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New Approach to 3-Aminothiophene-2-carboxylic Acid Derivatives: Access to 5-Aryl-4-(ethylsulfanyl) Compounds

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New Approach to 3-Aminothiophene-2-carboxylic Acid Derivatives: Access to 5-Aryl-4-(ethylsulfanyl) Compounds

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Abstract: Treatment of DMSO/water solutions of β-bromo-α-(ethylsulfanyl)cinnamonitriles with sodium sulphide and α-halo acetic acids derivatives followed by cyclization in a potassium carbonate/acetone/DMSO mixture gave the expected 3-amino-5-aryl-4-(ethylsulfanyl)thiophene-2-carboxylic acids derivatives in fair yields.

Keywords: 3-amino-5-aryl-4-(ethylsulfanyl)thiophene-2-carboxylic acids derivatives, β-bromo-α-(ethylsulfanyl)cinnamonitriles, (ethylsulfanyl)acetonitrile, methyl 3-amino-5-aryl-4-bromothiophene-2-carboxylate, sodium sulphide

INTRODUCTION

Several examples described syntheses of fused heterocycles using alkyl 3-aminothiophene-2-carboxylate[1] or carboxamide as starting materials. These synthons react easily to give structural analogues of pharmacophores.[2]

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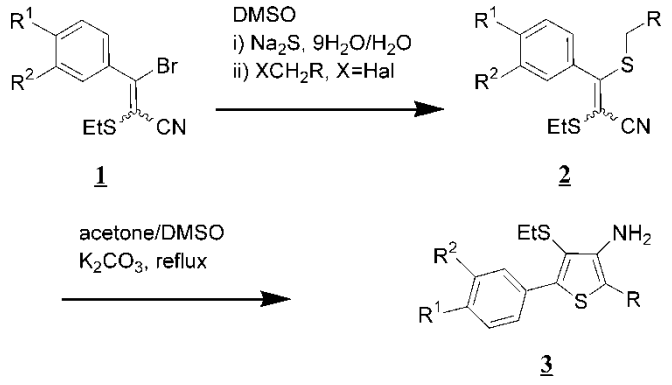


Scheme 1. R=CN: R^1=R^2=H;R^1=OMe, R^2=H. R=CO_2Me: R^1=Cl, R^2=H; R^1=OMe, R^2=H; R^1, R^2=OCH_2O. R=$CONH_2$: R^1=R^2=H; R^1=Cl, R^2=H; R^1, R^2=OCH_2O.

Following our ongoing interest in new biologically active molecules, we propose here an easy access to a new series of thiophenes **3** starting from β-bromo-α-(ethylsulfanyl)cinnamonitriles β-substituted by an aryl group **2** as depicted in Scheme 1.

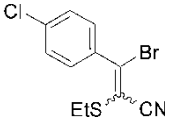
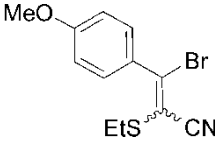
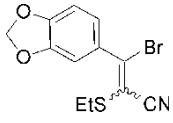
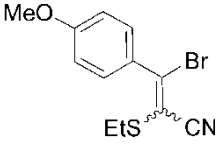
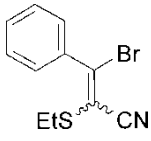
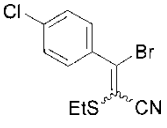
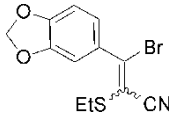
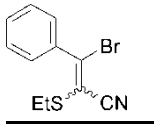
In our investigation, the 3-amino-5-aryl-4-(ethylsulfanyl)thiophene-2-carboxylic acids derivatives **3** were obtained in a four-step procedure starting from (ethylsulfanyl)acetonitrile.[3] Condensation with benzaldehydes followed by bromination afforded the β-bromo-α-(ethylsulfanyl)cinnamonitriles **1**, which were isolated as Z/E mixtures in good yields ranging from 70 to 80%.[4]

When treated with a slight excess of sodium sulphide in a DMSO/water mixture at room temperature, the compounds **1** were converted to the corresponding sodium thienolate, which was immediately trapped with various α-haloacetic acids derivatives (chloroacetonitrile, methyl bromoacetate, chloroacetamide). The resulting condensation products **2** were obtained in good yields (Table 1) and could be further used as such (the analysis of the ^{1}H NMR spectra showed that the crude products contained less than 5% of the starting compounds **1**).

The final cyclization using a K_2CO_3/acetone/DMSO mixture furnished the new family of 3-amino-5-aryl-4-(ethylsulfanyl)thiophene-2-carboxylic acids derivatives **3a** to **3c** in fair yields varying between 56 and 73%.

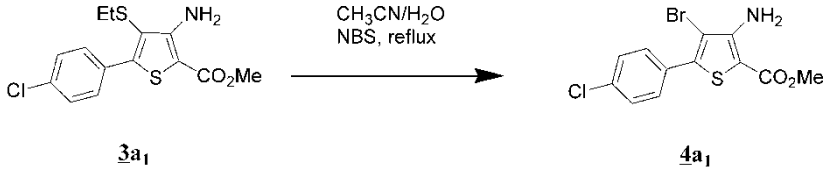
Furthermore, in the case of methyl 3-amino-5-aryl-4-(ethylsulfanyl)thiophene-2-carboxylate **3a**, we have observed that the ethylsulfanyl group could be replaced by a halogen,[5] bromine, using N-bromosuccinimide as reagent. Indeed, methyl 3-amino-5-aryl-4-bromothiophene-2-carboxylates, $\mathbf{4a_1}$ could be obtained from the corresponding thiophenes $\mathbf{3a_1}$, using N-Bromosuccinimide (NBS) excess in refluxing acetonitrile/water, as exemplified in Scheme 2.

Table 1. Synthesis of compounds **2** from β-bromo-α-(ethylsulfanyl)cinnamonitriles **1** and α-haloacetic acids derivatives

Substrate **1** (Z/E mixture)	α-Haloacetic acids derivatives	Products **2** (Z/E mixture)	Yield (%)
	$BrCH_2CO_2Me$	$\mathbf{a_1}$[a]	98
	$BrCH_2CO_2Me$	$\mathbf{a_2}$[a]	94
	$BrCH_2CO_2Me$	$\mathbf{a_3}$[a]	98
	$ClCH_2CN$	$\mathbf{b_1}$[a]	97
	$ClCH_2CN$	$\mathbf{b_2}$[a]	96
	$ClCH_2CONH_2$	$\mathbf{c_1}$[a]	96
	$ClCH_2CONH_2$	$\mathbf{c_2}$[b]	94
	$ClCH_2CONH_2$	$\mathbf{c_3}$[b]	93

[a]Products **2** were yellow to red colored oils.

[b]Compounds **2** were crystalline products: mp ($\mathbf{2c_2}$) 118–122°C, mp ($\mathbf{2c_3}$) 112–116°C.



3a$_1$ **4a$_1$**

Scheme 2.

CONCLUSION

This article described a simple and efficient method for preparation of a new thiophene family, involving the use of a single starting material in a four-step procedure. The versatility of these synthons could be of interest for preparing novel heterocyclic systems and consequently access to new compounds potentially endowed with biological properties.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 500-MHz spectrometer using chloroform-d as solvent, and chemical shifts refer to TMS on a δ scale. Melting points were determined on a Kofler apparatus and are uncorrected. Mass spectra were recorded in the electron impact (EI) mode on a Varian Mat 311. Elemental analyses were performed on a Carlo Erba Instrument EA-1112. Acetone and dimethyl sulphoxide were stored over a type 4Å molecular sieve. (Ethylsulfanyl)acetonitrile, and β-bromo-α-(ethylsulfanyl)-cinnamonitriles **1** were prepared according to described procedures.[3,4] Sodium sulphide nonahydrate, anhydrous potassium carbonate, chloroacetonitrile, methyl bromoacetate, and α-chloroacetamide were purchased from Aldrich. Analytical thin-layer chromatography (TLC) was performed on Merck silica-gel-coated plates ($60F_{254}$).

General Procedure for the Conversion of β-Bromo-α-(ethylsulfanyl)cinnamonitriles 1 into Compounds 2

To a stirred solution of starting compounds **1** (4.83 mmol) in DMSO (8 mL) cooled to 16°C, a solution of $Na_2S \cdot 9H_2O$, (5.82 mmol, 1.40 g) in 1.5 mL of H_2O was rapidly added. After 25 min, a solution of the appropriate α-haloacetic acid derivative (8.21 mmol) in DMSO (2 mL) was added in one drop to the resulting red mixture and stirred for a 1 h. The reaction was quenched with water (50 mL) and extracted with diethyl ether (compounds **2a$_1$**, **2a$_2$**, **2a$_3$**, **2b$_1$**, **2b$_2$**) or dichloromethane (compounds **2c$_1$**, **2c$_2$**, **2c$_3$**). The organic layer was washed twice with water and brine and dried with

Na_2SO_4. The solvents and the excess of liquid α-haloacetic acid derivative were removed under reduced pressure, yielding the sufficiently pure precursors **2** as Z/E mixture (Table 1).

General Procedure for the Preparation of 3-Amino-5-aryl-4-(ethylsulfanyl)thiophene-2-carboxylic Acids Derivatives (3)

A mixture of precursors **2** (3.05 mmol), anhydrous potassium carbonate (3.05 mmol), acetone (8 mL), and DMSO (2 mL) was vigorously stirred and refluxed under nitrogen. The reaction was monitored by TLC using CH_2Cl_2 as eluent. When the reaction was finished (reaction time 1 to 4 h), the cooled mixture was filtered over celite and concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (25 mL) and washed with 1 N aqueous HCl solution to give the crude product. The pure 3-amino-5-aryl-4-(ethylsulfanyl)thiophene-2-carboxylic acids derivative **3** was isolated after recrystallization (the solvent is given in the product description).

Methyl 3-Amino-5-(4-chlorophenyl)-4-(ethylsulfanyl)thiophene-2-carboxylate ($3a_1$)

Reaction time 1 h; this compound was obtained in 73% yield as pale yellows crystals, mp 122–124°C (CH_3CN/H_2O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.00$ (3H, t, CH_3, J 7.3 Hz), 2.52 (2H, q, CH_2, J 7.3 Hz), 3.85 (3H, s, CO_2CH_3), 5.97 (2H, br s, NH_2), 7.38 (2H, d, H3′ − 5′, J 8.5 Hz), 7.64 (2H, d, H2′ − 6′, J 8.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.77$ (CH_3), 29.35 (CH_2), 51.44 (OCH_3), 98.47 (C-2), 117.37 (C-4), 128.72 (C-3′ − 5′), 130.49 (C-2′ − 6′), 131.88 (C-1′), 135.13 (C-4′), 150.97 (C-5), 155.08 (C-3), 164.61 (C═O). Anal. calcd. for $C_{14}H_{14}ClNO_2S_2$: C, 51.29; H, 4.30; N, 4.27; S, 19.56. Found: C, 51.44; H, 4.26; N, 4.64; S, 19.74. EIMS: m/z calcd. for $C_{14}H_{14}ClNO_2S_2$: 327.01545. Found 327.0144 (M^+).

Methyl 3-Amino-4-(ethylsulfanyl)-5-(-4′-methoxyphenyl)thiophene-2-carboxylate ($3a_2$)

Reaction time 4 h; this compound was obtained in 63% yield as orange needles, mp 80–82°C (CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.01$ (3H, t, CH_3, J 7.4 Hz), 2.51 (2H, q, CH_2 J 7.4 Hz), 3.83 (3H, s, OCH_3), 3.84 (3H, s, CO_2CH_3) 5.98 (2H, br s, NH_2), 6.93 (2H, d, H3′ − 5′, J 8.8 Hz), 7.66 (2H, d, H2′ − 6′, J 8.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.72$ (CH3), 29.23 (CH2), 51.28 (CO2CH3), 55.29 (OCH3), 97.50 (C-2), 113.84 (C-3′ − 5′), 116.13 (C-4), 125.84 (C-1′), 130.47 (C-2′ − 6′),

152.53 (C-5), 155.26 (C-3), 160.26 (C-4′), 164.67 (C═O). Anal. calcd. for $C_{15}H_{17}NO_3S_2$: C, 55.70; H, 5.30; N, 4.33; S, 19.83. Found: C, 51.59; H, 5.26; N, 4.40; S, 19.98. EIMS: m/z calcd. for $C_{15}H_{17}NO_3S_2$: 323.06499. Found 323.06420 (M^+).

Methyl 3-Amino-5-(1,3-benzodioxol-5-yl)-4-(ethylsulfanyl)-thiophene-2-carboxylate ($3a_3$)

Reaction time 2 h; this compound was obtained in 67% yield as red needles, mp 106–108°C (CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.04$ (3H, t, CH_3, J 7.4 Hz), 2.53 (2H, q, CH_2, J 7.4 Hz), 3.84 (3H, s, CO_2CH_3), 5.97 (2H, br s, NH_2), 6.02 (2H, s, OCH_2O), 6.85 (1H, d, H-5′, J 8.1 Hz), 7.18 (1H, dd, H-6′, J 8.1, 1.7 Hz), 7.25 (1H, d, H-2′, J 1.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.75$ (CH_3), 29.25 (CH_2), 51.32 (OCH_3), 97.60 (C-2), 101.45 (OCH_2O), 108.31 (C-5′), 109.55 (C-2′), 116.44 (C-4), 123.32 (C-6′), 127.17 (C-1′), 147.61 (C-3′), 148.36 (C-4′), 152.24 (C-5), 155.15 (C-3), 164.64 (C═O). Anal. calcd. for $C_{15}H_{15}NO_4S_2$: C, 53.39; H, 4.48; N, 4.15; S, 19.01. Found: C, 51.44; H, 4.37; N, 4.43; S, 19.15.

3-Amino-4-(ethylsulfanyl)-5-(-4-methoxyphenyl)thiophene-2-carbonitriles ($3b_1$)

Reaction time 1.5 h; this compound was obtained in 56% yield as yellow needles, mp 130°C (CH_3CN). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.03$ (3H, t, CH_3, J 7.4 Hz), 2.51 (2H, q, CH_2, J 7.4 Hz), 3.85 (3H, s, OCH_3), 5.06 (2H, br s, NH_2), 6.95 (2H, d, H-3′ − 5′, J 8.8 Hz), 7.62 (2H, d, H-2′ − 6′, J 8.8 Hz). ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 14.69$ (CH_3), 29.37 (CH_2), 55.36 (OCH_3), 77.25 (C-2), 114.02 (C-2′ − 6′), 115.27 (CN), 116.01 (C-4), 124.90 (C-1′), 130.40 (C-3′ − 5′), 152.93 (C-3), 156.75 (C-5), 160.54 (C-4′). Anal. calcd. for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.65; S, 22.08. Found: C, 57.81.; H, 4.75; N, 9.71; S, 22.23.

3-Amino-4-(ethylsulfanyl)-5-phenylthiophene-2-carbonitriles ($3b_2$)

Reaction time 1 h; this compound was obtained in 59% yield as pale yellow needles, mp 124°C (CH_3CH_2OH). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.01$ (3H, t, CH_3, J 7.4 Hz), 2.51 (2H, q, CH_2, J 7.4 Hz), 5.10 (2H, br s, NH_2), 7.42–7.43 (3H, m, H-3′ − 4′ − 5′), 7.64–7.65 (2H, m, H-2′ − 6′). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.67$ (CH_3), 29.42 (CH_2), 78.05 (C-2), 115.11 (CN), 116.95 (C-4), 128.59 (C-3′ − 5′), 129.11 (C-2′ − 6′), 129.47 (C-4′), 132.47 (C-1′), 152.89 (C-5), 156.69 (C-3). Anal. calcd. for $C_{13}H_{12}N_2S_2$: C,

59.97; H, 4.65; N, 10.76; S, 24.63. Found: C, 59.98.; H, 4.62; N, 10.75; S, 24.75. EIMS: m/z calcd. for $C_{13}H_{12}N_2S_2$: 260.04419. Found 260.0447 (M^+).

3-Amino-5-(4-chlorophenyl)-4-(ethylsulfanyl)thiophene-2-carboxamide $3c_1$

Reaction time 1.5 h; this compound was obtained in 62% yield as yellow crystals, mp 156–158°C (CCl_4). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.01$ (3H, t, CH_3, J 7.4 Hz), 2.53 (2H, q, CH_2, J 7.4 Hz), 5.72 (2H, br s, $CONH_2$), 6.18 (2H, br s, NH_2), 7.39 (2H, d, H-3′ − 5′, J 8.4 Hz), 7.63 (2H, d, H-2′ − 6′, J 8.4 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.75$ (CH_3), 29.26 (CH_2), 99.52 (C-2), 118.62 (C-4), 128.69 (C-3′ − 5′), 130.51 (C-2′ − 6′), 131.64 (C-1′), 135.04 (C-4′), 145.36 (C-5), 154.45 (C-3), 166.55 (C = O). Anal. calcd. for $C_{13}H_{13}ClN_2OS_2$: C, 49.91; H, 4.19; N, 8.95; S, 20.50. Found: C, 49.88; H, 4.11; N, 8.83; S, 20.61.

3-Amino-5-(1,3-benzodioxol-5-yl)-4-(ethylsulfanyl)thiophene-2-carboxamide $3c_2$

Reaction time 1.5 h; this compound was obtained in 60% yield as white needles, mp 122°C (CH_3CN). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.04$ (3H, t, CH_3, J 7.4 Hz), 2.54 (2H, q, CH_2, J 7.4 Hz), 5.77 (2H, br s, $CONH_2$), 6.02 (2H, s, OCH_2O), 6.17 (2H, br s, NH_2), 6.84 (1H, d, H-5′, J 8.1 Hz), 7.15 (1H, dd, H-6′, J 1.7-8.1 Hz), 7.23 (1H, d, H-2′, J 1.7 Hz). ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 14.77$ (CH_3), 29.19 (CH_2), 98.79 (C-2), 101.46 (OCH_2O), 108.31 (C-5′), 109.61 (C-2′), 117.65 (C-4), 123.36 (C-6′), 126.96 (C-1′), 147.58 (C-3′), 148.28 (C-4′), 148.66 (C-5), 154.46 (C-3), 166.69 (C═O). Anal. calcd. for $C_{14}H_{14}N_2O_3S_2$: C, 52.16; H, 4.38; N, 8.69, S, 19.89. Found: C, 52.10; H, 4.31; N, 8.77; S, 20.25. EIMS: m/z calcd. for $C_{14}H_{14}N_2O_3S_2$: 322.04459. Found 322.04570 (M^+).

3-Amino-4-(ethylsulfanyl)-5-phenylthiophene-2-carboxamide $3c_3$

Reaction time 1.5 h; this compound was obtained in 70% yield as yellow crystals, mp 104–106°C (CCl_4). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.00$ (3H, t, CH_3, J 7.3 Hz), 2.52 (2H, q, CH_2, J 7.3 Hz), 5.81 (2H, br s, $CONH_2$), 6.18 (2H, br s, NH_2), 7.39–7.40 (3H, m, H-3′ − 4′ − 5′), 7.67 (2H, d, H-2′ − 6′, J 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.71$ (CH_3), 29.21 (CH_2), 99.50 (C-2), 118.20 (C-4), 128.39 (C-3′ − 5′), 128.95 (C-4′), 129.27 (C-2′ − 6′), 133.19 (C-1′), 148.90 (C-5), 154.42 (C-4), 166.75 (C═O). Anal. calcd. for $C_{13}H_{14}N_2OS_2$: C, 56.09; H, 5.07; N, 10.06; S, 23.04. Found: C, 56.01; H, 5.05; N, 10.4.98; S, 23.15.

Procedure for the Preparation of Methyl 3-Amino-4-bromo-5-(4-chloro-phenyl)thiophene-2-carboxylate ($4a_1$)

To a stirred solution of methyl 3-amino-4-(ethylsulfanyl)-5-(4-chlorophenyl) thiophene-2-carboxylate **3a1**, (0.500 g, 1.52 mmol) in a mixture of acetonitrile (6 mL) and water (0.5 mL), N-bromosuccinimide (0.680 g, 3.82 mmol) was added in small portions. The mixture was then heated under reflux for 1 h and cooled, and the solid was filtered. Recrystallization from acetonitrile yielded 65% (0.345 g) of pure bromothiophene **$4a_1$** as a white needles. Mp 152–154°C (CH_3CN). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.86$ (3H, s, CO_2Me), 5.74 (2H, br s, NH_2), 7.4 (2H, d, H-3′ − 5′, J 8.6 Hz), 7.56 (2H, d, H-2′ − 6′, J 8.6 Hz). ^{13}CNMR (75.5 MHz, $CDCl_3$): $\delta = 51.61$ (OCH_3), 99.28 (C-2), 100.51 (C-4), 128.96 (C-3′ − 5′), 130.09 (C-2′ − 6′), 130.91 (C-1′), 135.44 (C-4′), 141.93 (C-5), 151.00 (C-3), 164.09 (C═O). Anal. calcd. for $C_{12}H_9BrClNO_2S$: C, 41.68; H, 2.62; N, 4.04; S, 9.25. Found: C, 41.65; H, 2.55; N, 4.23; S, 9.45. EIMS: m/z calcd for $C_{12}H_9BrClNO_2S$: 344.92259. Found 344.9239 (M^+).

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