A Useful One-Pot Procedure for Obtaining 2-Aryl-5-nitrothiophenes from Bromonitromethane and 3-Aryl-3-chloro-propenals

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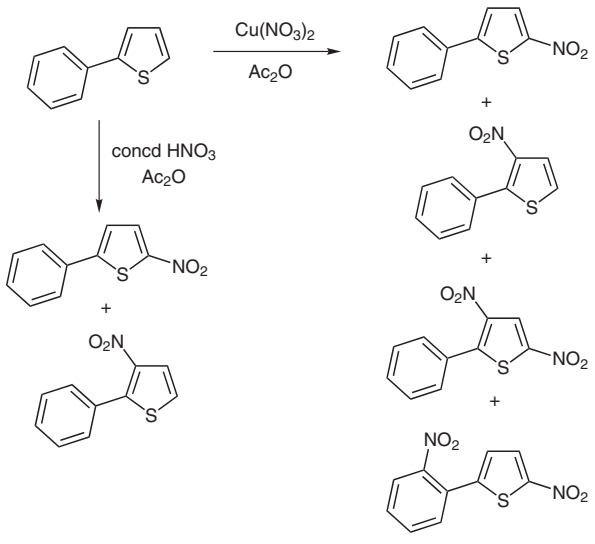
Abstract: A one-pot procedure was developed to prepare new 2-aryl-5-nitrothiophenes efficiently from bromonitromethane and 3-chloro-3-aryl-propenals. Nitrothiophenes were synthesized in good yields with a simple and easy workup procedure.

Key words: 5-nitrothiophenes, bromonitromethane, 3-aryl-3-chloro-propenals

2-Aryl-5-nitrothiophenes show inhibitory activity against some microorganisms[1] and are used as intermediates in the preparation of potent inhibitors of 5-lipoxygenase.[2] They were prepared by direct nitration of the 2-phenylthiophene with either nitric acid or different proportions of $Cu(NO_3)_2$ in acetic anhydride[3] but in all cases mononitration was not selective and also dinitration took place. When nitric acid was employed, a mixture of 2-nitro-5-phenyl and 3-nitro-2-phenylthiophenes was obtained. If the reaction was carried out with $Cu(NO_3)_2$, mixtures of 3-nitro-2-phenyl, 2-nitro-5-phenyl, 3,5-dinitro-2-phenyl, and 2-nitro-5-(2-nitrophenyl)thiophenes were recovered as final products (Scheme 1).



Scheme 1 Direct nitration of 2-phenylthiophene by either concentrated nitric acid or copper nitrate in acetic anhydride

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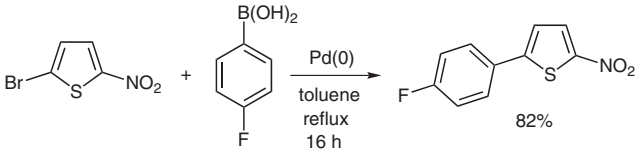
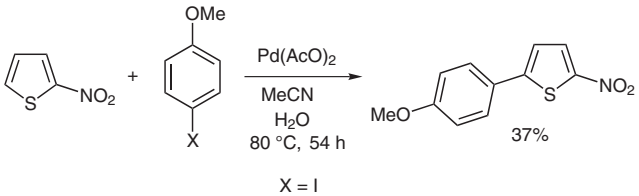
Another way for preparing 2-aryl-5-nitrothiophenes is the Suzuki coupling of the 2-bromo-5-nitrothiophene with the corresponding aryl boronic acids (Scheme 2).[2]



Scheme 2 Synthesis of the 5-(4-fluorophenyl)-2-nitrothiophene by Suzuki coupling (palladium complexes were used)

This coupling reaction was applied for the same purpose in order to obtain the 2-nitro-5-(4-methoxy)phenylthiophene from the corresponding iodophenyl derivative (Scheme 3).[4,5] Even if Suzuki coupling allows the obtainment of the aryl nitrothiophene in good yield (Scheme 2), usually palladium catalysis requires long reaction times to prepare the targeted derivatives (Schemes 2 and 3). In the case when *p*-iodoanisole was employed (Scheme 3), the isolated yield was low.[5]



Scheme 3 Synthesis of the 5-(4-methoxyphenyl)-2-nitrothiophene by Suzuki coupling (palladium acetate was used)

Bromonitromethane is a versatile reagent used in stabilized solutions as biocide,[6] in the synthesis of 1-bromo-1-nitroalkan-2-ols,[7] polyfunctionalized nitrocyclopropanes,[8] aryl nitromethanes, and as bromine donor.[9] It has also been utilized in the synthesis of 2-nitrobenzofuran and 2-nitro-2,3-dihydrobenzofuran-3-ols,[10,11] nitrobenzothiophenes, and nitrothiazoles.[12]

In the thiophene series only few examples have been described; in the case of 2-*tert*-butyl-5-nitrothiophene,[13] no experimental details are given. In order to synthesize new 2-aryl-5-nitrothiophenes, we have developed a one-pot procedure allowing access to thiophene derivatives in

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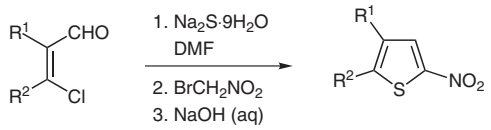
good yields with a simple workup procedure (Scheme 4).[14]

Starting 3-aryl-3-chloro-2-propenals were prepared as described earlier and spectroscopic data match with those reported in literature.[15] New 3-(3-bromophenyl)-3-chloro-2-propenal was adequately characterized.[16]

Bromonitromethane was prepared according to Fishwick et al.[12] Freshly distilled nitromethane was used and bromine was dropped in 5 seconds instead of 35 seconds as reported. With this slight modification only monobromination is effected and bromonitromethane could be used without further purification.[17]

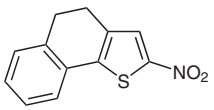
In order to obtain 2-nitrophenylthiophenes, we performed reactions in a one-pot procedure from 3-aryl-3-chloro-2-propenals, which are converted into the corresponding sodium 3-aryl propenal-3-thiolates by reacting with $Na_2S{\cdot}9H_2O$ in dimethylformamide. Addition of bromonitromethane and subsequent basic catalyzed intramolecular cyclization gave the desired mononitrothiophenes in good yields with an easy workup procedure.



Scheme 4 Developed procedure to obtain mononitrophenylthiophenes from 3-chloroacroleins and bromonitromethane

Structures of prepared compounds are referred to in Table 1.

Table 1 Prepared Mononitrophenylthiophenes

Entry	R^1	R^2	Yield (%)
1	H	4-Chlorophenyl	71.3
2	H	4-Fluorophenyl	61.7
3	H	4-Methylphenyl	82.6
4	H	4-Methoxyphenyl	73.5
5	H	4-Nitrophenyl	74.8
6	H	1,1′-Biphenyl-4-yl	61.5
7	H	3-Bromophenyl	70.6
8			85.2

All prepared nitrothiophenes were purified by recrystallization. Chemical properties and spectroscopic data of known and new 2-aryl-5-nitrothiophenes are shown.[18]

Acknowledgment

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(14) **Typical Experimental Procedure for Obtaining Mononitrophenylthiophenes**
Sodium sulfide ($Na_2S{\cdot}9H_2O$, 0.05 mol) was suspended in DMF (98 mL) and stirred at 40 °C for 30 min. After that time the corresponding 2-chloroacrolein (0.05 mol) was added. The mixture was then heated at 55 °C for 90 min and left to reach r.t. Bromonitromethane (0.05 mol) was slowly dropped at r.t. and left to stir at 55 °C for another 90 min. The reaction was followed by TLC (*n*-hexane–EtOAc, 3:1) and, once finished, NaOH (0.05 mol) in H_2O (10 mL) was added and the mixture was left to stir 30 min at the same temperature. The mixture was poured onto H_2O with good stirring and the obtained precipitate was filtered, washed with H_2O, and dried at r.t. until the weight was constant.
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(16) **3-(3-Bromophenyl)-3-chloro-2-propenal**
Yield 74.3%; orange solid, mp 64–65 °C (from EtOH). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 10.10 (d, *J* = 6.5 Hz, 1 H, HCO), 8.04 (d, *J* = 3.3 Hz, 1 H, PhH), 7.87 (dd, 1 H, PhH), 7.75 (dd, 1 H, PhH), 7.46 (m, 1 H, PhH), 7.04 (d, *J* = 6.6 Hz, 1 H, H2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 191.30, 148.43, 136.99, 134.49, 130.96, 129.53, 126.25, 125.39, 122.23. Anal. Calcd for C_9H_6BrClO (245.50): C, 44.03; H, 2.46; Br, 32.55; Cl, 14.44. Found: C, 43.99; H, 2.50; Br, 32.59; Cl, 14.41.
(17) Purity was checked by ^{1}H NMR spectroscopy using a Bruker 250 MHz instrument.

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(18) Reagents were purchased from ACROS Organics. Thin-layer chromatography (TLC) was carried out by using SilicaGel 60 F-254 plates and *n*-hexane–EtOAc (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 conducted in a LECO CHNS 932 instrument.
2-(4-Chlorophenyl)-5-nitrothiophene (**1**): mp 121–124 °C (from EtOH). IR (KBr): ν = 1534 (NO_2), 1333 (NO_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.19 (d, $J_{4,3}$ = 7.5 Hz, 1 H, H4), 7.88 (d, *J* = 10.0 Hz, 2 H, HPh), 7.72 (d, $J_{3,4}$ = 5.0 Hz, 1 H, H3), 7.58 (d, *J* = 10 Hz, 2 H, HPh). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 149.83, 149.57, 134.86, 131.27, 129.44, 129.31, 127.79, 124.56. Anal. Calcd for $C_{10}H_6ClNO_2S$ (239.68): C, 50.11; H, 2.52; Cl, 14.79; N, 5.84; S, 13.38. Found: C, 50.20; H, 2.60; Cl, 14.70; N, 5.80; S, 13.32.
2-(4-Fluorophenyl)-5-nitrothiophene (**2**): mp 124–126 °C (from EtOH); mp_{Lit} 129–130 °C.[2] IR (KBr): ν = 1536 (NO_2), 1334 (NO_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.14 (d, *J* = 4.25 Hz, 1 H), 7.87 (dd, 2 H, HPh), 7.63 (d, *J* = 4.25 Hz, 1 H), 7.33 (m, 2 H, HPh). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 161.1, 150.2, 131.3, 128.6, 128.4, 124.1, 116.8, 116.5.
2-(4-Methylphenyl)-5-nitrothiophene (**3**): mp 86–87 °C (from diisopropyl ether). IR (KBr): ν = 1510 (NO_2), 1333 (NO_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.13 (d, *J* = 4.45 Hz, 1 H), 7.71 (d, *J* = 8.07 Hz, 2 H, HPh), 7.61 (d, *J* = 4.37 Hz, 1 H), 7.30 (d, *J* = 7.72 Hz, 2 H, HPh), 2.34 (s, 3 H, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 151.85, 140.36, 131.37, 130.02, 128.71, 126.12, 123.38, 20.85. Anal. Calcd for $C_{11}H_9NO_2S$ (219.26): C, 60.26; H, 4.14; N, 6.39; S, 14.62. Found: C, 60.30; H, 4.19; N, 5.32; S, 14.68.
2-(4-Methoxyphenyl)-5-nitrothiophene (**4**): mp 129–131 °C (from cyclohexane); mp_{Lit} 135 °C.[5] IR (KBr): ν = 1536 (NO_2), 1337 (NO_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.14 (d, *J* = 5.0 Hz, 1 H, H4), 7.79 (d, *J* = 7.5 Hz, 2 H, HPh), 7.57 (d, $J_{3,4}$ = 5.0 Hz, 1 H, H3), 7.06 (d, *J* = 7.5 Hz, 2 H, HPh), 3.83 (s, 3 H, OCH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 160.95, 152.04, 148.05, 130.44, 127.47, 123.71, 122.66, 114.86, 55.19. Anal. Calcd for $C_{11}H_9NO_3S$ (235.26): C, 50.11; H, 2.52; Cl, 14.79; N, 5.84; S, 13.38. Found: C, 56.16; H, 3.86; N, 5.95; S, 13.63.
2-(4-Nitrophenyl)-5-nitrothiophene (**5**): mp 166–170 °C (from EtOH); mp_{Lit} 179 °C (from EtOH–H_2O).[3] IR (KBr): ν = 1516 (NO_2), 1345 (NO_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.29 (d, *J* = 8.65 Hz, 2 H, HPh), 8.21 (dd, 1 H), 8.09 (d, *J* = 8.75 Hz, 2 H, HPh), 7.87 (dd, 1 H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 151.17, 147.81, 137.35, 131.02, 130.27, 127.24, 126.51, 124.41.
2-[1,1′-Biphenyl]-4-yl-5-nitrothiophene (**6**): mp 166–169 °C (from EtOH). IR (KBr): ν = 1485 (NO_2), 1300 (NO_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.37–7.82 (m, 11 H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 152.2, 148.8, 148.7, 138.3, 132.1, 131.1, 128.3, 128.1, 127.5, 125.4, 125.1, 124.7. Anal. Calcd for $C_{16}H_{11}NO_2S$ (281.33): C, 68.31; H, 3.94; N, 4.98; S, 11.40. Found: C, 68.38; H, 4.01; N, 4.95; S, 11.36.
2-(3-Bromophenyl)-5-nitrothiophene (**7**): mp 76–79 °C (from EtOH). IR (KBr): ν = 1534 (NO_2), 1470 (NO_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.16 (d, *J* = 5.0 Hz, 1 H, H3-Thioph), 8.07–8.05 (m, 1 H), 7.82–7.79 (m, 1 H), 7.75 (d, *J* = 5.0 Hz, H4-Thioph), 7.68–7.64 (m, 1 H), 7.44 (t, 1 H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 150.06, 133.65, 132.81, 131.48, 131.08, 128.57, 125.34, 125.08, 122.74, 122.72. Anal. Calcd for $C_{10}H_6BrNO_2S$ (284.13): C, 42.27; H, 2.13; Br, 28.12; N, 4.93; S, 11.29. Found: C, 42.22; H, 2.16; Br, 28.08; N, 4.89; S, 11.25.
2-Nitro-4,5-dihydronaphtho[1,2b]thiophene (**8**): mp 114–116 °C (from EtOH). IR (KBr): ν = 1531 (NO_2), 1326 (NO_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.09 (s, 1 H, H3-Thioph), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.37–7.32 (m, 3 H), 2.96–2.93 (m, 2 H, CH_2), 2.87–2.84 (m, 2 H, CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 147.75, 143.91, 137.50, 136.20, 130.63, 130.03, 128.64, 128.49, 127.52, 123.99, 27.43, 22.78. Anal. Calcd for $C_{12}H_9NO_2S$ (231.27): C, 62.32; H, 3.92; N, 6.06; S, 13.87. Found: C, 62.40; H, 3.99; N, 6.10; S, 13.84.

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