂	Ph	63	oil	B	33	79
fu	<i>n</i> -C ₃ H ₇	Ph	65	oil	C	39	78

^a The lettering system of **9** and **10** follows the pattern: **2g** + **3u** → **9gu** → **10gu**. ^b Isolated yield based on **2**. ^c Reaction conditions for converting intermediates **9** into products **10**: A: ZnBr₂, dry CH₂Cl₂, reflux; B: ZnBr₂, dry toluene, reflux; C: AlCl₃, 1,2-dichloroethane, reflux. ^d Isolated yield based on **9**. ^e GC yield. ^f Not obtained.

Scheme 3

^a For the significance of **9** and **10**, see Table 2.

stituents in the 3-position. Electron-withdrawing (**3v,x**) and electron-donating (**3w**) groups in the aromatic ring of aryl isothiocyanates were also scanned during the preparation of products **6bv,dx,ew** (Scheme 1). The reactions were not greatly affected by the nature of a substituent from the point of view of the total yields. The low regioselectivities in the case of **6au,cu,dx** are believed to be caused by the substituent R¹ group. As expected, the final product **6ew** is less stable than **6bv** and **6dx** due to the presence of the more electron-rich methoxy group. Since 3-alkoxythiophenes with primary or secondary amino groups at the 2-position generally show low stability,² the aminothiophene obtained from 1-(2-ethoxyprop-2-enyl)benzotriazole (Scheme 2) was immediately converted to the methylated analogue **6gu** by quantitative *N*-methylation with methyl iodide; the product **6gu** was isolated in 43% yield.

2. Synthesis of 1,3-Disubstituted-2-methylthiopyrroles. During the cyclizations discussed above, the corresponding pyrrole analogues, such as **8** (Scheme 3), were not detected. However, 3-substituted-2-(methylthio)-1-phenyl-1*H*-pyrroles **10** were obtained when anions **7** were *S*-methylated in situ, and the intermediate 2-substituted-3-butenimidothioates **9** were cyclized with Lewis acids. During these cyclizations, no formation of quinolines **11** was observed.

Intermediates **9** were obtained in good yields and purified (Table 2). The condensations between **2g** and **3u–z** gave **9gu–gz** with very high regioselectivities. The

crude NMR spectra disclosed only single regioisomers **9gu–gz**. Compounds **2d,f** where R¹ is an alkyl group also gave **9du,fu** in reasonable yields. Though regioisomers of **9du,fu** were observed, they were easily separated from **9du,fu** by column chromatography. The reaction of benzoyl chloride and allyl chloride with the thiolate **7** was not successful.

Cyclizations readily occurred for **9gu,gv,gx–gz** with ZnBr₂ in dry methylene chloride under reflux for 1 h to provide **10gu,gv,gx–gz** (Table 2). The GC yields of the crude products are high. Isolated yields after column chromatography are moderate because of the instability of the electron-rich pyrroles. For **9gw**, which has a 4-methoxyphenyl group as R², no desired product was obtained, presumably because **10gw**, if generated, decomposes due to the low stability. The attempted cyclization of compound **9du** using anhydrous ZnBr₂ in dry methylene chloride or in 1,2-dichloroethane failed, probably because the allyl group is much less electron-donating than the methoxy group. Nevertheless, **9du** was successfully cyclized with anhydrous ZnBr₂ in refluxing dry toluene to give **10du** in good GC yield (79%). Product **10fu** decomposed in refluxing toluene, but, AlCl₃ in refluxing 1,2-dichloroethane successfully cyclized **9fu** into the pyrrole **10fu**.

In summary, the present work provides facile syntheses of relatively unstable novel 2-aminothiophenes **6** without needing purification of the intermediates and of 2-methylthiopyrroles **10** both starting from easily accessible 1-allylbenzotriazole (**1**), which complement known literature methods. Although the proposed procedure is sensitive to the substitution in the *N*-allylbenzotriazole intermediates, the expected products are typically obtained in about 50% overall yields under mild reaction conditions.

Experimental Section

General Procedure for the Preparation of 1-(1-Alkylprop-2-enyl)-1*H*-benzotriazoles **2a–f.** A solution of *n*-BuLi (1.47 M, 6.8 mL, 10.2 mmol) was added at –78 °C under argon atmosphere to a prechilled solution of allylbenzotriazole (**1**) (1.59 g, 10 mmol) in dry THF (50 mL). After 20 min, the electrophile of choice (10.2 mmol) was added dropwise, and the resulting mixture was allowed to react until complete conversion of the starting material was achieved (TLC control). Saturated solution of NH₄Cl (40 mL) was added, and the reaction was allowed to reach rt. The aqueous layer was extracted by Et₂O (3 × 30 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude reaction mixture was then subjected to purification on flash column chromatography on silica gel (pentane/Et₂O:2/1) to give the desired **2** as pure product.

1-(1-Ethylprop-2-enyl)-1*H*-1,2,3-benzotriazole (2a): Colorless oil; $^1\text{H NMR}$ δ 0.88 (t, $J = 7.4$ Hz, 3H), 2.16–2.39 (m, 2H), 5.17–5.28 (m, 3H), 6.12–6.23 (m, 1H), 7.34 (t, $J = 7.1$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.55 (d, $J = 8.3$ Hz, 1H), 8.07 (d, $J = 8.3$ Hz, 1H); $^{13}\text{C NMR}$ δ 10.4, 26.7, 63.8, 109.9, 117.6, 119.8, 123.5, 126.7, 132.3, 135.5, 146.0. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.33; H, 7.26; N, 22.89.

1-(1-Hexylprop-2-enyl)-1*H*-1,2,3-benzotriazole (2c): Colorless oil; $^1\text{H NMR}$ δ 0.82 (t, $J = 6.9$ Hz, 3H), 1.11–1.30 (m, 8H), 2.12–2.21 (m, 1H), 2.28–2.37 (m, 1H), 5.18 (d, $J = 17.1$ Hz, 1H), 5.29 (d, $J = 16.9$ Hz, 1H), 5.34–5.39 (m, 1H), 6.12–6.23 (m, 1H), 7.34 (t, $J = 7.1$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 8.3$ Hz, 1H); $^{13}\text{C NMR}$ δ 13.7, 22.2, 25.7, 28.4, 31.2, 33.3, 62.2, 109.9, 117.4, 119.7, 123.5, 126.7, 132.2, 135.7, 146.0. Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3$: H, 8.70; N, 17.27. Found: H, 8.90; N, 16.98.

General Procedure for the Preparation of Thioamides 4 (Scheme 1) and Butenimidothioates 9 (Scheme 3). 1-(1-Alkylprop-2-enyl)-1*H*-benzotriazoles **2a–g** (4 mmol) were dissolved in dry THF (30 mL) under argon atmosphere. The resulting solutions were cooled to -78 °C before the addition of a solution of *n*-BuLi in hexane (1.52 M, 2.6 mL, 4 mmol). After 10 min, the isothiocyanate of choice (4.1 mmol) was introduced. Then the mixtures were allowed to react for 30 min for compounds **4** before treatment with saturated aqueous NH_4Cl (30 mL). In the case of **9**, after 30 min, methyl iodide (3 equiv) was added, and the mixture was allowed to warm to room temperature overnight before treatment with saturated aqueous NH_4Cl (30 mL). Once separated from the organic layers, the aqueous layers were extracted with Et_2O (3×20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Compounds **4** admixed with isomers **5** were used in the next step without purification. Compounds **9** were purified by pentane/ Et_2O (3/1) on silica gel.

Methyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-2-ethoxy-*N*-phenyl-3-butenimidothioate (9gu): White microcrystals, mp 112.5–112.8 °C; $^1\text{H NMR}$ δ 1.04 (t, $J = 6.6$ Hz, 3H), 2.15 (br s, 3H), 2.50–2.80 (m, 1H), 3.56–3.61 (m, 1H), 5.75 (d, $J = 10.7$ Hz, 1H), 5.90 (d, $J = 17.5$ Hz, 1H), 6.00–6.20 (m, 2H), 6.80–7.00 (m, 3H), 7.14 (dd, $J = 11.0$, 17.6 Hz, 1H), 7.38 (dd, $J = 7.4$, 7.4 Hz, 1H), 7.53 (dd, $J = 7.9$, 7.9 Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 8.01 (d, $J = 8.3$ Hz, 1H); $^{13}\text{C NMR}$ δ 14.6, 14.7, 59.3, 94.2, 111.8, 117.6, 119.6, 119.8, 123.0, 124.2, 127.6, 128.1, 132.0, 132.3, 146.2, 147.9, 163.1. Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{OS}$: C, 64.75; H, 5.72; N, 15.90. Found: C, 64.42; H, 5.80; N, 15.87.

Methyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-*N*-(4-chlorophenyl)-2-ethoxy-3-butenimidothioate (9gx): White microcrystals, mp 78.0–79.0 °C; $^1\text{H NMR}$ δ 1.04 (t, $J = 6.8$ Hz, 3H), 2.17 (s, 3H), 2.69 (br s, 1H), 3.51–3.65 (m, 1H), 5.76 (d, $J = 11.7$ Hz, 1H), 5.90 (d, $J = 17.4$ Hz, 1H), 6.10 (br s, 2H), 6.94 (br s, 2H), 7.12 (dd, $J = 11.1$, 17.4 Hz, 1H), 7.39 (t, $J = 8.1$ Hz, 1H), 7.53 (t, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H); $^{13}\text{C NMR}$ δ 14.5, 14.9, 59.3, 94.1, 111.6, 118.9, 119.9, 120.0, 124.2, 124.3, 127.7, 128.0, 131.9, 132.0, 146.2, 146.5, 165.4. Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{ClN}_4\text{OS}$: C, 58.98; H, 4.95; N, 14.48. Found: C, 59.16; H, 5.09; N, 14.48.

General Procedure for the Preparation of Thiophenes 6 (Scheme 1) and Pyrroles 10 (Scheme 3). The crude reaction mixtures **4au, bu, bv, cu, dx, ew** (2 mmol) or pure compounds **9gu, gv, gx, gy, gz** (2 mmol) were dissolved in dry CH_2Cl_2 (30 mL) under argon atmosphere, and anhydrous ZnBr_2 (1.2 g, 5 mmol) was added. Similarly, **9du** (2 mmol) or **9fu** (2 mmol) was dissolved in dry toluene (30 mL) or 1,2-dichloroethane (30 mL) with ZnBr_2 or AlCl_3 , respectively, under reflux. The resulting solutions were allowed to react under reflux for 24 h (for **4au, bu, bv, cu, dx, ew, 9du, fu**) or 1 h (for **9gu, gv, gx–gz**) until the complete conversion of the starting material was observed (TLC control). After addition of aqueous NaOH solution (2 M, 30 mL), the aqueous layers were separated from the organic layers and extracted with Et_2O (2×20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude mixtures were purified by flash column chroma-

tography on silica gel (pentane/ Et_2O :10/1) to afford compounds **6** and **10** as pure products.

3-Ethyl-2-phenylaminothiophene (6au): Yellow oil; $^1\text{H NMR}$ δ 1.13 (t, $J = 7.4$ Hz, 3H), 2.46 (q, $J = 7.4$ Hz, 2H), 5.10 (br s, 1H), 6.64 (d, $J = 8.2$ Hz, 2H), 6.77 (t, $J = 7.4$ Hz, 1H), 6.85 (d, $J = 5.5$ Hz, 1H), 6.99 (d, $J = 5.8$ Hz, 1H), 7.16 (t, $J = 7.5$ Hz, 2H); $^{13}\text{C NMR}$ δ 14.5, 20.6, 113.6, 118.9, 120.8, 127.0, 129.1, 137.6, 139.0, 147.1. Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NS}$: C, 70.89; H, 6.44; N, 6.89. Found: C, 70.51; H, 6.58; N, 7.25.

3-[(2-Chlorophenyl)methyl]-2-phenylaminothiophene (6bu): Colorless oil; $^1\text{H NMR}$ δ 3.91 (s, 2H), 5.20 (s, 1H), 6.69–6.74 (m, 3H), 6.80 (t, $J = 7.1$ Hz, 1H), 6.96 (d, $J = 5.8$ Hz, 1H), 7.10–7.20 (m, 5H), 7.30–7.32 (m, 1H); $^{13}\text{C NMR}$ δ 31.2, 114.0, 119.3, 120.7, 126.8, 127.6, 127.7, 129.2, 129.4, 130.5, 133.6, 133.9, 137.9, 139.5, 146.6. Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{ClNS}$: C, 68.10; H, 4.71; N, 4.67. Found: C, 67.71; H, 4.64; N, 5.04.

3-Ethoxy-2-(methylthio)-1-phenyl-1*H*-pyrrole (10gu): Colorless oil; $^1\text{H NMR}$ δ 1.42 (t, $J = 6.9$ Hz, 3H), 2.02 (s, 3H), 4.10 (q, $J = 7.1$ Hz, 2H), 6.03 (d, $J = 3.3$ Hz, 1H), 6.77 (d, $J = 3.2$ Hz, 1H), 7.31–7.45 (m, 5H); $^{13}\text{C NMR}$ δ 15.1, 20.1, 66.6, 97.3, 107.6, 121.6, 126.0, 126.9, 128.6, 139.7, 151.3. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NOS}$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.73; H, 6.69; N, 6.35.

1-(4-Chlorophenyl)-3-ethoxy-2-(methylthio)-1*H*-pyrrole (10gx): White microcrystals, mp 40.0–42.0 °C; $^1\text{H NMR}$ δ 1.42 (t, $J = 6.8$ Hz, 3H), 2.02 (s, 3H), 4.10 (q, $J = 6.81$ Hz, 2H), 6.04 (d, $J = 3.0$ Hz, 1H), 6.75 (d, $J = 3.3$ Hz, 1H), 7.31 (d, $J = 8.7$ Hz, 2H), 7.39 (d, $J = 8.7$ Hz, 2H); $^{13}\text{C NMR}$ δ 15.1, 20.2, 66.6, 97.8, 107.6, 121.6, 127.2, 128.8, 132.7, 138.2, 151.6. Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{ClNOS}$: C, 58.31; H, 5.27; N, 5.23. Found: C, 58.15; H, 5.35; N, 5.15.

3-Allyl-2-methylthio-1-phenyl-1*H*-pyrrole (10du): Colorless oil; $^1\text{H NMR}$ δ 1.95 (s, 3H), 3.43 (d, $J = 6.6$ Hz, 2H), 5.01–5.02 (m, 1H), 5.09–5.16 (m, 1H), 5.95–6.09 (m, 1H), 6.19 (d, $J = 3.0$ Hz, 1H), 6.92 (d, $J = 2.7$ Hz, 1H), 7.34–7.47 (m, 5H); $^{13}\text{C NMR}$ δ 20.6, 31.8, 109.4, 114.7, 120.8, 124.5, 126.4, 127.1, 128.6, 129.6, 138.1, 140.0. Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NS}$: C, 73.32; H, 6.59; N, 6.11. Found: C, 72.99; H, 6.68; N, 6.38.

Procedure for the Preparation of *N*-(3-Ethoxythiophen-2-yl)-*N*-substituted Amines (6gu, Scheme 2). Compound **6gu** was first prepared similarly to the other derivatives **6** and further methylated before purification as follows. The crude product was dissolved in dry DMF (30 mL) under argon atmosphere before the introduction of sodium hydride (60% in mineral oil, 0.8 g, 20 mmol). The resulting solution was allowed to react for 10 min, methyl iodide (1.25 mL, 20 mmol) was added, and the mixture was stirred for 5 h at room temperature. After addition of water (10 mL), the reaction was extracted with Et_2O (3×30 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (pentane/ Et_2O :20/1) to afford compound **6gu** as a pure product.

3-Ethoxy-2-phenyl(methyl)aminothiophene (6gu): Colorless oil; $^1\text{H NMR}$ δ 1.25 (t, $J = 7.1$ Hz, 3H), 3.25 (s, 3H), 4.03 (q, $J = 7.1$ Hz, 2H), 6.76–6.80 (m, 4H), 6.97 (d, $J = 6.0$ Hz, 1H), 7.18–7.25 (m, 2H); $^{13}\text{C NMR}$ δ 15.3, 40.4, 66.8, 113.6, 118.1, 118.3, 119.7, 128.8, 129.9, 149.1, 150.2. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NOS}$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.97; H, 6.65; N, 6.30.

Acknowledgment. We thank Dr. Christophe Chassaing and Dr. Sergey Denisenko for their help with this work.

Supporting Information Available: ^1H , ^{13}C NMR spectra, and elemental analyses or HRMS for compounds **2b, d–f, 4au, 9gv, gw, gy, gz, du, fu, 6bv, cu, dx, ew, and 10gv, gy, gz, fu**. This material is available free of charge via the Internet at <http://pubs.acs.org>.