LABELLED COMPOUNDS OF INTEREST AS ANTITUMOUR AGENTS - VI[1]. ISOTOPICALLY EFFICIENT SYNTHESES OF [^{15}N]-NITROTHIOPHENECARBOXAMIDES

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SUMMARY

Reaction of 3-cyanothiophene with one equivalent of potassium nitrate in concentrated sulphuric acid causes nitration, concurrent with hydrolysis of the nitrile, to give 5-nitrothiophene-3-carboxamide in high yield. Similarly, 2-cyanothiophene gives 4-nitrothiophene-2-carboxamide and 5-nitrothiophene-2-carboxamide, benzonitrile gives 3-nitrobenzamide and 4-methylbenzonitrile gives 4-methyl-3-nitrobenzamide. Extension of this process to use of potassium [^{15}N]-nitrate, formed from [^{15}N]-nitric acid (95% isotopic enrichment), enables preparation of the corresponding [^{15}N]-nitrothiophenecarboxamides in high isotopic yield.

Introduction

As part of a programme of synthesis and evaluation of nitro-heterocycles as radiosensitisers, bioreductively-activated cytotoxins and inhibitors of repair of DNA[2-6], we required the three possible isomeric nitro-thiophene-carboxamides with the functional groups in the 'meta' relationship. These compounds can be regarded as heterocyclic analogues of 3-nitrobenzamide. We also required the corresponding [^{15}N]-nitro compounds for metabolic and other studies. Thiophenes are usually nitrated using acetyl nitrate in acetic acid or acetic anhydride[7-9], the nitric acid required for the formation of the reagent being taken in excess. Excess nitric acid in concentrated sulphuric acid has been used by Campaigne and Monroe[10] to form 5-nitrothiophene-3-carboxamide **2c** from thiophene-3-carboxamide. Both processes would be inefficient if applied to a ^{15}N-labelled synthesis. However, nitration of thiophene-2-carboxamide to form solely 4-nitrothiophene-2-carboxamide **2c** in high

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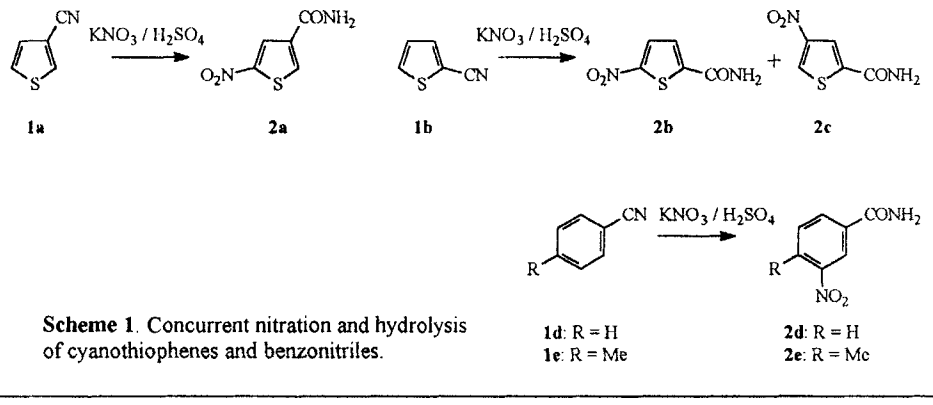


Scheme 1. Concurrent nitration and hydrolysis of cyanothiophenes and benzonitriles.

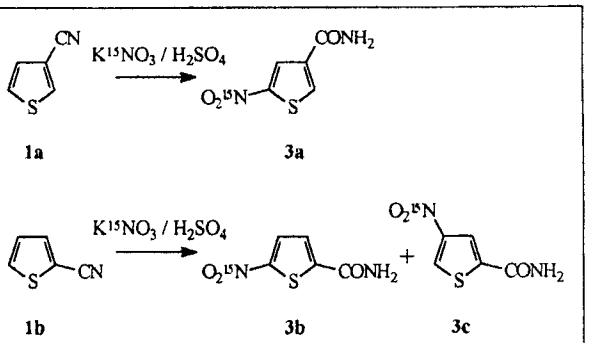
yield, using only one equivalent of potassium nitrate, has been reported by Dell'Erba *et al.*[7] Similarly, Östman[11] has described efficient nitration of 3-cyanothiophene **1a** and 2-cyanothiophene **1b** with one equivalent of nitric acid in trifluoroacetic acid, although mixtures of isomers of the corresponding cyanonitrothiophenes were produced. In this paper, we report our development of a method for direct conversion of cyano(hetero)arenes to nitro(hetero)arenecarboxamides.

Results and Discussion

The initial approach to development of potential isotopically efficient syntheses of the isomeric nitrothiophene-carboxamides was to investigate a two-step sequence from 3-cyanothiophene **1a** and 2-cyanothiophene **1b**, involving nitration, followed by hydrolysis of the nitrile. However, since the method of Östman[11] (HNO_3 / CF_3CO_2H) gives mixtures of isomers of cyanonitrothiophenes, the method of Dell'Erba[7] was applied to the cyanothiophenes **1a,b**. Unexpectedly, treatment of 3-cyanothiophene **1a** in concentrated sulphuric acid with one equivalent of potassium nitrate gave 5-nitrothiophene-3-carboxamide **2a** in 91% yield, rather than the corresponding nitrile, as shown in Scheme 1. No cyanonitrothiophenes were isolated. Clearly, the vigorously acidic conditions had been sufficient to hydrolyse the nitrile to the carboxamide. Application of this process to 2-cyanothiophene **1b** gave a mixture of 5-nitrothiophene-2-carboxamide **2b** and 4-nitrothiophene-2-carboxamide **2c** in good yield in *ca.* 4:3 ratio. These were easily separable by chromatography. No cyanonitrothiophenes were evident in the product mixture. The process was extended to the benzene series by high-yielding direct conversions of benzonitrile **1d** to 3-nitrobenzamide **2d** and 4-methylbenzonitrile **1e** to 4-methyl-3-nitrobenzamide **2e**.

For the syntheses introducing ^{15}N, potassium [^{15}N]-nitrate was prepared by neutralisation of [^{15}N]-nitric acid (95 atom %) with the calculated amount of potassium carbonate in water, followed by removal of the solvent by freeze-drying. Addition of this material to 3-cyanothiophene **1a** in concentrated sulphuric acid gave 5-[^{15}N]-nitrothiophene-3-carboxamide **3a** in excellent chemical and

isotopic yields (82%), as shown in Scheme 2. Similar [^{15}N]-nitration of **1b** gave satisfactory chemical yields of the isomeric [^{15}N]-nitrothiophene-carboxamides **3b,c**, after chromatographic separation. The total isotopic yield for this process was 52%.



Scheme 2. Synthesis of [^{15}N]-nitrothiophene-carboxamides.

The ^{15}N-labelled isotopomers **3a-c** were characterised by comparison of spectra and mpts with those of the unlabelled materials **2a-c**. In addition, ^{15}N NMR and mass spectrometry demonstrated that each product contained only one ^{15}N, as required. The ^{15}N NMR signals all appeared in the range δ 365 to δ 368, as appropriate for Ar^{15}NO$_2$. No coupling of ^{15}N to other nuclei was seen in the ^{15}N spectra, probably owing to insufficient digital resolution. However, couplings to ^{15}N were observed through ^{1}H and ^{13}C spectra. In the 5-nitrothiophene-3-carboxamide **3a**, ^{15}N coupled to protons on the thiophene ring with the three-bond coupling constant ^{3}J = 1.1 Hz. In contrast, ^{15}N-^{1}H coupling was only evident to the 3-H in **3c** and to the 4-H in **3c**, with ^{3}J = 1.1 Hz in both cases. One-bond ^{15}N-^{13}C coupling was clearly seen for all three compounds, with ^{1}J = *ca.* 20 Hz. The only three-bond ^{15}N-^{13}C coupling was in the spectrum of **3a**, between ^{15}N in the nitro group and the quaternary carbon 3-C bearing the carboxamide; ^{3}J = 3.7 Hz.

Conclusion

Direct rapid one-pot conversions of cyanothiophenes to nitrothiophene-carboxamides and of benzonitriles to 3-nitrobenzamides have been developed. In the thiophene cases, these have been extended to provide highly isotopically efficient syntheses of [^{15}N]-nitrothiophene-carboxamides. The source of ^{15}N is potassium [^{15}N]-nitrate, which is derived from the readily available and inexpensive [^{15}N]-nitric acid. This technique may have more general applications in introduction of ^{15}N in syntheses using stoichiometric amounts of [^{15}N]-reagents.

Experimental

[^{15}N]-Nitric acid (95 atom %, ca. 5 M) was purchased from MSD Isotopes. Infra-red spectra were obtained using potassium bromide discs. Jeol GX270 and EX400 instruments furnished the NMR spectra of solutions in $(CD_3)_2SO$. The ^{15}N chemical shifts are referenced externally to [^{15}N]-ammonium nitrate (2.9 M in 1.0 M aqueous hydrochloric acid: δ_N +24.90)[12]. Mass spectra were

obtained in the electron impact (EI) mode, except where noted. Melting points are uncorrected. Solvents were evaporated under reduced pressure. The chromatographic stationary phase was silica gel.

5-Nitrothiophene-3-carboxamide (2a). Potassium nitrate (1.85 g, 18.3 mmol) was added to 3-cyanothiophene **1a** (2.00 g, 18.3 mmol) in concentrated sulphuric acid (20 ml). The mixture was stirred at ambient temperature for 16 h before being poured onto ice and extracted with ethyl acetate. The extract was washed with water and with 10% aqueous sodium carbonate and was dried ($MgSO_4$). Evaporation and recrystallisation (ethanol) gave 5-nitrothiophene-3-carboxamide **2a** (2.86 g, 91%) as a pale buff solid: mp 161-162°C (lit.[13] mp 162-163°C); ν_{max} 3450, 3300, 1700, 1670 cm^{-1}; δ_H 7.63 (1 H, s, NH), 8.11 (1 H, s, NH), 8.47 (1 H, d, J = 0.8 Hz, 2-H), 8.51 (1 H, d, J = 0.8 Hz, 4-H); δ_C 128.11, 136.66, 136.90, 151.19, 161.85; *m/z* 172 (M).

5-Nitrothiophene-2-carboxamide (2b) and 4-nitrothiophene-2-carboxamide (2c). 2-Cyanothiophene **1b** was treated with potassium nitrate and concentrated sulphuric acid, as for the synthesis of **2a**. Chromatography (hexane / ethyl acetate 3:2) gave 4-nitrothiophene-2-carboxamide **2c** (41%) as a white solid: mp 151-152°C (lit.[7] mp 152-153°C); ν_{max} 3480, 1715, 1620 cm^{-1}; δ_H 7.82 (1 H, s, NH), 8.33 (1 H, s, NH), 8.42 (1 H, d, J = 1.5 Hz, 5-H), 8.94 (1 H, d, J = 1.5 Hz, 3-H); *m/z* 172 (M). From later fractions was obtained 5-nitrothiophene-2-carboxamide **2b** (32%) as a white solid: mp 191-193°C (compound reported by Occhipinti *et al.*[14] and by Johnson *et al.*[15] but no mp given); ν_{max} 3460, 1660, 1620 cm^{-1}; δ_H 7.79 (1 H, d, J = 4.4 Hz, 3-H), 7.99 (1 H, s, NH), 8.14 (1 H, d, J = 4.4 Hz, 4-H), 8.45 (1 H, s, N-H); *m/z* 172 (M).

3-Nitrobenzamide (2d). Benzonitrile **1d** was treated with potassium nitrate and concentrated sulphuric acid, as for the synthesis of **2a**, to give 3-nitrobenzamide **2d** (73%) as an pale orange solid: mp 136-138°C (lit.[16] mp 142-143°C); ν_{max} 3460, 3350, 1695, 1625 cm^{-1}; δ_H 7.75 (1 H, s, NH), 7.78 (1 H, t, J = 7.7 Hz, 5-H), 8.32 (1 H, dd, J 8.8, 1.1 Hz, 6-H), 8.37 (1 H, s, NH), 8.39 (1 H, ddd, J = 1.1, 1.5, 8.6 Hz, 4-H), 8.70 (1 H, *ca.* t, J *ca.* 1.5 Hz, 2-H); δ_C 122.24, 125.89, 130.06, 133.81, 135.77, 147.80, 165.71; *m/z* 166 (M).

4-Methyl-3-nitrobenzamide (2e). 4-Methylbenzonitrile **1e** was treated with potassium nitrate and concentrated sulphuric acid, as for the synthesis of **2a**, to give 4-methyl-3-nitrobenzamide **2e** (96%) as an off-white solid: mp 161-163°C (lit.[17] mp 168-169°C); ν_{max} 3450, 1685, 1615 cm^{-1}; δ_H 2.57 (3 H, s, Me), 7.61 (1 H, d, J = 8.1 Hz, 5-H), 7.65 (1 H, s, NH), 8.13 (1 H, dd, J = 7.7, 1.8 Hz, 6-H), 8.24 (1 H, s, NH), 8.47 (1 H, d, J = 1.8 Hz, 2-H); δ_C 19.54, 123.45, 131.89, 133.03, 133.44, 135.95, 148.84, 165.69; *m/z* (CI) 181 (M + H).

5-[^{15}N]-Nitrothiophene-3-carboxamide (3a). Potassium [^{15}N]-nitrate (79 mg, 0.77 mmol, 95 atom %) was added to 3-cyanothiophene **1a** (840 mg, 0.77 mmol) in concentrated sulphuric acid (1.0 ml). Isolation, as for the synthesis of **2a**, gave 5-[^{15}N]-nitrothiophene-3-carboxamide **3a** (110 mg, 82%) as a pale buff solid: mp 158-160°C (lit.[13] mp 162-163°C for **2a**); δ_H 7.62 (1 H, s, NH), 8.10 (1 H, s, NH), 8.46 (1 H, dd, $J_{H\text{-}H}$ = 1.8 Hz, $J_{H\text{-}N}$ = 1.1 Hz, 4-H), 8.51 (1 H, dd, $J_{H\text{-}H}$ = 1.8 Hz, $J_{H\text{-}N}$ = 1.1 Hz, 2-H); δ_C 128.05, 136.59 (d, $^3J_{C\text{-}N}$ = 3.7 Hz, 3-C), 136.85, 151.10 (d, $^1J_{C\text{-}N}$ = 20.3 Hz, 5-C), 161.79; δ_N +365.07; *m/z* (EI) 173 (M).

5-[^{15}N]-Nitrothiophene-2-carboxamide (3b) and 4-[^{15}N]-nitrothiophene-2-carboxamide (3c). Potassium [^{15}N]-nitrate (280 mg, 2.75 mmol, 95 atom %) was added to 2-cyanothiophene **1b** (840 mg, 0.77 mmol) in concentrated sulphuric acid (1.0 ml). Isolation and purification, as for the synthesis of **2b,c**, gave 4-[^{15}N]-nitrothiophene-2-carboxamide **3c** (180 mg, 38%) as a pale buff solid: mp 151-152°C (lit.[7] mp 152-153°C for **2c**); δ_H 7.80 (1 H, s, NH), 8.32 (1 H, s, NH), 8.40 (1 H, d, J = 1.5 Hz, 5-H), 8.93 (1 H, dd, $J_{H\text{-}H}$ = 1.5 Hz, $J_{H\text{-}N}$ = 1.1 Hz, 3-H); δ_C 122.49, 133.16, 141.48, 147.07 (d, $^1J_{C\text{-}N}$ = 18.4 Hz, 4-C), 161.32; δ_N +367.48; *m/z* (EI) 173 (M). Further elution gave 5-[^{15}N]-nitrothiophene-2-carboxamide **3b** (69 mg, 14%) as an off-white solid: mp 188-190°C; δ_H 7.78 (1 H, d, J = 4.4 Hz, 3-H), 7.98 (1 H, s, NH), 8.14 (1 H, dd, $J_{H\text{-}H}$ = 4.4 Hz, $J_{H\text{-}N}$ = 1.1 Hz, 4-H), 8.44 (1 H, s, NH); δ_C 127.87 (d, $^3J_{C\text{-}N}$ = 3.7 Hz, 2-C), 130.27, 146.93, 152.93 (d, $^1J_{C\text{-}N}$ = *ca.* 20 Hz, 5-C), 161.30; δ_N +367.52; *m/z* (EI) 173 (M).

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