Synthesis of 3-Amino-2-carbamoylthiophene and Its Reaction with Cycloalkanones to Form Imines

L. H. Klemm*, Jun Wang [1], and Lucas Hawkins [2]

Department of Chemistry, University of Oregon, Eugene, Oregon 97403-1253

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3-Amino-2-carbamoylthiophene (**2**) was obtained in 75% yield by reaction of methyl 3-aminothiophene-2-carboxylate with saturated aqueous ammonia containing ammonium chloride catalyst at room temperature over a period of 2.3 months. Treatment of **2** with cyclopentanone, cyclohexanone, and cycloheptanone in ethanol at *p*H 3.4 gave facile formation of 2-carbamoyl-3-cycloalkylidenaminothiophenes in yields of 73%, 86%, and 60%, respectively. Infrared and ^{1}H nmr spectra of these imines indicate that they occur in intramolecularly hydrogen-bonded form, *i.e.* with chelate rings. Comparison is made with reported syntheses and reactions of **2** and its isosteric 2-aminobenzamide.

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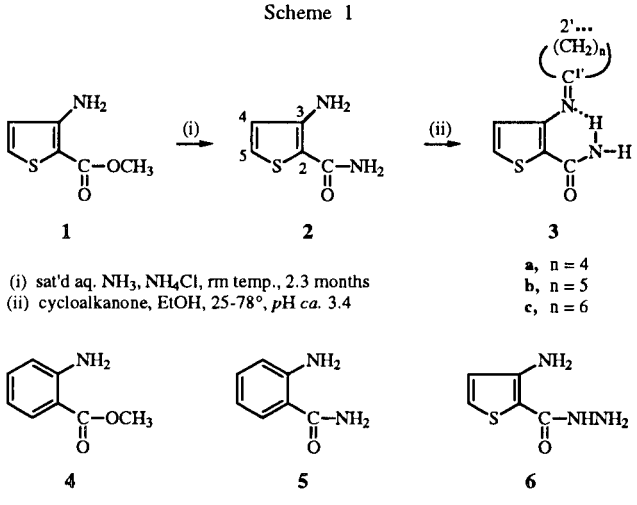
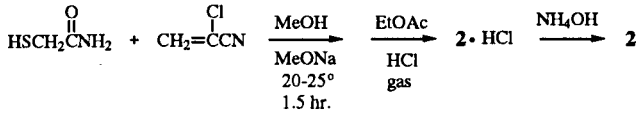
The aminolyses of methyl 3-aminothiophene-2-carboxylate (**1**) and its isosteric methyl 2-aminobenzoate (**4**) to form the corresponding aminoamides **2** and **5** have presented experimental difficulties. Adams and coworkers converted **4** into **5** (28% yield) by heating the former compound with liquid ammonia at 200° for ten hours in a bomb pressurized to 82 atm by means of hydrogen gas [3]. Our effort to effect the analogous conversion **1**→**2** by use of liquid ammonia in sealed pyrex tubes heated to 160°, an adaptation of the method of Audrieth and Kleinberg [4], was largely unsuccessful [5]. Use of 29% aqueous ammonia, in place of liquid ammonia, at a temperature of 160° for two hours, however, gave a yield of **2** as high as 27%, though results were irregular. Last of all we combined the methods of (a) LaForge for conversion of nicotinic ester into nicotinamide (quantitative yield) [6], (b) Cook *et al.* for the conversion **4**→**5** (yield not given) at room temperature and pressure over an extended period of time [7], and (c) use of ammonium chloride as a catalyst [8] to convert **1** into **2** in saturated aqueous ammonia solution in 70-77% yield at room conditions

Scheme 1



Scheme 2 [9]



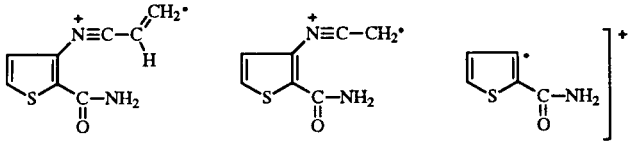
over a period of 2.3 months (Scheme 1). Meanwhile, Huddleston, Barker, *et al.* reported that they were unable to effect the transformation **1**→**2** despite various attempts [9]. Instead, these workers synthesized **2** in 36% overall yield by the procedure shown in Scheme 2. It is noteworthy, however, that **1** does react readily with hydrazine (more nucleophilic than ammonia) in either refluxing ethanol or butanol to form the aminohydrazide **6** (79-86% yield) [9-11].

Aminoamide **2** was characterized by infrared absorption bands at 3394 and 3296 cm^{-1} for the primary amino group, as well as 1647 plus 1584 and/or 1522 for the amide group [12]. These groups also give two broad overlapping signals (4 H total) at δ 5.90 and 5.72 in the ^{1}H nmr spectrum.

Treatment of **2** with cyclopentanone, cyclohexanone, and cycloheptanone in acidulated ethanol (*p*H 3.4, 0.4% hydrogen chloride by weight, or 0.096 *M* acid) yielded the imines **3a** (73%), **3b** (86%), and **3c** (60%), respectively. Compound **3b** precipitated immediately after mixing, while **3a** and **3c** precipitated after limited heating plus cooling. Both infrared and ^{1}H nmr spectra indicate that these imines exist as intramolecularly hydrogen-bonded structures, as shown in formula **3**. Thus, four infrared absorption bands occur in the region 3000-3400 cm^{-1} for both chelated and free NH stretching, an amide I band is found at 1620 ±4 cm^{-1} and amide II bands occur at 1521 ±7 and/or 1548 ±13 cm^{-1} [13]. The chelated NH proton resonates at 7.45 ±0.09 ppm and the free NH proton, at 7.00 ±0.05 ppm, when measured in hexadeuteriodimethyl sulfoxide. Interestingly, despite the use of 0.6-0.7 mole of

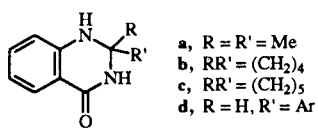
hydrogen chloride per mole of **2** in the reaction mixture, the imine **3** (a Schiff's base) does not precipitate as a salt. Moreover, the ^1H nmr spectrum of **3b** in deuteriotrifluoroacetic acid still shows the presence of separate chelated and free NH groups. It seems likely that salt formation by **3** may be precluded by the presence of the internal hydrogen bond. In fact, all three of the imines can be sublimed *in vacuo* without change.

The electron impact mass spectra of **3a-3c** are consistent with the presence of a cycloalkylidenamino function [14]. First, the most abundant ion occurs at m/z 179, corresponding to the loss of ethyl, propyl, and butyl fragments from **3a-3c**, respectively, to give $C_8H_7N_2OS^+$. This formula was confirmed by high resolution of the peak from **3c**. Other common peaks occur at m/z 166 (27-39%), corresponding to the loss of C_3H_6, C_4H_8, and C_5H_{10} from the molecular ions, and 126 (35-63%), for loss of C_5H_8N, $C_6H_{10}N$, and $C_7H_{12}N$ units, respectively. Based on the interpretations of Fischer and Djerassi [14] the ions should have structures as shown below. Chelation, if any, is not shown.



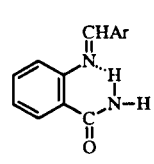
m/z 179 166 126

Our synthesis of **3** resembles literature procedures for the preparation of tetrahydroquinazolinones **7**. Böhme and Böing reported that use of ethanol saturated with hydrogen chloride at room temperature effected reaction of anthranilamide (**5**) with aldehydes and ketones, including acetone, cyclopentanone, and cyclohexanone to give compounds of structures **7a-7c** in high yield [15]. Compound **7a** melted at 182°. In contrast, Carrington found that refluxing a mixture of **5**, 3.5% hydrochloric acid and acetone for 15 hours gave a product of mp 262°, to which he also assigned structure **7a** [16]. Böhme and Böing believe his assignment is incorrect [15]. More recently von Weissenborn *et al.* prepared other compounds of structure **7** by using the acidic form of an ion exchange agent as a catalyst, instead of hydrogen chloride [17]. Imines were not reported by any of these workers.



a, R = R' = Me
b, RR' = $(CH_2)_4$
c, RR' = $(CH_2)_5$
d, R = H, R' = Ar

7



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However, Smith and Stephen found that various substituted benzaldehydes condense with **5** to form isolable, crystalline imines **8** in 50-97% yields merely by refluxing an ethanolic mixture of the two reactants for a few minutes [18,19]. Compounds **8** were then cyclized to **7d** usually by refluxing with aqueous ethanolic sodium hydroxide or by heating above the melting point at reduced pressure. In a few cases, *e.g.* for benzaldehyde itself, intermediates were not isolated, but refluxing ethanol gave **7d** directly. These workers did not investigate the reactions of ketones. Infrared, nmr, and mass spectral confirmation of structures **7** and **8** is still lacking.

EXPERIMENTAL [20]

3-Amino-2-carbamoylthiophene (**2**) [21].

A. At Ambient Conditions.

Into a two-liter pyrex pressure jug [22] containing a serum cap bearing two syringe needles (one for introduction of ammonia gas and the other for attachment to a Bunsen pressure valve) was placed a mixture of 20 g (0.127 mole) of methyl 3-aminothiophene-2-carboxylate (**1**) (Aldrich) [23], 4 g (0.075 mole) of ammonium chloride, and 1.7 l of 29% aqueous ammonium hydroxide. The mixture was stirred magnetically while ammonia gas was introduced to saturate the solution. The mixture was allowed to stand at room temperature for 2.3 months with brief periods of stirring and addition of more ammonia two or three times per week in order to maintain saturation. The reaction was monitored by thin-layer chromatography (chloroform/silica gel) until essentially all of **1** (R_f 0.71) had disappeared to leave an intense spot at R_f 0.19 for **2** and a minor spot at R_f 0 (impurity). The solution was evaporated to dryness, mixed with water (100 ml), extracted repeatedly with chloroform, and filtered to obtain some crude solid **2**. The gray solid from evaporation of the aqueous layer was triturated with acetone to leave recovered ammonium chloride (4.06 g). Additional amounts of crude **2** were obtained by evaporation of the chloroform and acetone solutions. Recrystallization from 95% ethanol (charcoal) and/or sublimation at 110° (0.03 mm) produced 12.7-14 g (70-77%) of white prisms, mp 122-124°, lit 118-120° [9,21]

B. In a Sealed Tube.

A mixture of 1.61 g (11.3 mmoles) of **1** and 40 ml of 29% aqueous ammonium hydroxide was heated in a sealed pyrex tube (85 ml internal volume) at 160° for two hours. The cooled mixture (containing one tan liquid phase) was evaporated to a volume of two ml or less. Addition of ether to the viscous residue produced a solid precipitate, which was collected by filtration, washed with ether, and dried in air, yield 388 mg (27%) of **2**, mp 119-120°, purified as in part A.

An analytically pure sample of **2** showed these characteristics—ir: 3394 and 3296 (NH_2), 3172, 1647 (amide I), 1584 and/or 1522 (amide II), 1459, 1394 cm^{-1} [12]; ^1H nmr (trideuterioacetonitrile): δ 7.27 (d, $J_{4,5}$ = 5.3 Hz, 1 H, H-5), 6.60 (d, 1 H, H-4), 5.90 and 5.72 (2 overlapping broad s, 4 H total, amino and amide protons); ms: m/z 142 (M^+, 100), 126 (30), 125 (M^+ -NH_3, 87), 97 (125$^+$ -CO, 27), 54 (26), 45 (CHS^+, 25).

Anal. Calcd. for $C_5H_6N_2OS$: C, 42.24; H, 4.26; N, 19.70.

Found: C, 42.32; H, 4.20; N, 19.68.

2-Carbamoyl-3-cyclopentylidenaminothiophene (**3a**).

A mixture of 2.03 g (14.3 mmoles) of aminoamide **2**, 1.6 ml (18.1 mmoles) of cyclopentanone, 100 ml of absolute ethanol, and 0.8 ml of concentrated hydrochloric acid (*p*H 3.4 as measured by test paper) was warmed to give a solution and then allowed to stand at room temperature overnight. Glistening plates of **3a** were collected by filtration. An additional crop was obtained by treatment of the mother liquor with charcoal, evaporation of the solvent, sublimation of the residue at 130° (0.04 mm), trituration of the sticky sublimate with warm absolute ethanol, and drying in air, total yield 2.17 g (73%), mp 248° dec, darkens slowly in daylight. Recrystallizations from absolute ethanol raised the melting point to 257-258° dec; ir: 3264, 3161, 3155, and 3072 (free and bonded NH stretching), 3018, 2979, 1616 (amide I), 1535 and/or 1515 (amide II), 1417, 783 cm^{-1} [13]; ^1H nmr (DMSO-d_6): δ 7.57 (d, $J_{4,5}$ = 4.8 Hz, 1 H, H-5), 7.54 (s, 1 H, chelated NH), 7.05 (s, 1 H, free NH) [24], 6.52 (d, 1 H, H-4), 1.76 (slightly split s, 4 H, 2 H-2', 2 H-5'), 1.61 (slightly split d, 4 H, 2 H-3', 2 H-4'); ms: m/z 208 (M^+, 52), 190 (M^+ -H_2O, 29), 180 (38), 179 (M^+ -C_2H_5, 100), 166 (M^+ -C_3H_6, 27), 126 (M^+ -C_5H_8N, 63), 125 (40).

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.47; H, 5.75; N, 13.38.

2-Carbamoyl-3-cyclohexylidenaminothiophene (**3b**).

Swirling a mixture of 2.32 g (16.3 mmoles) of **2**, 2.5 ml (24.3 mmoles) of cyclohexanone, and 100 ml of ethanolic hydrochloric acid (*p*H 3.4, vide supra) gave an immediate copious precipitate of white needles. The next day the crystals were collected by filtration, yield 3.12 g (86%), mp 264-267°, changed to a white powder, mp 266-267°, on sublimation at 200-210° (0.15 mm), insoluble in ether or chloroform; ir: 3356 and 3163 (free NH stretching), 3229 and 3027 (bonded NH stretching), 3065, 2957, 1621 (amide I), 1551 and/or 1522 (amide II), 1406, 784 cm^{-1} [13]; ^1H nmr (DMSO-d_6): δ 7.58 (d, $J_{4,5}$ = 5.4 Hz, 1 H, H-5), 7.36 (s, 1 H, chelated NH), 6.96 (broad s, 1 H, free NH) [24], 6.56 (d, 1 H, H-4), 1.9-1.1 (m, 10 H, 5 methylene groups); ^1H nmr (deuteriofluoroacetic acid): δ 8.29 (d, $J_{4,5}$ = 5.3 Hz, 1 H, H-5), 8.24 (d, J = 5.5 Hz, 1 H, chelated NH), 7.79 (d, 1 H, free NH), 7.70 (d, 1 H, H-4), 3.5-2.2 (m, 10 H, 5 methylene groups); ms: m/z 222 (M^+, 36), 179 (M^+ -C_3H_7, 100), 166 (M^+ -C_4H_8, 39), 126 (M^+ -$C_6H_{10}N$, 35).

Anal. Calcd. for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.45; H, 6.29; N, 12.57.

2-Carbamoyl-3-cycloheptylidenaminothiophene (**3c**).

A mixture of 2.01 g (14.2 mmoles) of **2**, 2.39 g (21.3 mmoles) of cycloheptanone, and 100 ml of ethanolic hydrochloric acid (*p*H 3.4, vide supra) was refluxed for 45 minutes and then refrigerated to give 1.99 g (60%) of **3c** as colorless platelets, mp 220-222° [25]. Sublimation at 190° (0.04 mm) and recrystallization from absolute ethanol changed the melting point to 222-223°; ir: 3304 and 3176 (free NH stretching), 3232 and 3024 (bonded NH stretching), 2936, 1624 (amide I), 1560 and/or 1528 (amide II), 1416, 784 cm^{-1} [13]; ^1H nmr (DMSO-d_6): δ 7.53 (d, $J_{4,5}$ = 5.1 Hz, 1 H, H-5), 7.48 (s, 1 H, chelated NH), 7.05 (s, 1 H, free NH) [24], 6.51 (d, 1 H, H-4), 1.7-2.0 (m, 4 H, 2 H-2', 2 H-7'), 1.46 (s, 8 H, 4 methylene groups); ms: m/z 236 (M^+, 38), 193 (M^+ -C_3H_7, 28), 179 (M^+ -C_4H_9, 100), 166 (M^+ -C_5H_{10}, 27), 126 (M^+ -$C_7H_{12}N$, 40).

Anal. Calcd. for $C_{12}H_{16}N_2OS$: C, 60.99; H, 6.83; N, 11.85; exact mass, 236.098. Found: C, 60.94; H, 6.69; N, 11.77; exact mass, 236.099. Calcd. for $C_8H_7N_2OS$: exact mass, 179.028. Found: exact mass, 179.028.

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[19] We represent **8** as internally hydrogen-bonded although this was not suggested by the authors.

[20] Infrared spectra were determined on potassium bromide wafers by means of a Nicolet Magna IR 500 spectrometer and ^1H nmr spectra by means of a General Electric QE-300 instrument. Electron-impact mass spectra were obtained at 70 eV by Dr. Richard Wielesek of this laboratory on a VG 12-250 instrument. Elemental analyses were conducted by Desert Analytics, Tucson, Arizona.

[21] Now available, albeit expensive, from Lancaster Synthesis, Inc.

[22] A suction flask may be used instead.

[23] For the synthesis of **1** see P. R. Huddleston and J. M. Barker, *Synth. Commun.*, **9**, 731 (1979).

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[25] Evaporation of the mother liquor yielded some lower-melting crystals which were not investigated further.