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One-pot synthesis of substituted 3-amino-2-nitrothiophenes and selenophenes

David Thomae [a], Juan Carlos Rodriguez Dominguez [a], Gilbert Kirsch [a,*], Pierre Seck [b]

[a] *Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique, Institut Jean Barriol, FR CNRS 2843, 1 Boulevard Arago, 57070 METZ, France*
[b] *Laboratoire de Chimie, Faculté des Sciences, de la Technologie et de la Communication, Université du Luxembourg, 162a, avenue de la Fäiencerie, L-1511 Luxembourg, Luxembourg*

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Abstract

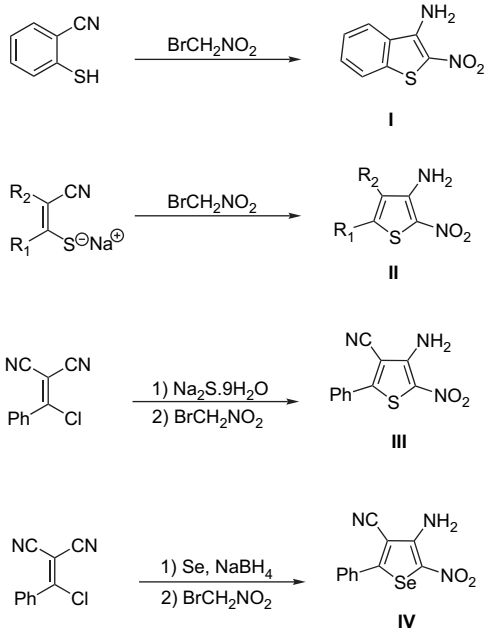
In this work, we described an easy preparation of substituted 3-amino-2-nitrothiophenes and selenophenes. Substituted β-chloroacrylonitriles were reacted with sodium sulfide or sodium selenide and bromonitromethane to yield the expected compounds in a one-pot three-step procedure in good yields.

Keywords: 3-Amino-2-nitrothiophenes; 3-Amino-2-nitroselenophenes; Bromonitromethane; Substituted β-chloroacrylonitriles

1. Introduction

Nitrothiophene derivatives have some versatile biological uses.[1,2] It has been showed that they inhibit the growth of *Escherichia Coli, Micrococcus Luteus* and *Aspergillus Niger*.[1] They were also used as the precursors of *N*-(5-substituted)-thiophene-2-alkylsulfonamides, which are potent inhibitors of 5-lipoxygenase.[2] Moreover, 3-amino-2-nitrobenzo[*b*]thiophene was used as starting material for the preparation of dyes.[3]

The synthesis of substituted 3-amino-2-nitrothiophenes has not been very much described especially by using bromonitromethane as one of the reagents. Only a few teams worked in this field of investigation. Fishwick et al. described the preparation of 3-amino-2-nitrobenzo[*b*]thiophene (**I**) starting from 2-sulfanylbenzonitrile and bromonitromethane (Scheme 1).[4] In the same paper, they synthesized some 3-amino-2-nitrothiophenes starting from the sodium salt of disubstituted 3-sulfanyl-2-propenenitriles and bromonitromethane (Scheme 1).[4] They obtained compounds (**II**) in yields ranging from 30% to 70%. Only one thiophene (**III**) was synthesized by Gewald and Hain starting



Scheme 1. 3-Amino-2-nitrophenes and 3-amino-2-nitroselenophene in the literature. R_1=−S−Me, R_2=−CN, $-CO_2Et$, $-CONH_2$; R_1=−NH−Ph, R_2=−CN, $-CO_2Et$, $-SO_2PH$.

* Corresponding author. Tel.: +33 3 87 31 52 95; fax: +33 3 87 31 58 01.
E-mail address: kirsch@univ-metz.fr (G. Kirsch).

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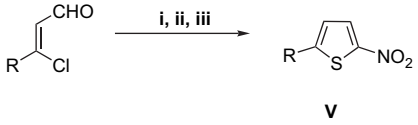
from a disubstituted β-chloroacrylonitrile using sodium sulfide and bromonitromethane.[5] In the same publication, they described the formation of 5-phenyl-3-amino-2-nitroselenophene **IV** (Scheme 1).

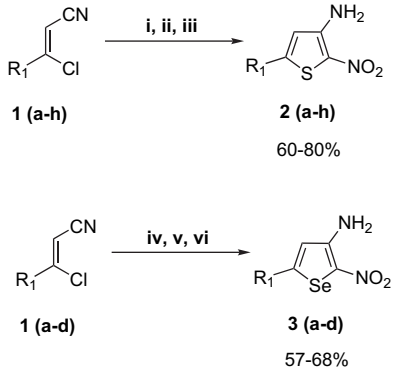
Recently, we have described some examples of preparation of substituted 2-nitrothiophenes **V** starting from β-substituted-β-chloroacroleins (Scheme 2).[10] In this work, in continuation of previous research on the synthesis of 3-aminothiophenes and selenophenes and their use for condensed systems,[6–9] we describe the preparation of new substituted 3-amino-2-nitrothiophenes and selenophenes (Scheme 2).



Scheme 2. Substituted 2-nitrothiophenes synthesized by our team. (i) $Na_2S·9H_2O$, DMF; (ii) $BrCH_2NO_2$; (iii) NaOH.

2. Results and discussion

From β-chloroacroleins, the access to the β-chloroacrylonitriles gave us the opportunity to prepare the substituted 3-amino-2-nitrothiophenes **2**(**a**–**h**) and 3-amino-2-nitroselenophenes **3**(**a**–**d**) in a one-pot procedure (Scheme 3).



Scheme 3. 3-Amino-2-nitrothiophenes and 3-amino-2-nitroselenophenes. (i) $Na_2S·9H_2O$, DMF; (ii) $BrCH_2NO_2$; (iii) NaOH; (iv) Na_2Se, DMF; (v) $BrCH_2NO_2$; (vi) NaOH.

Starting material **1** was prepared by Vilsmeier–Haack–Arnold reaction, oximation and dehydration. This method has already been described by different groups.[6–8,11] Bromonitromethane was obtained with a slight modification to the method established by Fishwick et al.[4] Freshly distilled nitromethane was used and bromine was added at 0 °C in only 5 s instead of 35 s as reported. With this change, bromonitromethane was obtained in 61% yield avoiding the formation of dibromonitromethane and tribromonitromethane as we described recently.[10a] Bromonitromethane was used without further purification.

Preparation of substituted 3-amino-2-nitrothiophenes **2**(**a**–**h**) was very straightforward. Sodium sulfide nonahydrate was added to β-chloroacrylonitriles **1**(**a**–**h**) in DMF and heated at 55 °C to form the thiolate. Bromonitromethane was added dropwise at room temperature. Cyclization was performed by the addition of a solution of sodium hydroxide. Pouring the reaction mixture in water gave the compounds **2**(**a**–**h**) in good yields (Table 1).

Table 1.
Prepared substituted 3-amino-2-nitrothiophenes

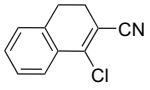
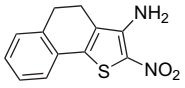
Entry	Substituted β-chloroacrylonitrile **1**	Substituted 3-amino-2-nitrothiophene **2**	Yield (%)
a	R_1=*p*-CH_3–Ph–	R_1=*p*-CH_3–Ph–	60
b	R_1=*p*-CH_3O–Ph–	R_1=*p*-CH_3O–Ph–	62
c	R_1=*p*-Cl–Ph–	R_1=*p*-Cl–Ph–	64
d	R_1=*t*-Bu–	R_1=*t*-Bu–	70
e	R_1=*p*-F–Ph–	R_1=*p*-F–Ph–	80
f	R_1=*p*-NO_2–Ph–	R_1=*p*-NO_2–Ph–	70
g	R_1=*p*-Ph–Ph–	R_1=*p*-Ph–Ph–	78
h			80

Table 2.
Prepared substituted 3-amino-2-nitroselenophenes

Entry	Substituted β-chloroacrylonitrile **1**	Substituted 3-amino-2-nitroselenophene **3**	Yield (%)
a	R_1=*p*-CH_3–Ph–	R_1=*p*-CH_3–Ph–	58
b	R_1=*p*-CH_3O–Ph–	R_1=*p*-CH_3O–Ph–	66
c	R_1=*p*-Cl–Ph–	R_1=*p*-Cl–Ph–	57
d	R_1=*t*-Bu–	R_1=*t*-Bu–	62

As for **2**(**a**–**h**), the preparation of substituted 3-amino-2-nitroselenophenes **3**(**a**–**d**) was very straightforward. Sodium selenide was prepared by a known method.[9a] Freshly prepared sodium selenide reacts with β-chloroacrylonitriles **1**(**a**–**d**) in DMF at 60 °C to form the selenolate. After 2 h, bromonitromethane was added dropwise at 0 °C and then heated to 60 °C for 2 h. Cyclization was performed by the addition of a solution of sodium hydroxide. Pouring the reaction mixture in water gave compounds **3**(**a**–**d**) in good yields (Table 2).

3. Conclusion

In conclusion, an easy way of synthesizing 3-amino-2-nitrothiophenes and selenophenes was developed. These new compounds open many possibilities for further synthesis.

4. Experimental section

4.1. General

Reagents were purchased from ACROS Organics. Thin Layer Chromatography (TLC) was carried out by using Silica Gel 60 F-254 plates and *n*-hexane/ethyl acetate (3:1) as an eluent. Melting points were determined on a Stuart Scientific SMP 3 capillary melting point apparatus and are uncorrected. IR spectra were performed in a Perkin Elmer Spectrum BxFT-IR spectrophotometer. Elemental analyses were done in a LECO CHNS 932 equipment.

4.2. Synthesis of substituted β-chloroacrylonitriles 1(a–h): general procedure

Compounds **1**(**a**–**h**) were prepared as described earlier.[6–8,11] Derivatives **1**(**a**–**h**) recrystallized in cyclohexane gave better

yields in the following reaction as when using the crude product.

4.3. Synthesis of substituted 3-amino-2-nitrothiophenes **2(a–h)**: general procedure

$Na_2S \cdot 9H_2O$ (0.05 mol) was suspended in DMF (98 mL) and stirred at 40 °C for 30 min. After that time, the corresponding β-chloroacrylonitriles **1**(**a**–**h**) (0.05 mol) were added. The mixture is heated at 55 °C for 90 min and left to reach room temperature. Bromonitromethane (0.05 mol) was slowly dropped at room temperature and left to stir at 55 °C for another 90 min. The reaction was followed by TLC [*n*-hexane/ethyl acetate (3:1)] and once finished NaOH (0.05 mol) in water (10 mL) was added and left to stir 30 min at the same temperature. The mixture was poured onto water (500 mL) with good stirring. The precipitate was filtered, washed with water, dried at room temperature until constant weight and purified by recrystallization or column chromatography.

4.3.1. 3-Amino-5-(4-methylphenyl)-2-nitrothiophene (**2a**)

Yield: 60%. Recrystallization in EtOH gave a brown solid; mp 224–227 °C. IR (KBr): 3437 (s), 3307 (s), 1554 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 2.29 (s, 3H, CH_3), 6.98 (s, 1H, C*H*), 7.22 (d, *J*=7.5 Hz, 2H, 2×C*H*), 7.61 (d, *J*=7.5 Hz, 2H, 2×C*H*), 8.20 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 20.91, 114.29, 125.90, 128.68, 129.94, 140.76, 149.89, 152.10, 155.56. Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.55; H, 4.51; N, 11.72.

4.3.2. 3-Amino-5-(4-methoxyphenyl)-2-nitrothiophene (**2b**)

Yield: 62%. Recrystallization in EtOH gave a yellow solid; mp 213–215 °C. IR (KBr): 3430 (s), 3307 (s), 1552 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 3.83 (s, 3H, CH_3O), 6.92 (s, 1H, C*H*), 7.05 (d, *J*=7.5 Hz, 2H, 2×C*H*), 7.67 (d, *J*=7.5 Hz, 2H, C*H*), 8.18 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 55.44, 113.37, 114.78, 119.58, 123.90, 127.68, 149.97, 152.33, 161.23. Anal. Calcd for $C_{11}H_{10}N_2O_3S$: C, 52.79; H, 4.03; N, 11.19. Found: C, 52.68; H, 4.17; N, 11.03.

4.3.3. 3-Amino-5-(4-chlorophenyl)-2-nitrothiophene (**2c**)

Yield: 64%. Recrystallization in EtOH gave a yellow solid; mp 269–270 °C. IR (KBr): 3433 (s), 3284 (s), 1561 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 7.04 (s, 1H, C*H*), 7.57 (d, *J*=7.5 Hz, 2H, 2×C*H*), 7.73 (d, *J*=7.5 Hz, 2H, 2×C*H*), 8.22 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 115.63, 120.34, 127.80, 129.41, 130.30, 135.21, 148.00, 151.82. Anal. Calcd for $C_{10}H_7ClN_2O_2S$: C, 47.16; H, 2.77; N, 11.00. Found: C, 47.23; H, 2.61; N, 10.82.

4.3.4. 3-Amino-5-tert-butyl-2-nitrothiophene (**2d**)

Yield: 70%. Recrystallization in cyclohexane/ethanol gave a yellow solid; mp 132–134 °C. IR (KBr): 3431 (s), 3312 (s), 1557 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 1.25 (s, 9H, 3×CH_3), 6.46 (s, 1H, C*H*), 8.02 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 30.60, 35.00, 114.66, 115.95, 151.63, 165.40. Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 47.84; H, 6.14; N, 14.18.

4.3.5. 3-Amino-5-(4-fluorophenyl)-2-nitrothiophene (**2e**)

Yield: 80%. Filtration while hot in ethanol gave a green solid; mp 230–232 °C. IR (KBr): 3442 (s), 3304 (s), 1525 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 6.97 (s, 1H, C*H*), 7.32 (m, 2H, 2×C*H*), 7.75 (m, 2H, 2×C*H*), 8.18 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 115.13, 116.25, 120.17, 128.41, 148.39, 151.92, 161.30, 165.26. Anal. Calcd for $C_{10}H_7FN_2O_2S$: C, 50.41; H, 2.96; N, 11.76. Found: C, 50.16; H, 2.77; N, 11.96.

4.3.6. 3-Amino-2-nitro-5-(4-nitrophenyl) thiophene (**2f**)

Yield: 70%. Recrystallization in EtOH gave a brown solid; mp 244–246 °C. IR (KBr): 3458 (s), 3308 (s), 1511 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 7.19 (s, 1H, C*H*), 7.96 (d, *J*=7.5 Hz, 2H, 2×C*H*), 8.26 (s, 2H, NH_2), 8.28 (d, *J*=7.5 Hz, 2H, 2×C*H*). ^{13}C NMR (62.9 MHz, DMSO): δ 117.80, 121.39, 124.44, 127.24, 137.33, 146.05, 148.01, 151.84. Anal. Calcd for $C_{10}H_7N_3O_4S$: C, 45.28; H, 2.66; N, 15.84. Found: C, 45.13; H, 2.79; N, 15.72.

4.3.7. 3-Amino-5-[1,1′-biphenyl]-4-yl-2-nitrothiophene (**2g**)

Yield: 78%. Column chromatography with eluent cyclohexane/ethyl acetate (8/2) gave a brown solid; mp 126–128 °C (dec). IR (KBr): 3420 (s), 3305 (s), 1560 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 7.06 (s, 1H, C*H*), 7.50 (m, 4H, 4×C*H*), 7.75 (m, 5H, 5×C*H*), 8.22 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 114.95, 120.23, 126.59, 127.25, 127.49, 128.12, 129.04, 130.39, 138.80, 142.10, 149.13, 151.59. Anal. Calcd for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45. Found: C, 65.01; H, 4.27; N, 9.22.

4.3.8. 3-Amino-2-nitro-4,5-dihydronaphtho[1,2-b]-thiophene (**2h**)

Yield: 80%. Recrystallization in EtOH gave a yellow solid; mp 217–218 °C. IR (KBr): 3432 (s), 3307(s), 1545 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 2.71 (t, *J*=7.5 Hz, 2H, CH_2), 2.97 (t, *J*=7.5 Hz, 2H, CH_2), 7.34 (m, 3H, 3×C*H*), 7.43 (d, *J*=7.5 Hz, 2H, 2×C*H*), 8.18 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 20.14, 26.85, 119.86, 124.06, 126.43, 127.31, 128.01, 128.44, 130.32, 136.59, 142.04, 150.10. Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.23; H, 4.22; N, 11.41.

4.4. Preparation of sodium selenide: general procedure

Selenium (0.01 mol) was added to a solution of NaOH (0.056 mol) and sodium formaldehyde sulfoxylate (0.024 mol) in water (10 mL). After stirring for 1 h at 50 °C, the white precipitate was filtered under an inert atmosphere and rapidly used in the next step.

4.5. Synthesis of substituted 3-amino-2-nitroselenophenes **3(a–d)**: general procedure

Na_2Se (0.01 mol) was suspended in DMF (10 mL) and stirred at 60 °C for 30 min. After that time, the corresponding β-chloroacrylonitriles **1**(**a**–**d**) (0.01 mol) dissolved in 5 mL of

DMF was added. The mixture was heated at 60 °C for 2 h and cooled to 0 °C. Bromonitromethane (0.01 mol) was slowly dropped at 0 °C. After addition, the mixture was heated for 2 h at 60 °C. The reaction is followed by TLC (CH_2Cl_2) and once finished NaOH (0.01 mol) in water (7 mL) was added and left to stir for 1 h at the same temperature. The mixture was poured onto water (150 mL) with good stirring. The precipitated was filtered, washed with water, dried at room temperature until constant weight and recrystallized in EtOH.

*4.5.1. 3-Amino-5-(4-methylphenyl)-2-nitro-3-selenophene (**3a**)*

Yield: 76%. Recrystallization in EtOH gave a green solid; mp 246–248 °C. IR (KBr): 3427 (s), 3305 (s), 1606 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 2.33 (s, 3H, CH_3), 7.23 (s, 1H, C*H*), 7.22 (d, J=7.5 Hz, 2H, 2×C*H*), 7.44 (d, J=7.5 Hz, 2H, 2×C*H*), 8.44 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 20.89, 117.88, 118.28, 126.19, 129.27, 129.52, 140.87, 154.36, 154.79. Anal. Calcd for $C_{11}H_{10}N_2O_2Se$: C, 46.99; H, 3.58; N, 9.96. Found: C, 46.89; H, 3.39; N, 10.01.

*4.5.2. 3-Amino-5-(4-methoxyphenyl)-2-nitro-3-selenophene (**3b**)*

Yield: 66%. Recrystallization in EtOH gave a yellow solid; mp 228–230 °C. IR (KBr): 3441 (s), 3325 (s), 1597 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 3.78 (s, 3H, CH_3), 7.04 (d, J=7.5 Hz, 2H, 2×C*H*), 7.17 (s, 1H, C*H*), 7.58 (d, J=7.5 Hz, 2H, 2×C*H*), 8.38 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 55.44, 103.55, 114.34, 114.59, 117.21, 127.97, 129.76, 154.62, 161.31. Anal. Calcd for $C_{11}H_{10}N_2O_3Se$: C, 44.46; H, 3.39; N, 9.43. Found: C, 44.32; H, 3.27; N, 9.55.

*4.5.3. 3-Amino-5-(4-chlorophenyl)-2-nitro-3-selenophene (**3c**)*

Yield: 57%. Recrystallization in EtOH gave a green solid; mp 274–276 °C. IR (KBr): 3420 (s), 3280 (s), 3160 (s), 1624 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 7.29 (s, 1H, C*H*), 7.52 (d, J=7.5 Hz, 2H, 2×C*H*), 7.65 (d, J=7.5 Hz, 2H, 2×C*H*), 8.41 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 97.63, 119.37, 128.05, 129.56, 130.32, 135.22, 152.81, 154.00. Anal. Calcd for $C_{10}H_7ClN_2O_2Se$: C, 39.82; H, 2.34; N, 9.29. Found: C, 39.73; H, 2.22; N, 9.41.

*4.5.4. 3-Amino-5-tert-butyl-2-nitro-3-selenophene (**3d**)*

Yield: 62%. Recrystallization in EtOH gave an orange solid; mp 136–138 °C. IR (KBr): 3415 (s), 3302 (s), 2965 (s), 1617 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO): δ 1.23 (s, 9H, 3×CH_3), 6.74 (s, 1H, C*H*), 8.28 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO): δ 31.40, 36.78, 117.60, 118.23, 153.90, 172.07. Anal. Calcd for $C_8H_{12}N_2O_2Se$: C, 38.88; H, 4.89; N, 11.33. Found: C, 38.95; H, 4.71; N, 11.47.

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