

A convenient and efficient conversion of 2-carboxyheteroarenes into *N*-(2-thienyl- and 2-selenophenyl)-1-methylpyrrole-2-carboxamides

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Abstract

Nitrogen-linked five-membered heteroaryls are obtained by conversion of 2-carboxyheteroarenes into *N*-(2-heteroaryl)-1-methylpyrrole-2-carboxamides. The procedure is based on a simple thermal rearrangement of thiophene or selenophene carbonyl azides in neat 1-methylpyrrole at 90 °C.

Keywords: Thermal rearrangement, carbonyl azides, thiophene

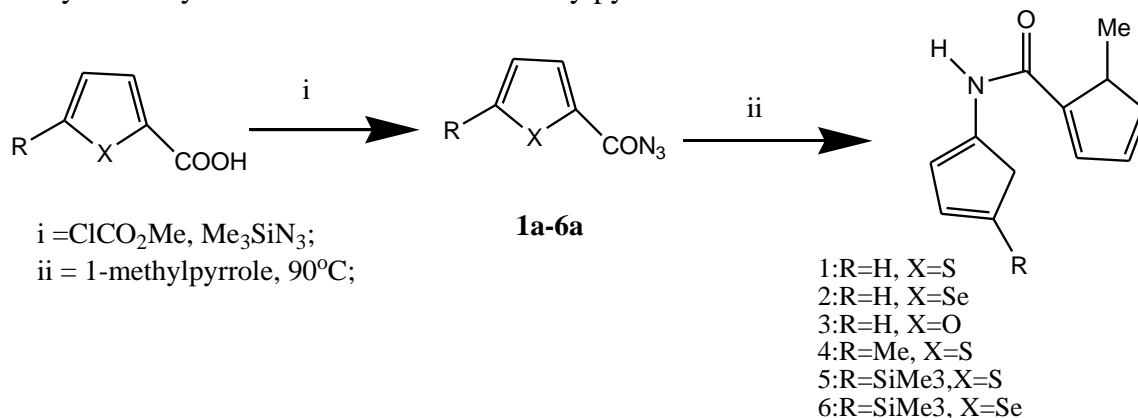
Introduction

Pseudohalides, as azide and isocyanate, are important functional groups in synthetic organic chemistry and have been widely used as regio- and stereo-controlled precursors of the amino function.¹ The azido transfer reaction of lithiated five-membered 2- and 3-heteroaryls with tosyl azide provides a convenient entry to the otherwise problematic nitrogen-linked heteroaryls containing one heteroatom² but, unfortunately, there are drawbacks.³ The 2-heteroaryl azides show a general tendency to suffer from a low-temperature ring cleavage fragmentation and are often only formed in low yield.⁴ The conversion of certain aryl isocyanates into amines has been investigated^{1c} and those derived from five-membered heteroaryls remain virtually unexplored, although their preparation is readily feasible from available carbonyl azido precursors.⁵

The literature contains a number of similar procedures for the conversion of heteroaryl isocyanates into amines,⁵ and these have been classified according to their stability. Most such procedures deal with the conversion of the initial isocyanate into amides under protic or Lewis acid conditions, or by the addition of organometallic reagents.⁶

In recent years thiophenecarbonyl azides, normally available from the corresponding carboxylic acid via the acyl chloride and trimethylsilyl azide, have been valuable materials in nitrogen-linked thiophene synthesis.⁷

As a continuation of our research on the synthesis of nitrogen-linked five-membered heteroaryls we now report an efficient conversion of 2-carboxyheteroarenes into *N*-(2-heteroaryl)-1-methylpyrrole-2-carboxamides. The procedure is based on a simple thermal rearrangement of heteroaryl carbonyl azides **1a-6a** in neat 1-methylpyrrole.



A number of synthetic analogues of the potent antitumoral *distamycin* and *netropsin* have been found to have excellent cytotoxicity and anticancer activity. The 1-methylpyrrole-2-carboxamides, formed by amino-heteroaryl derivatives, are of special interest as a potential nitrogen mustard of the *distamycin* type⁸ and the heteroaryl amide linkage might be considered to play a synergistic role on bioactivity.⁹

Results and Discussion

The starting carbonyl azides **1a-6a** were prepared in high yields (90-72%) from readily available carboxylic acids by the procedure developed by Weinstock,¹⁰ partially modified by using the less hazardous treatment of mixed carboxylic-carbonic anhydrides with trimethylsilyl azide instead of acyl chlorides and sodium azide.

Significantly 1-methyl-*N*-(2-thiophene)-(1), 1-methyl-*N*-(2-selenophene)-(2) and 1-methyl-*N*-(2-furano)-(3) -1*H*-pyrrole-2-carboxamide are obtained in good yields by mild thermal rearrangement (at 90°C) of the appropriate carbonyl azides **1a**, **2a** and **3a** in 1-methylpyrrole.

Table 1. Yields, physical features and IR, MS and δ_{H} NMR spectral data of carboxamides 1-6

| compd | Yield (%) | mp/ $^\circ\text{C}$ | IR(film) | | MS m/z (M ⁺) | $\delta(\text{ppm})200\text{MHz}$, CDCl_3 | | | | | | | |
|-------|-----------|----------------------|----------|------|-----------------------------|---|------|-------------------|------|------|-------------------|------|------|
| | | | NH | CO | | H-3 | H-4 | H-5 | H-3' | H-4' | H-5' | NH | Me |
| 1 | 83 | 170-72 | 3300 | 1635 | 206 | 6.70 | 6.88 | 6.87 ^a | 6.75 | 6.15 | 6.81 _e | 8.27 | 4.00 |
| 2 | 70 | 175-77 | 3295 | 1630 | 254 | 6.78 | 7.12 | 7.54 ^b | 6.75 | 6.16 | 6.81 _e | 8.58 | 4.00 |

| | | | | | | | | | | | | | |
|---|----|----------|----------|----------|-----|------|-------------------|-------------------|------|------|-------------------|------|----------------------------|
| 3 | 74 | resinous | 330 0 | 166 0 | 190 | 6.33 | 6.39 | 7.08 ^c | 6.70 | 6.13 | 6.79 _e | 7.96 | 3.97 |
| 4 | 68 | resinous | 323 0 | 163 0 | 220 | 7.64 | 6.78 ^d | - | 6.75 | 6.11 | 6.70 _e | 8.33 | 4.00 /2.52 ^f |
| 5 | 81 | res. oil | 329 5 | 163 0 | 278 | 6.75 | 6.98 ^d | - | 6.74 | 6.13 | 6.77 _e | 8.38 | 4.01 /0.30 ^g |
| 6 | 78 | res. oil | 330 0 | 163 5 | 326 | 6.90 | 7.31 ^d | - | 6.64 | 6.17 | 6.81 _e | 8.78 | 4.00 /0.32 ^g |

J are in Hz; ^a*J*_{Th} 5.5, 3.7, 1.5; ^b*J*_{Se} 6.1, 4.0, 1.3; ^c*J*_{Fu} 3.3, 2.0, 1.05; ^d*J*₃₄ 3.85; ^e*J*_{Py} 4.05, 2.6, 1.7; ^f Me, *J*_{Me-4} 1.0; ^g SiMe₃

This study was likewise extended to *para*-like substituted thiophene carbonyl azides **4a** and **5a** (R = Me, SiMe₃; X = S), and selenophene **6a** (R = SiMe₃; X = Se) (Scheme 1). The reactions of **1a-6a** were followed by GC-MS analysis. This analysis of the thermolysis mixtures supports the evidence that the rearrangement results almost exclusively in the formation of the corresponding methyl 1*H*-pyrrole-2-carboxamides **1-6** (*m/z* 206, 254, 190, 220, 278 and 326, respectively).

Products **1-6** were purified by chromatography and the precise structures were confirmed by: ¹H-, ¹³C-NMR, IR and high-resolution mass spectra (Table 1). The mass spectra (E.I 70 eV) exhibit appropriate molecular ions and a base peak corresponding to the favourable cleavage of the C-N amide bond to give the 1-methylpyrrole acyl cation (*m/z* 108) as the primary fragmentation product.

Moreover, the thermal reaction of **1a** also takes place in neat pyrrole affording a high yield of (2-thiophene)-1*H*-pyrrole-2-carboxamide, whose structural assignment was made on the basis of ¹H NMR spectroscopy as follows: δ_H (200 MHz, CDCl₃/ *J*/Hz) 7.15 (1H, m), 7.10 (1H, m), 7.02 (1H, q, *J* 5.4 and 1.6), 6.97 (1H, q, *J* 5.4 and 3.7), 6.92 (1H, q, *J* 3.7 and 1.6) and 6.29 (1H, m). The pyrrole ring protons were confirmed by D₂O exchange, giving a typical ABX system, *J* being 1.45, 2.50 and 3.75 Hz.

There is only one definite example of thermal attack of thiophenecarbonyl azide onto an adjacent pyrrole substituent. This is represented by intramolecular cyclization at 130 °C of 2-(1*H*-pyrrol-1-yl)-3-thiophenecarbonyl azide to pyrrolo[1,2-*a*]thieno[3,2-*e*]pyrazin-5-(4*H*)-one.¹¹ Consequently, our intermolecular thermal fragmentation of heteroaryl carbonyl azides most likely involves a mechanism that requires further investigation. Photochemical Curtius rearrangements are often characterised by the final presence of nitrene trapping by-products; however thermolysis is a concerted process, faster than nitrene formation.¹² On thermolysis of carbonyl azides **1a-6a** in 1-methylpyrrole, the resulting pyrrole-2-carboxamides are presumed to involve the intermediacy of the corresponding isocyanate. In this case, the successful outcome of such thermal reactions is ascribable to the pronounced acidic property of the pyrrole 2-proton.¹³

In conclusion, in the present report we have shown that the thermal rearrangement of chosen heteroarylcarbonyl azides in neat 1-methylpyrrole (or pyrrole) can be usefully employed in the preparation of a series of potentially bioactive pyrrole-*N*-(2-heteroaryl)-2-carboxamides.

Experimental Section

General Procedures. All reactions were carried out under nitrogen atmosphere. The ^1H - and ^{13}C -NMR spectra were recorded at 200 and 50 MHz. The chemical shifts are reported in ppm (δ) relative to TMS in CDCl_3 and J values are given in Hz. The IR spectra were recorded in cm^{-1} on a Perkin Elmer 257 and mass spectra were recorded on a VG Analytical 7070E instrument. Carboxylic acids were prepared according to the literature.¹⁴

1-Methyl-*N*-(2-thiophene)-1*H*-pyrrole-2-carboxamide (1). Typical procedure. A solution of 2-thiophenecarbonyl azide 1a (5 mmol) in 4 mL of neat 1-methylpyrrole was allowed to react in a sealed tube at 90 °C and in the dark for *ca.* 1 h. After careful removal of the excess 1-methylpyrrole under vacuum, the residue was purified by chromatography (Al_2O_3) using dry petroleum ether (bp. 40-60 °C)/diethyl ether (1:1) as eluant: ^{13}C NMR: 37.4(q, J 139.0), 108.1(d, J 173.8), 111.9(d, J 167.0), 112.7(s), 113.0(d, J 168.6), 118.0(d, J 186.5), 124.3(d, J 168.3), 129.6(d, J 184.5), 139.5(s), 158.4(s). m/z , 206(M^+ , 26.0%), 108($\text{M}-98$, 100), 80(7.4), 53(17.1), 39(16.2) (Found: M^+ , 206.0514, $\text{C}_{10}\text{H}_{10}\text{N}_2\text{OS}$ requires M , 206.0514).

1-Methyl-*N*-(2-selenophene)-1*H*-pyrrole-2-carboxamide (2). ^{13}C NMR: 37.4(q, J 140.5), 108.2(d, J 173.9), 111.8(d, J 163.3), 112.7(s), 112.9(d, J 168.5), 123.2(d, J 187.0), 126.3(d, J 163.1), 129.7(d, J 189.5), 141.7(s), 158.1(s). m/z , 254(M^+ , 13.6%), 108($\text{M}-146$, 100), 80(6.5), 53(17.6), 39(12.3) (Found: M^+ , 253.9958, $\text{C}_{10}\text{H}_{10}\text{N}_2\text{OSe}$ requires M , 253.9958).

1-Methyl-*N*-(2-furano)-1*H*-pyrrole-2-carboxamide (3). ^{13}C NMR: 37.3(q, J 140.0), 95.6(d, J 182.5), 108.1(d, J 174.0), 112.0(d, J 175.0), 113.2(d, J 168.5), 113.5(s), 129.6(d, J 184.5), 135.9(d, J 205.1), 145.8(s), 158.2(s). m/z , 190(M^+ , 17.5%), 108($\text{M}-82$, 100), 80(7.0), 53(13.6), 39(11.2) (Found: M^+ , 190.0741, $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$ requires M , 190.0742).

1-Methyl-*N*-(5-methyl-2-thiophene)-1*H*-pyrrole-2-carboxamide (4). ^{13}C NMR: 15.2(q, 128.9), 37.3(q, J 140.4), 108.0(d, J 173.5), 112.1(d, J 163.6), 112.8(d, J 168.8), 114.0(s), 121.9(d, J 165.5), 129.3(d, J 184.2), 134.5(s), 151.4(s), 158.4(s). m/z , 220(M^+ , 26.6%), 108($\text{M}-112$, 100), 80(7.8), 53(18.7), 39(14.6) (Found: M^+ , 220.0670, $\text{C}_{11}\text{H}_{12}\text{N}_2\text{OS}$ requires M , 220.0670).

1-Methyl-*N*-(5-trimethylsilyl-2-thiophene)-1*H*-pyrrole-2-carboxamide (5). ^{13}C NMR: 0.2(q, 119.7), 37.3(q, J 140.3), 108.1(d, J 173.8), 111.9(s), 113.1(d, J 168.8), 113.5(d, J 165.3), 129.6(d, J 184.2), 131.5(d, J 165.9), 144.4(s), 158.4(s). m/z , 278(M^+ , 21.4%), 108($\text{M}-170$, 100), 73(12.6), 57(6.5), 53(10.7), 39(9.0) (Found: M^+ , 278.0909, $\text{C}_{13}\text{H}_{18}\text{N}_2\text{OSSi}$ requires M , 278.0909).

1-Methyl-*N*-(5-trimethylsilyl-2-selenophene)-1*H*-pyrrole-2-carboxamide (6). ^{13}C NMR: 0.7(q, 119.9), 37.4(q, J 140.3), 108.3(d, J 173.7), 111.9(s), 113.0(d, J 168.6), 113.9(d, J 162.1), 129.8(d, J 187.5), 133.5, (d, J 165.9), 146.3(s), 158.1(s). m/z , 326(M^+ , 21.4%), 108($\text{M}-218$, 100), 73(12.6), 53(10.7), 39(9.0) (Found: M^+ , 326.0355, $\text{C}_{13}\text{H}_{18}\text{N}_2\text{OSeSi}$ requires M , 326.0354).

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