

Synthesis of Arylamino-thieno-oxobutanamides and reactivity studies on the cyclisation with the Lawesson's reagent

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Abstract - 1-aryl-2-thienyl-substituted pyrroles and 5-arylamino-2,2'-bithiophenes were synthesized by treatment of arylamino-thieno-oxobutanamides with Lawesson's reagent. These in turn were prepared by direct amidation of 4-oxo-(2-thienyl)butanoic acid through DCC/BtOH mediated reactions.

Keywords: arylamino-thieno-oxobutanamides, Lawesson's reagent, 1-aryl-2-(2'-thienyl)pyrroles, 5-arylamino-2,2'-bithiophenes, non-linear optical material, NLO applications.

Introduction

Thiophene and pyrrole moieties play important roles in natural product chemistry,¹⁻² non-linear optics,³⁻⁴ and supramolecular chemistry.⁵ The development of new methods of synthesis of these heterocycles is therefore important. 2-Aryl- and 2-heteroaryl-substituted pyrroles are also of great interest to the pharmaceutical industry, for instance, as precursors in the synthesis of chemotherapeutics.^{1,6-7} Some of these molecules, in particular the thienylpyrroles, have served as prospective monomers for non-linear optical materials and organic conductive polymers.⁸⁻¹⁸

The latter combine high electrical conductivity, with thermal and environmental stability. The synthesis of thienylpyrroles containing substituents at the nitrogen atom attracts considerable attention because the substitution makes it possible to modify the properties of polymers, including the synthesis of chiral conducting polymeric materials with better properties for NLO.^{8,10,18-19}

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Generally, pyrroles are synthesized by the condensation of 1,4-dicarbonyl compounds with primary amines through the Paal-Knorr reaction.¹

In view of their importance, there is a continuous interest in developing versatile synthetic routes.

In this work we wish to report the synthesis of 1-aryl-2-thienyl-substituted pyrrole derivatives from arylamino-thieno-oxobutanamides through the Lawesson's reaction. As far as we can know it is the first time that 1-aryl-2-thienyl-substituted pyrroles are described *via* a combination of the Friedel-Crafts and the Lawesson reactions.

Discussion

Recently we described the synthesis of 5-*N,N*-dialkyl-4-(2'-thienyl)-4-oxobutanamides, and 5-alkoxy- and 5-*N,N*-dialkylamino-2,2'-bithiophenes *via* a combination of the Friedel-Crafts and the Lawesson's reaction.²⁰ In continuation of our work²⁰⁻²³ and in order to obtain new material with potential application in NLO we try to synthesise 5-arylamino-2,2'-bithiophenes, by treatment of aryl-4-(2'-thienyl)-4-oxobutanamides with the Lawesson's reagent. In our study, instead of the expected 5-arylamino-2,2'-bithiophenes we obtained 1-aryl-2-(2'-thienyl)pyrroles or a mixture of 1-aryl-2-(2'-thienyl)pyrroles and 5-arylamino-2,2'-bithiophenes, 1-aryl-2-(2'-thienyl)pyrroles being always the major products.

The synthesis of aryl-4-(2'-thienyl)-4-oxobutanamides **1a-f** was achieved by direct amidation of 4-oxo-(2-thienyl)butanoic acid²⁴ with several commercial arylamines through DCC-BtOH mediated reactions²⁰ (Scheme 1i). No secondary products were detected and the yields were fair to good (30-64%) depending on the nucleophilicity of the arylamine (Table 1). The different effect of substituents in the anilines used is noteworthy.

The above aryl-4-(2'-thienyl)-4-oxobutanamides **1a-f** showed to be good starting materials for the synthesis of the corresponding pyrrole derivatives **2a-f**, by treatment at reflux with Lawesson's reagent in toluene (Scheme 1ii). Therefore attempts to convert the aryl-4-(2'-thienyl)-4-oxobutanamides **1a-f** into the corresponding 5-arylamino-2,2'-bithiophenes **3** gave only the thienylpyrroles **2c** (49%), (Table 1, entry 3) or a mixture of thienylpyrroles **2** (32-58%) and bithiophene derivatives **3** (Table 1, entries 1-2 and 4-6) in low yields (7-19%), pyrroles being the major compounds (Table 1).

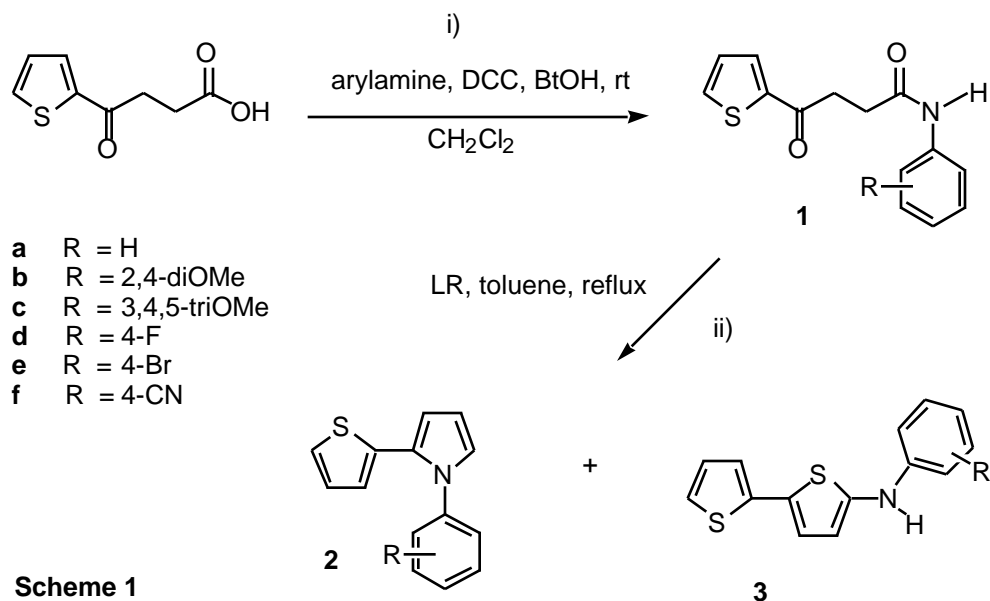


Table 1. Yields obtained in the synthesis of amides **1**, 1-aryl-(2'-thienyl)pyrroles **2** and 5-arylamino-2,2'-bithiophenes **3**.

Entry	R	Compound 1	Yield (%)	Compound 2	Yield (%)	Compound 3	Yield (%)
1	H	1a	42	2a	58	3a	9
2	2,4-diOMe	1b	64 ²⁰	2b	32	3b	12
3	3,4,5- triOMe	1c	49	2c	49	3c	---
4	4-F	1d	41	2d	58	3d	8
5	4-Br	1e	30	2e	34	3e	7
6	4-CN	1f	31	2f	32	3f	19

A plausible mechanism for the formation of pyrroles **2** and bithiophenes **3** from the secondary amides **1**, has already been proposed.²⁵

1-Aryl-2-(2'-thienyl)pyrroles have been prepared from aryl-4-(2'-thienyl)-4-oxobutanamides **1a-f** as major compounds, through a combination of the Friedel-Crafts and Lawesson reactions. The corresponding bithiophene derivatives were also obtained as by-products, generally in low yields.

The conjugated 1-aryl-2-(2'-thienyl)pyrroles **2** and the 5-arylamino-2,2'-bithiophenes **3**, as strong π -electron donor moieties, could be used as precursors in the preparation of compounds with potential application in NLO.^{11-15,20}

General experimental procedure (example)

Synthesis of 4''-Cyanophenyl-4-(2'-thienyl)-4-oxobutanamide **1f**

Amide **1f** was obtained using the experimental method described in ref. 20, by reacting 4-oxo-(2-thienyl)butanoic acid (5.4 mmol) in CH₂Cl₂ with 1,3-dicyclohexylcarbodiimide (7.1 mmol) and BtOH (7.1 mmol) and adding 4-cyanoaniline at rt.

4''-Cyanophenyl-4-(2'-thienyl)-4-oxobutanamide 1f. Colourless solid (31%). Mp 206.9-208.1 °C (EtOH). IR (Nujol) ν 3341 (NH), 2224 (CN), 1704 (C=O), 1644 (C=O), cm⁻¹. ¹H NMR (CDCl₃) δ 2.83 (t, 2H, $J=6.3$ Hz, CH₂), 3.43 (t, 2H, $J=6.3$ Hz, CH₂), 7.16-7.19 (m, 1H, 4'-H), 7.60 (d, 2H, $J=8.7$ Hz, 2xAr-H), 7.67 (d, 2H, $J=8.7$ Hz, 2xAr-H), 7.70 (dd, 1H, $J=5.1$ and 1.2 Hz, 5'-H), 7.81 (dd, 1H, $J=3.5$ and 1.2 Hz, 3'-H), 8.14 (br s, 1H, NH). Anal. Calcd for C₁₅H₁₂N₂O₂S: C, 63.54; H, 4.44; N, 9.78; S, 11.51. Found: C, 63.35; H, 4.22; N, 9.85; S, 11.26.

Synthesis of 1-(4''-cyanophenyl)-2-(2'-thienyl)pyrrole **2f** and 5-(4''-cyanoanilino)-2,2'-bithiophene **3f** by treatment of amide **1g** with the Lawesson's reagent

A mixture of the Lawesson reagent (2.3 mmol) and the amide **1f** (2.3 mmol) was heated at reflux in toluene (12 ml) during 15 min.. The reaction mixture was cooled and the solvent was evaporated under reduced pressure to give the crude mixture of arylpyrrole **2f** and bithiophene **3f**, which was purified by "flash" chromatography on silica with increasing amounts of ether in light petroleum as eluent. The first component eluted was *1-(4''-cyanophenyl)-2-(2'-thienyl)pyrrole 2f* as a beige solid (32 %). Mp 114.2-

115.5 °C (ether). IR (Nujol) ν 2227 (CN) cm^{-1} . ^1H NMR (Acetone- d_6) δ 6.38-6.42 (m, 1H, 4-H), 6.52 (dd, 1H, $J=3.5$ and 1.8 Hz, 3-H), 6.72 (dd, 1H, $J=3.6$ and 1.2 Hz, 3'-H), 6.97-7.02 (m, 1H, 4'-H), 7.14-7.18 (m, 1H, 5-H), 7.40 (dd, 1H, $J=5.1$ and 1.2 Hz, 5'-H), 7.50 (d, 2H, $J=8.7$ Hz, 2'' and 6''-H), 7.88 (d, 2H, $J=8.7$ Hz, 3'' and 5''-H). MS (EI) m/z (%): 250 (M^+ , 100), 140 (5), 122 (16), 102 (11). HRMS: m/z (EI) for: $\text{C}_{15}\text{H}_{10}\text{N}_2\text{S}$; calcd 250.0565; found: 250.0566. The second component eluted was 5-(4''-cyanoanilino)-2,2'-bithiophene **3f** as a yellow solid (19 %). Mp 139.6-141.1 °C (ether). IR (Nujol) ν 3272 (NH), 2213 (CN) cm^{-1} . ^1H NMR (Acetone- d_6) δ 6.83 (d, 1H, $J=3.6$ Hz, 4-H), 7.08-7.12 (m, 1H, 4'-H), 7.13 (m, 3H, 3, 2'' and 6''-H), 7.24 (dd, 1H, $J=3.6$ and 1.2 Hz, 3'-H), 7.43 (dd, 1H, $J=5.1$ and 1.2 Hz, 5'-H), 7.63 (d, 2H, $J=8.7$ Hz, 3'' and 5''-H), 8.39 (br s, 1H, NH). MS (EI) m/z (%): 282 (M^+ , 100), 180 (11), 153 (6), 141 (5), 121 (7), 96 (11). HRMS: m/z (EI) for: $\text{C}_{15}\text{H}_{10}\text{N}_2\text{S}_2$; calcd 282.0285; found: 282.0288.

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