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Synthesis of Ethyl 3-Amino-5-arylthiophene-2-carboxylates Based on α-Chlorocinnamonitriles

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Abstract—A new procedure was developed for preparation of ethyl 3-amino-5-arylthiophene-2-carboxylates by the reaction of α-chlorocinnamonitriles and their analogs with ethyl mercaptoacetate for a wide range of substrates. The reaction products form in high yields.

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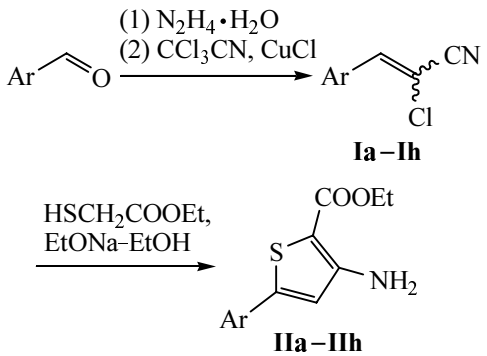
A combination of carboxy and amino groups at the thiophene ring of the 3-amino-5-arylthiophenecarboxylic acids opens wide synthetic opportunities for further modification. Based on their derivatives quite a number of biologically active substances were obtained [1–4].

These compounds were formerly synthesized by reactions of β-chlorocinnamonitriles and also of β-aroylacrylonitriles with esters of the mercaptoacetic acid [5, 6]. Besides a single example was published of a reaction between α-chlorocinnamonitrile with ethyl mercaptoacetate in the presence of sodium ethylate resulting in the corresponding thiophene derivative in a 75% yield [7].

Scheme.



Ar = 4-ClC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**), 4-$NMe_2C_6H_4$ (**c**), 4-$NO_2C_6H_4$ (**d**), 2-naphthyl (**e**), 1-naphthyl (**f**), 2-thienyl (**g**), 4-MeC_6H_4 (**h**).

We investigated the possibility to obtain ethyl 3-amino-5-arylthiophene-2-carboxylates with various aryl substituents by a reaction of α-chlorocinnamonitriles with ethyl mercaptoacetate.

We formerly demonstrated that the initial nitriles were easily prepared by catalytic olefination of aromatic aldehydes hydrazones with trichloroacetonitrile in the presence of catalytic quantity of copper(I) chloride [8].

We followed the known preparation method of esters of aminothiophenecarboxylic acids [7]. In the published procedure the reaction with ethyl mercaptoacetate was carried out in the presence of a triple excess of sodium ethylate. We showed that at the use of a freshly prepared sodium ethylate in a 20% excess the reaction occurred within 10 min and furnished the target product in a high yield. The reaction of the ethyl mercaptoacetate with nitriles under study proceeded regioselectively and afforded a single isomer of the corresponding ethyl aminothiophenecarboxylate (see the scheme) as proved by NMR, IR spectra, and comparison with the published data.

Hence we prepared a series of ethyl 3-amino-5-arylthiophene-2-carboxylates and demonstrated that the reaction of α-chlorocinnamonitriles with the ethyl mercaptoacetate is of a general character, and it was easy to obtain the corresponding substituted thiophenes from substrates containing both donor and acceptor substituents, and also heterocyclic and polyaromatic fragments.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from mulls in mineral oil. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Varian VXR-400 (operating frequencies 400 and 100 MHz respectively) from solutions in DMSO-d_6, internal reference TMS. TLC was performed on Merck 60 F_{254} plates.

Ethyl 3-amino-5-arylthiophene-2-carboxylates IIa–IIh. In 3 ml of ethanol was dissolved 0.083 g (3.6 mmol) of Na. To the obtained solution of sodium ethylate was added at stirring 0.43 g (3.6 mmol) of ethyl mercaptoacetate. Then at stirring to this mixture was added dropwise within 2 min a solution of 2.8 mmol of α-chlorocinnamonitrile in 2 ml of ethanol. The mixture was stirred for another 30 min where the precipitate formation was observed. The reaction mixture was quenched with 30 ml of water, the reaction product was filtered off and recrystallized from ethanol.

Ethyl 3-amino-5-(4-chlorophenyl)thiophene-2-carboxylate (IIa). Yield 72%, yellow crystals, mp 106–107°C [5]. ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, *J* 7.2 Hz), 4.20 q (2H, *J* 7.2 Hz), 6.57 br.s (2H, NH_2), 6.98 s ($1H_{thiophene}$), 7.48 d ($2H_{arom}$, *J* 8.7 Hz), 7.64 d ($2H_{arom}$, *J* 8.7 Hz).

Ethyl 3-amino-5-(4-methoxyphenyl)-thiophene-2-carboxylate (IIb). Yield 64%, greenish crystals, mp 118–120°C (publ.: mp 119–120°C [5]). ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, *J* 7.2 Hz), 3.78 s (3H, OMe), 4.19 q (2H, *J* 7.2 Hz), 6.53 br.s (2H, NH_2), 6.85 s ($1H_{thiophene}$), 6.98 d ($2H_{arom}$, *J* 8.5 Hz), 7.56 d ($2H_{arom}$, *J* 8.5 Hz).

Ethyl 3-amino-5-(4-*N*,*N*-dimethylaminophenyl)-thiophene-2-carboxylate (IIc). Yield 64%, greenish crystals, mp 167–168°C. IR spectrum, ν, cm^{-1}: 3420, 3310 (NH_2), 1630 (CO). ^{1}H NMR spectrum, δ, ppm: 1.24 t (3H, *J* 7.2 Hz), 2.94 s (6H, NMe_2), 4.17 q (2H, *J* 7.2 Hz), 6.48 br.s (2H, NH_2), 6.72 d ($2H_{arom}$, *J* 9.1 Hz), 6.75 C ($1H_{thiophene.}$), 7.43 d ($2H_{arom}$, *J* 9.1 Hz). ^{13}C NMR spectrum, δ, ppm: 163.64, 155.86, 150.70, 148.90, 126.43, 120.27, 113.04, 112.04, 94.85, 59.12, 39.70 (NMe_2), 14.51. Found, %: C 61.88; H 5.93. $C_{15}H_{18}N_2O_2S$. Calculated, %: C 62.04; H 6.25.

Ethyl 3-amino-5-(4-nitrophenyl)thiophene-2-carboxylate (IId). Yield 69%, red crystals, mp 139–141°C (publ.: mp 140–147°C [5]). ^{1}H NMR spectrum, δ, ppm: 1.26 t (3H, *J* 7.2 Hz), 4.21 q (2H, *J* 7.2 Hz), 6.67 br.s (2H, NH_2), 7.20 s ($1H_{thiophene}$), 7.88 d ($2H_{arom}$, *J* 8.5 Hz), 8.24 d ($2H_{arom}$, *J* 8.5 Hz).

Ethyl 3-amino-5-(2-naphthyl)thiophene-2-carboxylate (IIe). Yield 58%, yellow crystals, mp 90–92°C. IR spectrum, ν, cm^{-1}: 3430, 3340 (NH_2), 1660 (CO). ^{1}H NMR spectrum, δ, ppm: 1.26 t (3H, *J* 7.2 Hz), 4.23 q (2H, *J* 7.2 Hz), 6.63 br.s (2H, NH_2), 6.85 s ($1H_{thiophene}$), 7.62–7.53 m ($4H_{arom}$), 8.02–7.98 m ($2H_{arom}$), 8.18–8.14 m ($1H_{arom}$). ^{13}C NMR spectrum, δ, ppm: 163.56, 154.85, 145.74, 133.40, 131.06, 130.39, 129.21, 128.50, 127.46, 127.00, 126.33, 125.38, 124.62, 120.74, 59.42, 14.45. Found, %: C 68.33; H 5.22. $C_{17}H_{15}N_2O_2S$. Calculated, %: C 68.66; H 5.08.

Ethyl 3-amino-5-(1-naphthyl)thiophene-2-carboxylate (IIf). Yield 56%, yellow crystals, mp 124–127°C. IR spectrum, ν, cm^{-1}: 3420, 3330 (NH_2), 1670 (CO). ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, *J* 7.2 Hz), 4.22 q (2H, *J* 7.2 Hz), 6.60 br.s (2H, NH_2), 7.12 s ($1H_{thiophene}$), 7.56–7.51 m ($2H_{arom}$), 7.77–7.74 m ($1H_{arom}$), 8.01–7.91 m ($3H_{arom}$), 8.22 s ($1H_{arom}$). ^{13}C NMR spectrum, δ, ppm: 163.58, 155.49, 147.37, 132.95, 132.91, 130.18, 128.71, 128.23, 127.55, 126.81, 126.72, 124.36, 123.40, 116.53, 59.44, 14.44. Found, %: C 68.95; H 5.16. $C_{17}H_{15}N_2O_2S$. Calculated, %: C 68.66; H 5.08.

Ethyl 3-amino-5-(2-thienyl)thiophene-2-carboxylate (IIg). Yield 68%, yellowish crystals, mp 107°C. IR spectrum, ν, cm^{-1}: 3415, 3300 (NH_2), 1640 (CO). ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, *J* 7.0 Hz), 4.18 q (2H, *J* 7.0 Hz), 6.55 br.s (2H, NH_2), 6.78 s (1H, 2,3,5-substituted thiophene.), 7.11 d.d ($1H_{arom}$, *J* 3.6 Hz, *J* 5.1 Hz), 7.39 d ($1H_{arom}$, *J* 3.6 Hz), 7.60 d ($1H_{arom}$, *J* 5.1 Hz). ^{13}C NMR spectrum, δ, ppm: 163.44, 155.13, 140.68, 135.77, 128.51, 127.13, 125.64, 115.98, 96.01, 59.45, 14.44. Found, %: C 51.85; H 4.24. $C_{11}H_{11}NO_2S_2$. Calculated, %: C 52.15; H 4.38.

Ethyl 3-amino-5-(4-methylphenyl)thiophene-2-carboxylate (IIh). Yield 63%, light-green crystals, mp 110–111°C. IR spectrum, ν, cm^{-1}: 3450, 3350 (NH_2), 1670 (CO). ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, *J* 7.2 Hz), 2.31 s (3H, Me), 4.19 q (2H, *J* 7.2 Hz), 6.54 br.s (2H, NH_2), 6.92 s ($1H_{thiophene}$), 7.23 d ($2H_{arom}$, *J* 8.1 Hz), 7.51 d ($2H_{arom}$, *J* 8.1 Hz). ^{13}C NMR spectrum, δ, ppm: 163.60, 155.51, 147.63, 138.74, 130.05, 129.65, 125.38, 115.56, 115.32, 59.34, 20.74, 14.44. Found, %: C 64.13; H 5.83. $C_{14}H_{15}NO_2S$. Calculated, %: C 64.34; H 5.79.

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