Synthesis and Structure Elucidation of the Condensation Products Between Thiophene Dicarbaldehydes and Aromatic Amines. Potential Analgesic and Anti-inflammatory Agents

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Thiophene-3,4-dicarbaldehyde **1** reacts in the presence of 2-mercaptoethanol to yield *N*-aryl-5,6-dihydro-4-oxo-4*H*-thieno[3,4-*c*]pyrroles **2** and *N*-aryl-4-arylimino-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrroles **3**, while thiophene 2,3-dicarbaldehyde **4** reacts with aromatic amines to give *N*-aryl-5,6-dihydro-6-oxo-4*H*-thieno[2,3-*c*]pyrroles **5** in good yields. Labeling experiments and nmr spectral analysis give evidences for the possible reaction mechanism.

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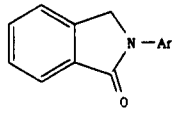
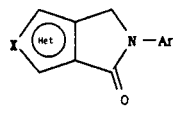
In the last decade, research on analgesic and anti-inflammatory agents containing an isoindoline moiety, **A**, has led to various types of aryl-substituted compounds [1-3], but to our knowledge no five-membered-ring heterocycle analogue, **B**, has been reported.



A



B X= O, S, N

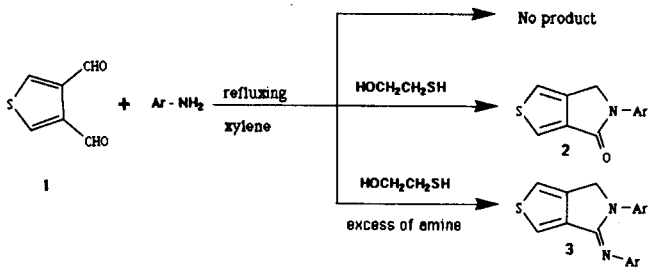
Part of this is probably due to the commercial availability of phthalaldehyde. Heterocyclic *ortho*-dicarbaldehydes usually require multiple-step synthesis [4-5] or low yields are obtained [6]. The reactions involving phthalaldehyde and amines are pretty easy and gave good yields under dilute conditions [7]. However some side-reactions lead to other condensation products and/or to polymeric materials [8], depending on molar ratios of the reactants and their concentrations.

In this paper we will report the syntheses, characterization, and mechanism of formation of *N*-aryl-5,6-dihydro-4-oxo-4*H*-thieno[3,4-*c*]pyrroles **2**, *N*-aryl-4-arylimino-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrroles **3**, and *N*-aryl-4,5-dihydro-6-oxo-4*H*-thieno[2,3-*c*]pyrroles **5**.

Thiophene-3,4-dicarbaldehyde **1** does not react with aromatic amines under the conditions in which phthalaldehyde gave isoindolines. Even with increasing the temperature, **1** remains unreacted. The compounds **2** were produced in high yields using a four-fold molar excess of 2-mercaptoethanol.

The di-adducts **3** were obtained with an excess of amine (see Scheme 1). All reactions were carried out in dilute solutions in order to avoid the formation of polymeric material (see Experimental).

Scheme 1

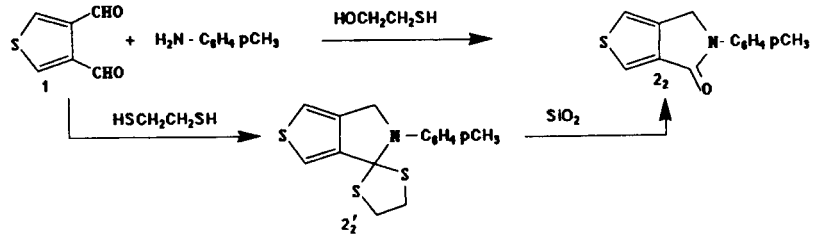


Compound **1** reacted with aromatic amines to give **2** under the conditions described above. But when 1,2-ethanedithiol was used, the carbonyl protected compound **6** was isolated in the case of *p*-toluidine. This result demonstrates that the chelating agent favors the formation of **2** (see Scheme 2).

The *N*-aryl-5,6-dihydro-4-oxo-4*H*-thieno[3,4-*c*]pyrroles **2** have been obtained in high yields (69 to 79%) from various aromatic amines. Compounds **3** were produced in lower yields (40 to 66%).

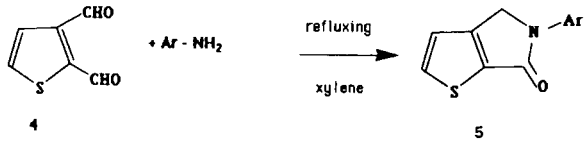
Either in the presence or absence of 2-mercaptoethanol thiophene-2,3-dicarbaldehyde **4** reacted with aromatic amines in refluxing xylene leading to the *N*-aryl-5,6-dihy-

Scheme 2



dro-6-oxo-4*H*-thieno[2,3-*c*]pyrroles **5** (see Scheme 3). Even with an excess of amine the formation of the di-adduct was not observed.

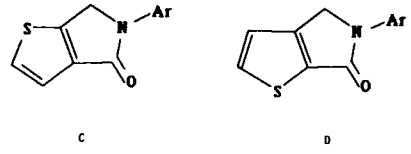
Scheme 3



The structure elucidation of compounds **2** and **5** was easily achieved on the basis of their ir and nmr data. The carbonyl absorptions arose in the range 1670-1690 cm^{-1} and the imine stretching bands were found in the 1638-1645 cm^{-1} region.

The nmr signals for all the thiophene protons appeared as two sharp resonances between 6.89 and 7.84 ppm, with the expected coupling constants, and the cyclic methylene protons appeared between 3.86 and 4.77 ppm (see Experimental).

For the unsymmetrical series, two isomers **C** and **D**, are theoretically obtainable but only one of them was isolated from the reaction mixture.

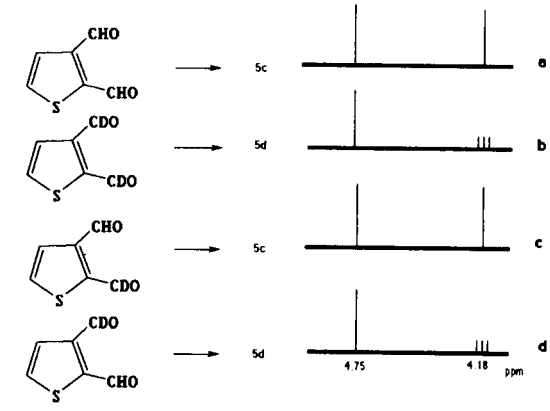


Firstly, the pmr spectroscopic data were not sufficiently explicit to determine whether the structure of the product is **C** or **D**. Secondly, it was not possible for the *N*-benzyl derivatives of **5** to uniquely assign the structure on the basis of chemical shift expectations for the two methylene proton resonances appearing at 4.1 and 4.75 ppm.

In order to solve the isomer structure problem and to give the nmr signals assignment, deuterium labelled compounds were prepared. Moreover, the analysis of the labelled products gave significant data about the mechanism of their formation.

Scheme 4 displays the profile of the pmr spectra in the 4-5 ppm region.

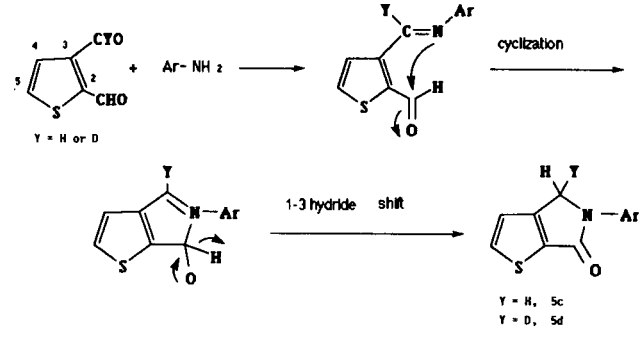
Scheme 4



From the spectra (a) and (b) it is obvious that the methylene in the five-membered-ring is the high-field singlet. Analysis of spectrum (c) proves that the deuterium atom was lost during the reaction because the two singlets were still present. The definitive proof is afforded by examination of the fourth spectrum (d). The deuterium atom in the 3 position of the dicarbaldehyde was retained through the transformation and the resonance at 4.18 ppm looked like a broad triplet due to the coupling with the deuterium atom. Therefore, the structure of all the compounds and the mechanism of their formation may be deduced from these data. Scheme 5 summarizes the proposed mechanism.

The proof that the reaction began by the condensation with the aldehyde group in position 3 was given by the retention of the deuterium atom in that position. Otherwise, it would be lost during the 1,3-hydride shift [9].

Scheme 5



EXPERIMENTAL

All melting points are uncorrected and were obtained with a Kofler hot-stage apparatus. The ir spectra were recorded on a Perkin-Elmer 580B instrument on 1% potassium bromide disks. The nmr spectra (δ scale) were recorded at the Burgundy's University nmr facility (CEREMA) on a Bruker WM400 spectrometer (400 MHz, deuteriochloroform, TMS as internal standard, J in Hz). Multiplicities are given as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (M). Analyses were performed by the "Service Central du C.N.R.S.".

General Procedure for the Preparation of **2**, **3**, and **5**.

N-Aryl-5,6-dihydro-4-oxo-4*H*-thieno[3,4-*c*]pyrroles **2**.

A solution of the aromatic amine (0.00275 mole) in 20 ml of anhydrous xylene was added dropwise under reflux to a stirred solution of **1** (0.0025 mole, 0.35 g) and (0.01 mole, 0.7 ml) of 2-mercaptoethanol in 200 ml of anhydrous xylene. After 4 hours under reflux the reaction mixture was quenched with water, and the organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under vacuum and the residue chromatographed on a silica gel column. Recrystallization afforded yellow-to-red crystals.

N-Phenyl-5,6-dihydro-4-oxo-4*H*-thieno[3,4-*c*]pyrrole **2a**.

Compound **2a** was obtained using the general procedure described above. Elution with ether/hexane (1/1) mixture and recrystallization from methylene chloride/hexane give **2a** in 69% yield, mp 148-149°; ir: ν C=O 1691.5 cm^{-1}; pmr: δ 7.84 (d, H_3, 2.3 Hz), 7.18 (dt, H_1, 2.3 and 1.1 Hz), 7.20-7.77 (M, C_6H_5), 4.77 (d, CH_2, 1.1 Hz).

Anal. Calcd. for $C_{12}H_9NOS$: C, 66.97; H, 4.18; N, 6.51; O, 7.44; S, 14.88. Found: C, 66.82; H, 4.16; N, 6.30; O, 7.63; S, 14.75.

N-(*p*-Tolyl)-5,6-dihydro-4-oxo-4*H*-thieno[3,4-*c*]pyrrole **2b**.

Compound **2b** was obtained using the general procedure described above. Elution with ether/hexane (1/1) mixture and recrystallization from methylene chloride/hexane gave **2b** in 79% yield, mp 190-191°; ir: ν C=O 1688.0 cm^{-1}; pmr: δ 7.82 (d, H_3, 2.3 Hz), 7.16 (dt, H_1, 2.3 and 1.2 Hz), 7.21-7.63 (M, C_6H_4), 4.73 (d, CH_2, 1.2 Hz), 2.35 (s, CH_3).

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.12; H, 4.80; N, 6.11; O, 6.98; S, 13.97. Found: C, 68.46; H, 4.78; N, 5.99; O, 7.08; S, 14.08.

N-Benzyl-5,6-dihydro-4-oxo-4*H*-thieno[3,4-*c*]pyrrole **2c**.

Compound **2c** was obtained using the general procedure described above. Elution with ether/hexane (2/1) mixture and recrystallization from methylene chloride/hexane gave **2c** in 79% yield, mp 95-96°; ir: ν C=O 1678.2 cm^{-1}; pmr: δ 7.76 (d, H_3, 2.3 Hz), 7.03 (dt, H_1, 2.3 and 1.2 Hz), 7.20-7.40 (M, C_6H_5), 4.72 (s, CH_2(2)), 4.15 (d, CH_2(6), 1.2 Hz).

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.12; H, 4.80; N, 6.11; O, 6.98; S, 13.97. Found: C, 68.32; H, 4.75; N, 6.29; O, 6.83; S, 13.70.

N-(1-Phenylethyl)-5,6-dihydro-4-oxo-4*H*-thieno[3,4-*c*]pyrrole **2d**.

Compound **2d** was obtained using the general procedure described above. Elution with ether/hexane (2/1) mixture and recrystallization from methylene chloride/hexane gave **2d** in 73% yield, mp 104-105°; ir: ν C=O 1678.2 cm^{-1}; pmr: δ 7.74 (d, H_2, 2.3 Hz), 7.03 (ddd, H_1, 2.3, 1.2 and 1.2 Hz), 7.20-7.40 (M, C_6H_5), 5.74 (q, CH, 7.5 Hz), 1.66 (d, CH_3, 7.5 Hz), 4.22 (dd, CH(6), 15.5 and 1.2 Hz), 3.87 (dd, CH(6), 15.5 and 1.2 Hz).

Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.13; H, 5.35; N, 5.76; O, 6.58; S, 13.17. Found: C, 69.35; H, 5.27; N, 5.70; O, 6.88; S, 13.28.

N-Aryl-4-arylimino-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrroles **3**.

The same procedure as above (except 0.0055 mole of amine) led to compounds **3**.

N-Phenyl-4-phenylimino-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrole **3a**.

Compound **3a** was obtained using the general procedure described above. Elution with ether/hexane (1/5) mixture and recrystallization from ether/hexane gave **3a** in 57% yield, mp 148-149°; ir: ν C=N 1644.8 cm^{-1}; pmr: δ 6.29 (d, H_3, 2.4 Hz), 7.00 (dt, H_1, 2.4 and 1.3 Hz), 7.00-7.96 (M, C_6H_5), 4.82 (d, CH_2, 1.3 Hz).

Anal. Calcd. for $C_{16}H_{14}N_2OS$: C, 74.48; H, 4.83; N, 9.66; S, 11.03. Found: C, 74.59; H, 4.91; N, 9.36; S, 11.27.

N-(*p*-Tolyl)-4-(*p*-tolyl)imino-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrole **3b**.

Compound **3b** was obtained using the general procedure described above. Elution with ether/hexane (1/5) mixture and recrystallization from ether/hexane gave **3b** in 67% yield, mp 167-168°; ir: ν C=N 1638.1 cm^{-1}; pmr: δ 6.32 (d, H_3, 2.3 Hz), 7.00 (dt, H_1, 2.3 and 1.2 Hz), 6.80-7.80 (M, C_6H_4), 4.77 (d, CH_2, 1.2 Hz), 2.36 (s, CH_3), 2.33 (s, CH_3).

Anal. Calcd. for $C_{20}H_{18}N_2S$: C, 75.47; H, 5.66; N, 8.81; S, 10.06. Found: C, 75.07; H, 5.78; N, 8.55; S, 9.84.

N-Benzyl-4-benzylimino-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrole **3c**.

Compound **3c** was obtained using the general procedure described above. Elution with ether/hexane (3/1) mixture and recrystallization from ether/hexane gave **3c** in 66% yield, mp 76-77°; ir: ν C=N 1644.8 cm^{-1}; pmr: δ 7.66 (d, H_3, 2.3 Hz), 6.98 (dt, H_1, 8.3 and 1.3 Hz), 7.20-7.50 (M, C_6H_5), 4.82 (s, CH_2), 5.00 (s, CH_2), 4.18 (d, CH_2(6), 1.3 Hz).

Anal. Calcd. for $C_{20}H_{18}N_2S$: C, 75.47; H, 5.66; N, 8.81; S, 10.06. Found: C, 75.42; H, 5.69; N, 8.69; S, 10.16.

N-(1-Phenylethyl)-4-(1-phenylethyl)imino-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrole **3d**.

Compound **3d** was obtained using the general procedure described above. Elution with ether/hexane mixture gave **3d** as an oily compound in 40% yield; ir: ν C=N 1638.1 cm^{-1}; pmr: δ 7.59 (d, H_3, 2.3 Hz), 6.89 (ddd, H_1, 2.3, 1.2 and 1.2 Hz), 7.20-7.60 (M, C_6H_5), 5.90 (q, CH, 7.2 Hz), 5.27 (q, CH, 6.4 Hz), 1.60 (d, CH_3, 7.2 Hz), 1.54 (d, CH_3, 6.4 Hz), 4.15 (dd, CH(6), 14.7 and 1.2 Hz), 3.86 (dd, CH(6), 14.7 and 1.2 Hz).

Anal. Calcd. for $C_{22}H_{22}N_2S$: C, 76.30; H, 6.36; N, 8.09; S, 9.25. Found: C, 76.59; H, 6.38; N, 7.86; S, 9.11.

N-Aryl-5,6-dihydro-6-oxo-4*H*-thieno[2,3-*c*]pyrroles **5**.

Compounds **5** are obtained from thiophene-2,3-dicarbaldehyde **4** using the procedure described for **2** without 2-mercaptoethanol.

N-Phenyl-5,6-dihydro-6-oxo-4*H*-thieno[2,3-*c*]pyrrole **5a**.

Compound **5a** was obtained using the general procedure described above. Elution with ether/hexane mixture and recrystallization from methylene chloride/hexane gave **5a** in 27% yield, mp 161-162°; ir: ν C=O 1671.0 cm^{-1}; pmr: δ 7.75 (d, H_2, 4.7 Hz), 7.10 (d, H_3, 4.7 Hz), 7.20-7.50 (M, C_6H_5), 4.79 (s, CH_2).

Anal. Calcd. for $C_{12}H_9NOS$: C, 66.97; H, 4.18; N, 6.51; O, 7.44; S, 14.88. Found: C, 67.12; H, 4.34; N, 6.41; O, 7.65; S, 14.65.

N-(*p*-Tolyl)-5,6-dihydro-6-oxo-4*H*-thieno[2,3-*c*]pyrrole **5b**.

Compound **5b** was obtained using the general procedure described above. Elution with ether/hexane (1/1) mixture and recrystallization from methylene chloride/hexane gave **5b** in 24% yield, mp 161-162°; ir: ν C=O 1675.0 cm^{-1}; pmr: δ 7.68 (d, H_2, 4.8 Hz), 7.09 (d, H_3, 4.8 Hz), 7.20 (d, C_6H_4, 7.1 Hz), 7.62 (d, C_6H_4, 7.1 Hz), 4.75 (s, CH_2), 2.29 (s, CH_3).

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.12; H, 4.80; N, 6.11; O, 6.98; S, 13.97. Found: C, 68.05; H, 4.89; N, 5.98; O, 6.98; S, 14.19.

N-Benzyl-5,6-dihydro-6-oxo-4*H*-thieno[2,3-*c*]pyrrole **5c**.

Compound **5c** was obtained using the general procedure described above. Elution with ether/hexane (1/1) mixture and recrystallization from ether/hexane gave **5c** in 32% yield, mp 102-103°; ir: ν C=O 1670.0 cm^{-1}; pmr: δ 7.64 (d, H_2, 4.7 Hz), 7.00 (d, H_3, 4.7 Hz), 7.20-7.40 (M, C_6H_5), 4.75 (s, CH_2), 4.18 (s, CH_2 (4)).

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.12; H, 4.80; N, 6.11; O, 6.98; S, 13.97. Found: C, 68.29; H, 4.71; N, 6.11; O, 6.98; S, 14.38.

For the labelled compound **5d**, the same procedure was used starting from the appropriate deuterated thiophenedicarbaldehyde [10].

N-Benzyl-5,6-dihydro-6-oxo-4*H*-thieno[2,3-*c*]pyrrole (4-D) **5d**.

Compound **5d** was obtained using the general procedure described above. Elution with ether/hexane (1/1) mixture and recrystalllization from ether/hexane gave **5d** in 21% yield, mp 101-102°; ir: ν C=O 1670.0 cm^{-1}; pmr: δ 7.61 (d, H_2, 4.7 Hz), 6.97 (d, H_3, 4.7 Hz), 7.20-7.40 (M, C_6H_5), 4.75 (s, CH_2), 4.15 (s, CH(4)).

Anal. Calcd. for $C_{13}H_{10}DNOS$: C, 67.50; H + D/2, 5.22; N, 6.05; S, 13.86. Found: C, 67.50; H + D/2, 4.82; N, 5.98; S, 13.75.

N-(1-Phenylethyl)-5,6-dihydro-6-oxo-4*H*-thieno[2,3-*c*]pyrrole **5e**.

Compound **5e** was obtained using the general procedure described above. Elution with ether/hexane (1/1) mixture and recrystallization from diisopropylether/hexane gave **5e** in 23% yield, mp 80-81°; ir: ν C=O 1671.5 cm^{-1}; pmr: δ 7.60 (d, H_2, 4.7 Hz), 6.96 (d, H_3, 4.7 Hz), 7.30-7.40 (M, C_6H_5), 5.71 (q, CH, 7.2 Hz), 1.68 (d, CH_3, 7.2 Hz).

Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.13; H, 5.35; N, 5.65; O, 6.58; S, 13.17. Found: C, 69.15; H, 5.48; N, 5.65; O, 6.87; S, 13.39.

Preparation of Compound **2b** *via* **6**.

A solution of *p*-toluidine (0.0025 mole, 0.30 g) in 50 ml of absolute ethanol was added dropwise at 0° to a mixture of **1** (0.0025 mole, 0.35 g) and 1,2-ethanedithiol (0.0025 mole, 0.20 ml) in 100 ml of absolute ethanol. The reaction mixture was stirred for 3 hours at room temperature, acidified with dilute hydrochloric acid, and extracted with ether. Recrystallization from benzene/hexane afforded 0.31 g (41%) of **6**, mp 208°; pmr: δ 2.30 (s, CH_3), 2.65 (broad s, SCH_2CH_2S), 5.99 (s, CH_2), 6.89 (d, *ortho*-H, 7.3 Hz), 7.04 (s, thio-H), 7.14 (d, *meta*-H, 7.3 Hz).

Anal. Calcd. for $C_{15}H_{15}NS_3$: C, 59.01; H, 4.91; N, 4.59; S, 31.47. Found: C, 59.14; H, 4.93; N, 4.53; S, 31.82.

This later compound were chromatographed on a silica gel column (eluting mixture: ether/hexane, 1/1) giving **2b** in quantitative yield.

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