Preparation and Reactions of *N*-Ethoxycarbonylthiophene-2-carboxamide and *N*-Ethoxycarbonylthiophene-2-thiocarboxamide

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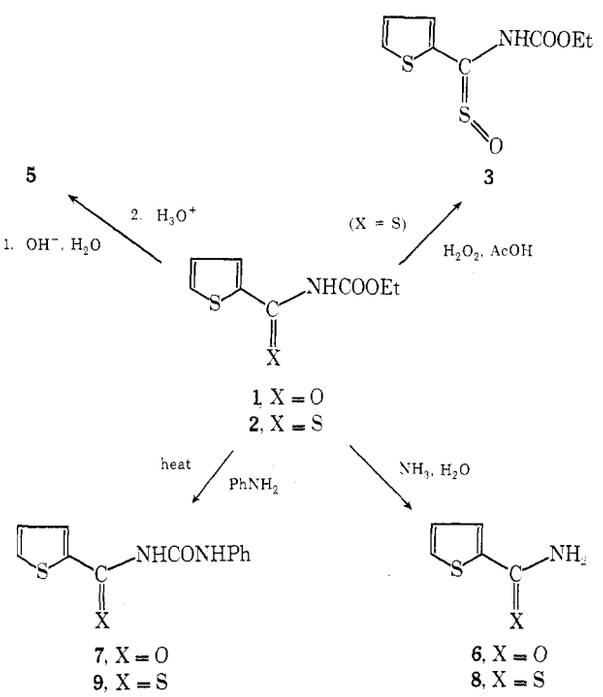
In the presence of anhydrous stannic chloride, thiophene reacts with ethoxycarbonyl isocyanate and isothiocyanate to yield the title compounds, which exhibit considerable reactivity toward nucleophilic reagents at both carbonyl and thiocarbonyl groups.

The reactions of pyrrole with ethoxycarbonyl isocyanate and isothiocyanate proved to be convenient sources of a variety of 2-pyrrolyl derivatives.[1] Some of these compounds were found to undergo cyclization reactions resulting in the formation of a new five-membered ring fused to the original pyrrole ring at positions 1 and 2. In no case, however, was ring closure observed to occur between positions 2 and 3 of the pyrrole ring. It was of interest to investigate the chemistry of the corresponding derivatives of thiophene, which, like pyrrole, reacts with isocyanates at position 2.[2,3] Cyclization of an initially formed 2-thienyl derivative, if it occurred, would have to involve position 3 of the ring.

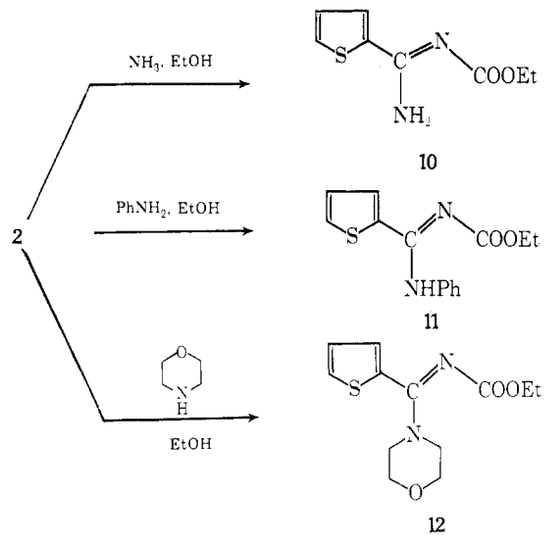
The reactivity of thiophene toward ethoxycarbonyl isocyanate and isothiocyanate has been found to be much less pronounced than that of pyrrole. A mixture of thiophene with either reagent remains unchanged for several days. However, the anticipated reactions occur at a convenient rate in the presence of anhydrous stannic chloride and yield *N*-ethoxycarbonylthiophene-2-carboxamide (**1**) and *N*-ethoxycarbonylthiophene-2-thiocarboxyamide (**2**), respectively. The reaction with the isocyanate appears to proceed more slowly, in spite of the otherwise greater reactivity of this reagent compared with the isothiocyanate. The structures assigned to the products of these reactions are in complete agreement with their ir and nmr spectra and are supported by the oxidation of **2** to **1** by alkaline hydrogen peroxide in ethanol. It is interesting to note that hydrogen peroxide in acetic acid oxidizes **2** to *N*-ethoxycarbonylthiophene-2-thiocarboxamide *S*-oxide (**3**), just as observed in the case of the corresponding derivative of pyrrole.[1b]

In contrast to the behavior of *N*-ethoxycarbonylpyrrole-2-carboxamide (**4a**) and *N*-ethoxycarbonylpyrrole-2-thiocarboxamide (**4b**), neither **1** nor **2** undergo cyclization upon treatment with boiling quinoline, but yield instead tarry materials. Other than that, the reactions of thiophene derivatives **1** and **2** are similar to those of the corresponding pyrrole derivatives. However, it is more difficult to cause nucleophilic attack to occur selectively at the ester carbonyl of **1** or **2** than for the pyrrole compounds, where the reactivity of the carbonyl or thiocarbonyl attached to the ring is decreased considerably by the nucleophilic character acquired by the pyrrole ring following loss of the NH proton.[4] Thus, partial hydrolysis of **4a** to pyrrole-2-carboxamide and **4b** to pyrrole-2-thiocarboxamide is brought about easily by the action of hot aqueous sodium hydroxide.[1] In the present case, the alkaline hydrolysis of **1** or **2** cannot be stopped effectively at the amide or thio amide stage and thiophene-2-carboxylic acid (**5**) is the isolated product. Thiophene-2-carboxamide (**6**) is nevertheless obtained from **1** by the action of hot, aqueous ammonia, under pressure. A similar treatment of **2** results in the formation of thiophene-2-thiocarboxamide

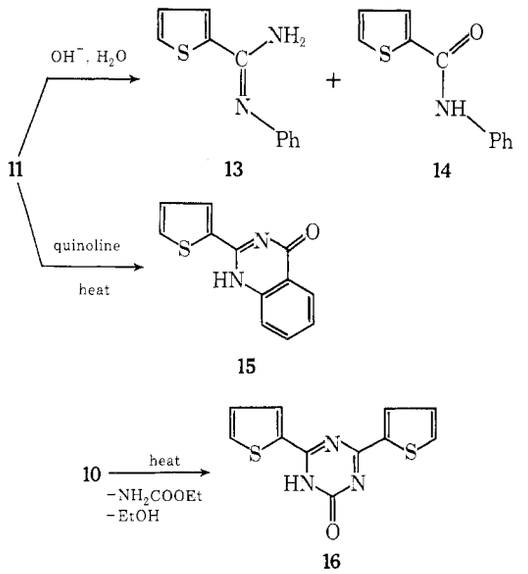


(**8**). Momentary boiling with aniline causes reaction to occur at the ester carbonyl and converts **1** into *N*-phenylcarbamoylthiophene-2-carboxamide (**7**) and **2** into the corresponding thiocarboxamide derivative **9**. The evolution of H_2S, in the latter case, is indicative of a competing reaction occurring at the thiocarbonyl, as described below. Alkaline hydrogen peroxide oxidizes the thio amides **8** and **9** to the amides **6** and **7**, respectively.

As in the case of the corresponding pyrrole derivative **4b**,[1b] the thiocarbonyl group of **2** shows considerable reactivity toward ammonia and primary or secondary amines. Thus **2** reacts with hot, alcoholic ammonia, under pressure, to yield *N'*-ethoxycarbonylthiophene-2-carboxamidine (**10**). Treatment with aniline at room temperature or with a hot, dilute solution of aniline in ethanol converts **2** into *N'*-ethoxycarbonyl-*N*-phenylthiophene-2-carboxamidine (**11**). Similarly, the morpholine derivative **12** is obtained when **2** is boiled briefly with a solution of morpholine in ethanol. The fact that the carbonyl stretching band in the ir spectra of **11** and **12** appears at nearly the same place (1660 cm^{-1} for **11** and 1680 cm^{-1} for **12**) supports the α,β-unsaturated ester structure for **11** rather than the isomeric carbamate structure. Hot, dilute hydrochloric acid hydrolyzes the amidines **10**, **11**, and **12** to *N*-ethoxycarbonylthiophene-2-carboxamide (**1**). Hydrolysis of **10** and **12** under alkaline conditions proceeds as expected to form thiophene-2-carboxylic acid, but a similar treatment of **11** yields, instead, *N'*-phenylthiophene-2-carboxamidine



(13) together with a smaller amount of *N*-phenylthiophene-2-carboxamide (14). Since further refluxing of amidine 13 with aqueous sodium hydroxide does not convert it to anilide 14, it may be concluded that the former is not an intermediate in the formation of the latter.



In complete analogy with the behavior of the corresponding pyrrole derivative,[1b] when heated above its melting point amidine 11 undergoes a cyclization reaction involving the benzene ring to yield 2-(2-thienyl)quinazolin-4(1*H*)-one (15), or its 3*H* tautomer. On the other hand, a condensation reaction involving two molecules of amidine 10 occurs when this compound is heated at 160–180°. Ethyl carbamate and ethanol are eliminated and a high-melting compound is produced which is formulated as 4,6-bis(2-thienyl)-1,3,5-triazin-2(1*H*)-one (16). The ir spectrum of this product, which contains a strong absorption band at 1680 cm^{-1}, is consistent with an α,β-unsaturated carbonyl group and more in keeping with the structure of the 1*H* than the symmetrical 5*H* tautomer, because of its rather complex appearance. The nmr spectrum displays only the typical signals of the ring protons of a 2-substituted thiophene. No signal for the NH proton has been detected, probably as a result of the low concentration of the solution used, due to the low solubility of the compound.

Further support for structure 16 is found in the analogous formation of 4,6-diphenyl-1,3,5-triazin-2(1*H*)-one, together with ethyl carbamate and ethanol, upon heating of *N'*-ethoxycarbonylbenzamidine at about 150°.[5]

Experimental Section[6]

***N*-Ethoxycarbonylthiophene-2-carboxamide (1).** A mixture of 8.4 g (0.10 mol) of thiophene, 11.5 g (0.10 mol) of ethoxycarbonyl isocyanate,[7a] and 10 ml of anhydrous stannic chloride was allowed to stand for 24 hr[8] and the resulting solid was ground into a powder and thoroughly mixed with dilute hydrochloric acid. Filtration followed by washing of the precipitate first with dilute hydrochloric acid and then with water yielded 15.5 g (78%) of crude 1, mp 130–135°. The pure compound was obtained by recrystallization from carbon tetrachloride–ethyl acetate (1:1) in the form of colorless crystals: mp 142–143°; ir 3260 (NH), 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.3 (t, 3, $-CH_3$), 4.2 (q, 2, $-OCH_2-$), 7.0 (m, 1, ring C-4 proton), 7.5 (m, 1, ring C-5 proton), 7.7 (m, 1, ring C-3 proton), and 8.5 ppm (s, 1, NH).

Anal. Calcd for $C_8H_9O_3NS$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.38; H, 4.65; N, 6.99.

***N*-Ethoxycarbonylthiophene-2-thiocarboxamide (2).** A mixture of 8.4 g (0.10 mol) of thiophene, 13.1 g (0.10 mol) of ethoxycarbonyl isothiocyanate,[7b] and 10 ml of anhydrous stannic chloride solidified completely when allowed to stand for 4 hr.[8] The product was worked up as for 1 to yield 17.5 g (81%) of crude 2, mp 101–103°. Recrystallization from carbon tetrachloride yielded the pure compound as dark red crystals: mp 107–108; ir 3250 (NH), 1730 (C=O), 1190 cm^{-1} (C=S); nmr ($CDCl_3$) δ 1.3 (t, 3, $-CH_3$), 4.2 (q, 2, $-OCH_2-$), 6.9 (m, 1, ring C-4 proton), 7.4 (m, 2, ring C-3 and C-5 protons), and 9.1 ppm (s, 1, NH).

Anal. Calcd for $C_8H_9O_2NS_2$: C, 44.63; H, 4.21; N, 6.51. Found: C, 44.81; H, 4.03; N, 6.45.

***N*-Ethoxycarbonylthiophene-2-thiocarboxamide *S*-Oxide (3).** Hydrogen peroxide (30%, 3 ml) was added to a solution of 0.50 g of 2 and 1.5 g of sodium acetate in 6 ml of acetic acid and the resulting mixture was let stand for 30 min. Dilution with water and filtration yielded 0.40 g (75%) of 3, mp 118–119° dec. The pure compound was obtained as yellow crystals by recrystallization from ethyl acetate: mp 120–121° dec; ir 3160 (NH), 1720 (C=O), 990 cm^{-1} (S=O); nmr δ 1.3 (t, 3, $-CH_3$), 4.2 (q, 2, $-OCH_2-$), 7.2 (m, 1, ring C-4 proton), 7.9 (m, 2, ring C-3 and C-5 protons), and 10.5 ppm (broad s, 1, NH).

Thiophene-2-carboxylic Acid (5). A. From 1. A mixture of 0.50 g of 1 and 10 ml of 10% aqueous sodium hydroxide was heated on the steam bath for 30 min. Following a cooling treatment, acidification of the solution yielded 0.25 g (78%) of 5, mp 126–127°. Recrystallization from water raised the melting point to 128–129° (lit.[9] mp 129–130°): ir 1690 cm^{-1} (C=O); nmr δ 6.9 (m, 1, ring C-4 proton), 7.5 (m, 2, ring C-3 and C-5 protons), and 11.5 ppm (broad s, 1, -COOH).

B, From 2. Acidification of the solution obtained by refluxing 1.0 g of 2 and 25 ml of 10% aqueous sodium hydroxide for 15 min yielded 0.40 g of 5, mp 120–125°.

Thiophene-2-carboxamide (6). A mixture of 1.0 g of 1, 5 ml of concentrated aqueous ammonia, and 5 ml of water was placed in a pressure bottle and heated on a steam bath for 30 min. The resulting solution was cooled and let stand in an open flask overnight to yield 0.40 g (63%) of 6, mp 172–175°. Recrystallization from water raised the melting point to 179–180° (lit.[10] mp 179–180°): ir 3360, 3160 (NH), 1650 cm^{-1} (C=O); nmr δ 7.0 (m, 1, ring C-4 proton) and 7.6 ppm (m superimposed on broad signal, 4, ring C-3 and C-5 protons, $-NH_2$).

***N*-Phenylcarbamoylthiophene-2-carboxamide (7).** After a mixture of 0.50 g of 1 and 2 ml of aniline had been boiled for a few moments, it was cooled and diluted with ethanol to yield 0.50 g (81%) of pure 7 as colorless crystals: mp 222–223° (lit.[11] mp 206°); ir 3240 (NH), 1700 (C=O), 1660 cm^{-1} (C=O); nmr δ 7.0–7.5 (m, 6, C-4 thienyl and phenyl protons), 7.9 (m, 1, C-5 thienyl proton), 8.2 (m, 1, C-3 thienyl proton), 10.5 (s, 1, NH), and 10.7 ppm (s, 1, NH).

Anal. Calcd for $C_{12}H_{10}O_2N_2S$: C, 58.52; H, 4.09; N, 11.38. Found: C, 58.62; H, 4.11; N, 11.34.

Thiophene-2-thiocarboxamide (8). A mixture of 1.0 g of 2 and 10 ml of concentrated aqueous ammonia was placed in a pressure bottle and heated on a steam bath for 1 hr. After it had been cooled, the resulting solution was acidified to yield 0.20 g (30%) of crude 8, mp 98–100°. Recrystallization from benzene yielded the pure compound in the form of yellow crystals: mp 107–109° (lit.[12] mp 108°); ir 3380 3270, 3170 (NH), 1050 cm^{-1} (C=S); nmr δ 7.0

(m, 1, ring C-4 proton), 7.5 (m, 2, ring C-3 and C-5 protons), and 9.3 ppm (broad, partly resolved d, 2, $-NH_2$).

N-**Phenylcarbamoylthiophene-2-thiocarboxamide (9).** As for **7**, from 0.50 g of **2** and 2 ml of aniline, there was obtained 0.20 g (33%) of crude **9**, mp 203–205° dec. Recrystallization from ethanol yielded the pure compound in the form of yellow crystals: mp 225–226° dec; ir 3260 (NH), 1690 cm^{-1} (C=O); nmr δ 6.9–7.5 (m, 6, phenyl and C-4 thienyl protons), 7.8 (m, 2, C-3 and C-5 thienyl protons), 10.6 (s, 1, NH), and 10.1–11.8 ppm (very broad, diffuse signal, 1, NH).

Anal. Calcd for $C_{12}H_{10}ON_2S_2$: C, 54.94; H, 3.84; N, 10.68. Found: C, 55.09; H, 3.66; N, 10.62.

N'-**Ethoxycarbonylthiophene-2-carboxamidine (10).** A solution of 5.0 g of **2** in 30 ml of ethanol saturated with ammonia at 0° was placed in a pressure bottle and heated on a steam bath for 35 min. Following a cooling treatment, dilution with water yielded 3.5 g (76%) of **10**, mp 150–152°. The pure compound was obtained by recrystallization from aqueous ethanol as colorless crystals: mp 153.5–154.5°; ir 3370 (NH), 3200–3300 (NH), 1660 cm^{-1} (C=O); nmr δ 1.2 (t, 3, $-CH_3$), 4.0 (q, 2, $-OCH_2-$), 7.0 (m, 1, ring C-4 proton), 7.6 (m, 1, ring C-5 proton), 7.9 (m, 1, ring C-3 proton), and 8.9 ppm (s, 2, $-NH_2$).

Anal. Calcd for $C_8H_{10}O_2N_2S$: C, 48.47; H, 5.09; N, 14.13. Found: C, 48.64; H, 4.98; N, 14.16.

N'-**Ethoxycarbonyl-***N*-**phenylthiophene-2-carboxamidine (11).** A solution of 3.0 g of **2** and 6 ml of aniline in 50 ml of ethanol was heated on a steam bath until the initial red color had been discharged (about 2 hr). Following filtration to remove a small amount of insoluble material (**9**), steam distillation of the filtrate left a gummy residue which was crystallized from aqueous ethanol to yield 2.6 g (68%) of **11**, mp 98–101°. Recrystallization from the same solvent afforded the pure compound as colorless crystals: mp 101–102°; ir 3310 (NH), 1660 cm^{-1} (C=O); nmr δ 1.0 (t, 3, $-CH_3$), 3.7 (q, 2, $-OCH_2-$), 6.6–7.4 (m, 7, thienyl C-4, C-5, and phenyl protons), 7.6 (m, 1, thienyl C-3 proton), and 9.6 ppm (s, 1, NH).

Anal. Calcd for $C_{14}H_{14}O_2N_2S$: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.47; H, 4.96; N, 10.29.

Hydrolysis of 11. Refluxing for 2 hr of a mixture of 2.0 g of **11** and 20 ml of 10% aqueous sodium hydroxide, followed by cooling and filtration, yielded 1.2 g of a solid, mp 106–136°. This was mixed thoroughly with dilute hydrochloric acid and the mixture was filtered to give 0.40 g (27%) of crude **14**. The melting point of this product, initially 130–133°, became 143–145° after recrystallization from aqueous ethanol and was undepressed upon admixture with independently prepared **14** (lit.[13] mp 144–145°). Further, its ir and nmr spectra were superimposable on those of authentic **14**: ir 3300 (NH), 1625 cm^{-1} (C=O); nmr δ 7.0–7.7 (m, 7, thienyl C-4, C-5, and phenyl protons), 7.9 (m, 1, thienyl C-3 proton), and 10.1 ppm (s, 1, NH). When the filtrate from the separation of **14** was made alkaline by addition of 10% aqueous sodium hydroxide, a precipitate was formed and filtration yielded 0.70 g (47%) of **13**, mp 140–142°. Recrystallization from aqueous ethanol yielded the pure compound as colorless crystals: mp 143–144° (lit.[14] mp 144–145°); ir 3425, 3300, 3150, 1625, 1600, 1580 cm^{-1}; nmr δ 6.2 (s, 2, $-NH_2$), 6.6–7.6 ppm (m, 8, thienyl and phenyl protons).

Anal. Calcd for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.50; H, 5.26; N, 13.91.

Amidine **13** was recovered unchanged after it had been refluxed with 10% aqueous sodium hydroxide for 2 hr. Similarly, treatment with hydrochloric acid under a variety of conditions, followed by neutralization, led to recovery of the original compound.

N'-**Ethoxycarbonyl-***N*,*N*-**oxybis(ethylene)thiophene-2-carboxamidine (12).** A solution of 1.0 g of **2** and 2 ml of morpholine in 5 ml of ethanol was boiled for 3 min, then cooled and diluted with water to yield 0.90 g (73%) of **12**, mp 84–86°. The pure compound was obtained in the form of colorless crystals by recrystallization from cyclohexane: mp 85.5–87°; ir 1680 (C=O), 1580 cm^{-1} (C=N); nmr δ 0.9 (t, 3, $-CH_3$), 3.5 (m, 8, morpholine CH protons), 3.8 (q, 2, $-OCH_2-$), 7.0 (m, 2, thienyl C-4 and C-5 protons), and 7.6 ppm (m, 1, thienyl C-3 proton).

Anal. Calcd for $C_{12}H_{16}O_3N_2S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.84; H, 5.91; N, 10.30.

2-(2-Thienyl)quinazolin-4(1*H* **or 3***H***)-one (15).** A mixture of 1.0 g of **11** and 5 ml of quinoline was boiled briefly, then cooled and diluted with petroleum ether (bp 65–75°) to yield 0.60 g (73%) of pure **15** as colorless crystals: mp 285–286° (sealed capillary); ir 3170 (NH), 1670 (C=O), 1590 (C=N), 770 cm^{-1} (ortho-disubstituted benzene ring); nmr δ 7.0–8.1 (m, 7, thienyl and phenyl protons) and 12.3 ppm (s, 1, NH).

Anal. Calcd for $C_{12}H_8ON_2S$: C, 63.14; H, 3.53; N, 12.27. Found: C, 63.28; H, 3.36; N, 12.18.

4,6-Bis(2-Thienyl)-1,3,5-triazin-2(1*H***)-one (16).** When 1.0 g of **10** had been heated at 180–200° for about 10 min, initial melting of the substance was accompanied by decomposition, resolidification, and formation of a condensate which was identified as ethyl carbamate on the basis of its ir and nmr spectra. The residue (0.60 g, 91%) was recrystallized from 1-butanol to yield pure **16** as colorless crystals: mp >300°; ir 1680 (C=O), 1560, 1540, 1500 cm^{-1}; nmr δ 7.3 (m, 1, thienyl C-4 proton), 8.0 (m, 1, thienyl C-5 proton), 8.2 ppm (m, 1, thienyl C-3 proton).

Anal. Calcd for $C_{11}H_7ON_3S_2$: C, 50.56; H, 2.70; N, 16.08. Found: C, 50.75; H, 2.74; N, 15.87.

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Registry No.—**1**, 51774-58-4; **2**, 51774-59-5; **3**, 51774-60-8; **5**, 527-72-0; **6**, 5813-89-8; **7**, 19382-27-5; **8**, 20300-02-1; **9**, 51774-61-9; **10**, 51774-62-0; **11**, 51774-63-1; **12**, 51774-64-2; **13**, 3737-39-1; **14**, 6846-13-5; **15**, 51774-65-3; **16**, 51774-66-4; thiophene, 110-02-1; ethoxycarbonyl isocyanate, 19617-43-7; ethoxycarbonyl isothiocyanate, 16182-04-0.

References and Notes

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