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Dyes Derived from Aminothiophenes. Part 4: Synthesis of Some Nitro-substituted Thiophene-based Azo Disperse Dyes

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ABSTRACT

A series of thienylazo dyes has been prepared from nitro-substituted 2- and 3-aminothiophenes; colorants from the former were reddish–blue to green, whereas those from the latter were yellow to orange. The 2-aminothiophenes were obtained either by the amination of an activated chlorothiophene or by the functionalisation of thiophenes synthesised using the Gewald reaction. The thienyl-3-azo dyes were prepared from derivatised 3-amino-2-methoxycarbonylthiophenes. The ^{13}C NMR chemical shifts of a nitrothienyl-2-azo dye are reported together with those of a 5-nitrothiazolyl-2-azo analogue.

Keywords: Aminothiophenes, heterocycle azo dyes, synthesis, disperse dyes, ^{13}C NMR spectra.

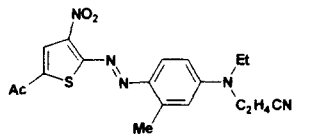
1. INTRODUCTION

While nitrothienylazo disperse dyes have been known for around 40 years,[1] their commercial exploitation as replacements for blue anthraquinone disperse dyes[2,3] has occurred only over the last two decades. The first investigations into monoazo dyes based on 2-amino-5-nitrothiazole[4] and 5-acetyl-2-amino-3-nitrothiophene[1] by Eastman Kodak in the 1950s found that these colorants had commercially desirable bathochromism and performance. However, whereas the marketing of thiazolylazo dyes followed, the use of the thienylazo derivatives was not viable industrially owing to the unfavourable economics

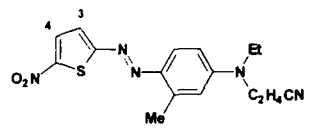
of the available chemistry,[3,5] which involved the ammonolysis of activated halothiophenes. It appears that nitrothiophene-derived dyes were not manufactured until the early 1970s when ICI developed an economic Gewald-based synthesis of 2-amino-3,5-dinitrothiophene.[6,7] Much patent activity ensued, especially concerning dyes derived from the dinitro component, and interest in 5-acyl-3-nitrothienylazo dyes was revived by the disclosure of a new route to the diazo component.[3,7]

Despite the success of nitrothienyl-2-azo disperse dyes, very little specific information exists outside the patent literature that is pertinent to the synthesis of such colorants.[8,9,10,11] Preparative details concerning nitrothienyl-3-azo dyes are scarcer still.[12,13]

This paper reports the synthesis of an example, **1**, of the earliest nitrothienyl type together with some of the later generation of analogues, **2**, whose diazo components were obtained via Gewald chemistry. The 5-nitrothiazolyl-2-azo dye **3** was prepared for comparative purposes. The dyes were obtained from a coupler, *N*-2-cyanoethyl-*N*-ethyl-*m*-toluidine, typically utilised in the manufacture of polyester colorants; two of the diazo components were also used to synthesise the dyes **4**, prepared from a coupler commonly employed in the production of bathochromic dyes for polyester. Three thienyl-3-azo dyes **5**, isomeric with either **2** (3-CO_2Me) or **2** (3-CO_2Me-4-Me), were prepared.

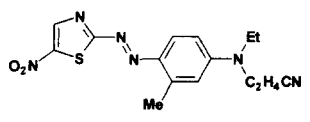


1



2

3 = CO_2Me, CO_2Et, CO_2Bu, NO_2
4 = H, Me



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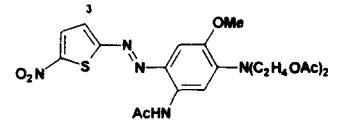

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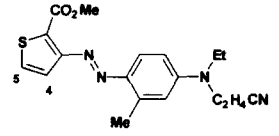
3 = CO_2Me, NO_2



5

4 = H, Me, NO_2
5 = H, NO_2

2. RESULTS AND DISCUSSION

2.1. Preparation of the diazo components

The procedure of Dickey *et al.* for the synthesis of 5-acetyl-2-amino-3-nitrothiophene[1] was used with one modification. Marsden[14] noted that their method of nitration of 5-acetyl-2-chlorothiophene by addition of the material to mixed acid gave 2-chloro-3,5-dinitrothiophene, and that the desired 5-acetyl-2-chloro-3-nitrothiophene could be prepared instead by adapting the method of Hurd and Kreuz[15] in which mixed acid was added to the thiophene derivative. The latter process was employed successfully in this investigation, furnishing a product which could be aminated by nucleophilic substitution as reported by Dickey *et al.*[1]

The first step in the preparation of the 2-amino-5-nitrothiophene-based diazo components was the synthesis of the relevant 2-aminothiophenes using the Gewald reaction (see Fig. 1). The amino group of each compound was first protected by an acetyl group, the products were nitrated in mixed acid and the acyl group was then removed by hydrolysis in acidic alcohol. The method proved to be satisfactory for all but the 3-cyano derivative.

An attempt at preparing 2-acetylamino-3-cyanothiophene from 2-amino-3-carbamylthiophene after Robba *et al.*[16] by simultaneous *N*-acetylation and dehydration in acetic anhydride failed, even when large excesses, extended times and continuous removal of acetic acid by distillation were employed; the *N*,*N*′-diacetylated derivative **6** was obtained instead. (As shown in Fig. 1, **6** was nitrated and hydrolysed to 2-amino-3-carbamyl-5-nitrothiophene like the monoacetylated derivative.) *N*-Acetylation of 2-amino-3-cyanothiophene, prepared by the Gewald synthesis, was successful. Nitration of this compound in mixed acid caused hydration of the cyano group to give 2-acetylamino-3-carbamyl-5-nitrothiophene; a similar conversion, the hydration of 2-amino-3-ethoxycarbonyl-4-methyl-5-cyanothiophene to the 5-carboxamide over 24 h in concentrated sulphuric acid at 0°C, is known.[17] Nitration was performed without attack on the cyano group by using a modification of a patent method utilising nitric acid in an acetic acid/acetic anhydride mixture at an elevated temperature.[18] Unfortunately, the cyano group was hydrated when the product was heated with ethanolic sulphuric acid (1%) to hydrolyse the acetylamino group in the same manner as the other 5-nitro derivatives: analysis by thin layer chromatography (TLC), differential scanning calorimetry (DSC) and Fourier transform IR (FTIR) indicated that 2-amino-3-carbamyl-5-nitrothiophene had been obtained.

Derivatisation of 2-amino-3-methoxycarbonyl-5-nitrothiophene was undertaken: transesterification through refluxing the ester in an excess of the alcohol corresponding to the target ester with titanium isopropoxide under

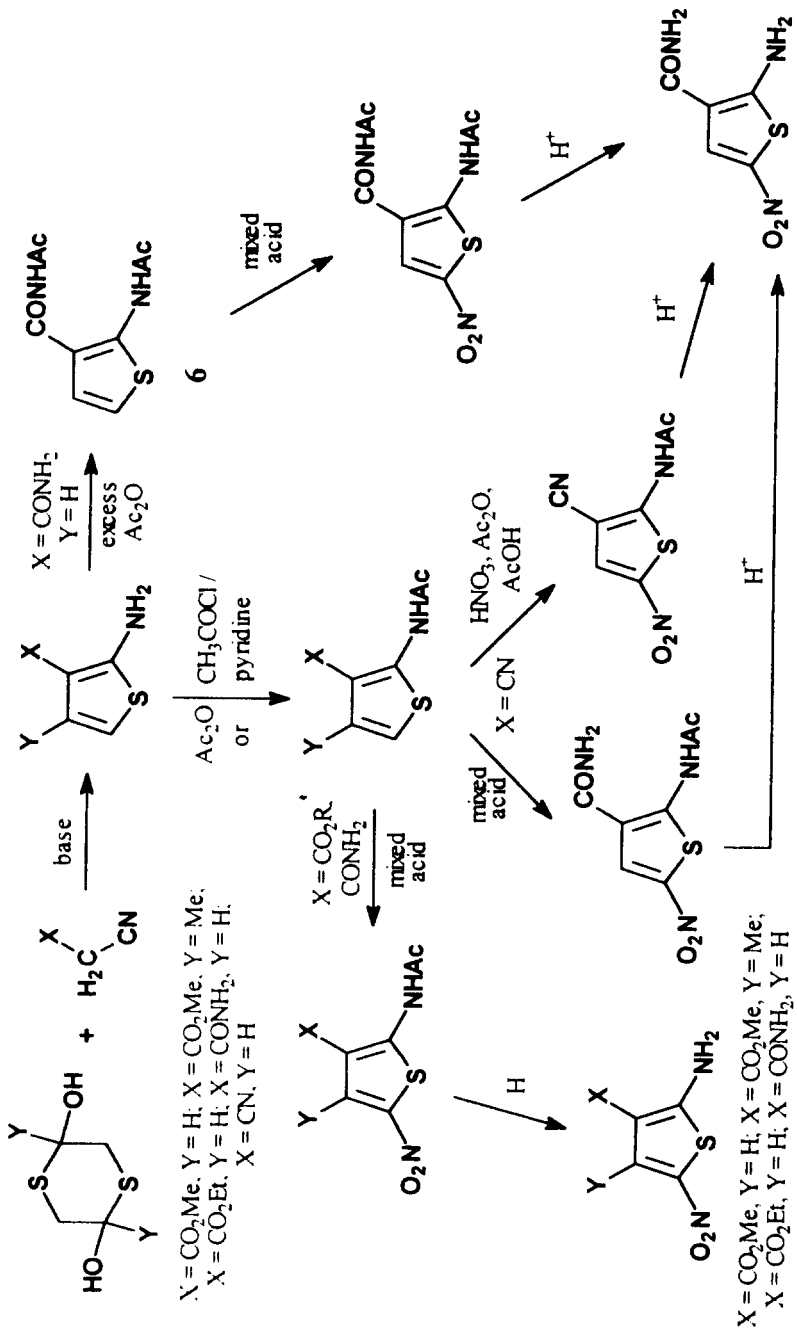


Fig. 1. Synthetic routes to the 2-amino-3-substituted-5-nitrothiophenes.

nitrogen is useful because of the mild conditions involved.[19] Conversion to the butyl ester was successful, but not to the ethyl ester, presumably because of the higher boiling point of the solvent in the former case and the consequent reflux temperature. The ethyl ester was instead prepared from derivatisation of 2-amino-3-ethoxycarbonylthiophene prepared by the Gewald synthesis (see Fig. 1).

Three nitro-substituted 3-aminothiophenes were obtained from 3-amino-2-methoxycarbonylthiophene and 3-amino-2-methoxycarbonyl-4-methylthiophene (see Fig. 2). The former compound was *N*-acetylated and nitrated to give an isomeric mixture; NMR evidence suggested that the 5-nitro derivative accounted for about 70% of the crude product (see Fig. 2a). Acid hydrolysis and column chromatography yielded the 5-nitro and 4-nitro isomers in a proportion of roughly 4:1, respectively.

The other precursor was not *N*-acetylated successfully with an excess of refluxing acetic anhydride (as opposed to the former, possibly because of steric hindrance by the methyl group) although acetyl chloride in pyridine proved satisfactory. 3-Amino-2-methoxycarbonyl-4-methyl-5-nitrothiophene was otherwise obtained similarly with little difficulty in high yield (see Fig. 2b).

2.2. Preparation of the dyes

Each diazo component was diazotised satisfactorily using nitrosylsulphuric acid, with one exception; the yield and purity of **2** (3-$CONH_2$) was so poor that purification was not attempted. Since a method for the synthesis of 1,2,3-triazin-4-ones involves diazotisation of aryl[20] and hetaryl[21] *o*-amino-carboxamides, which undergo cyclisation in an intramolecular self-coupling reaction, it is conceivable that such a side reaction may occur during the diazotisation of 2-amino-3-carbamyl-5-nitrothiophene, especially as

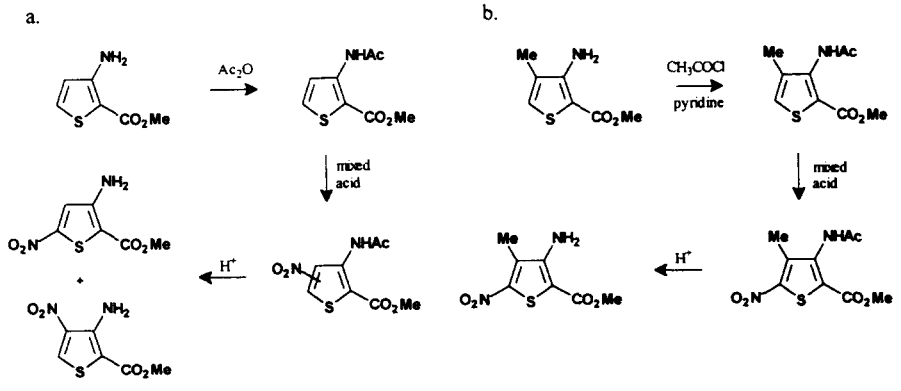


Fig. 2. Synthetic routes to the nitro-substituted 3-aminothiophenes.

thieno[2,3-*d*]-1,2,3-triazin-4-ones have been prepared from 2-amino-3-carbamylthiophenes[22] (see Fig. 3). The crude dye **2** (3-$CONH_2$) could possibly contain a triazinone impurity, which may partly explain the relatively low yield of this dye (and its previously described[23] 4,5-tetramethylene analogue).

Purification of the dyes involved a combination of digestion, recrystallisation and column chromatography. The solubilities of the thienyl-2-azo dyes were generally so low as to make column chromatography unfeasible so that dyes such as **2** (3-CO_2Me) and **2** (3-NO_2) were digested in hot solvent to remove impurities, most of which were more soluble than the dyes themselves, and then recrystallised. An exception was **2** (3-CO_2Bu) whose butyl group conferred enough solubility to make this process inefficient; fortunately, the increase in solubility made column chromatography viable.

Qualitatively, the 3-aminothiophenes gave dyes with fewer impurities than the corresponding 2-amino analogues. A similar trend was observed between the crude thiazole dye **3** and its thiophene analogues, the former being in a purer state.

2.3. Physical properties of the dyes

When examined by TLC (silica), the hetaryl-2-azo dyes furnished red-blue to green spots, whereas the thienyl-3-azo dyes were yellow to orange and produced spots of slightly higher R_f values; this finding is consistent with the dyes being of lower polarity than their thienyl-2-azo analogues.

2.3.1. Melting points

The melting points of the purified dyes, as expected for pure compounds, were sharp and well-defined (see Table 1). Despite the complex dependence

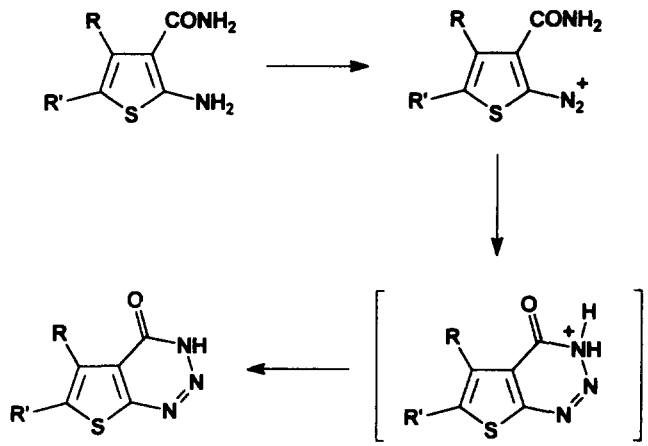


Fig. 3. Thieno[2,3-*d*]-1,2,3-triazin-4-one formation.

of melting point on a variety of factors, the influence of structure can be identified in a few instances.

The dyes generally had higher melting points than their counterparts lacking nitro groups, which can be ascribed to their greater polarity; for example, replacing the nitro group of **1** with a methoxycarbonyl function lowers the melting point from 228–230°C to 174.5–175°C.[24]

Of the isomeric methoxycarbonylnitrothienyl dyes, **2** (3-CO_2Me) had the highest melting point (246–246.5°C), followed by **5** (5-NO_2) with 203–203.5°C and **5** (4-NO_2), whose relatively low melting point (101.5–102°C) could possibly be a result of the non-planarity of the molecule caused by steric interaction between the *ortho* groups on the thiophene ring and the azo group. The introduction of a methyl group into **5** (5-NO_2) caused a

TABLE 1
Methods of Synthesis and Purification of the Thiophene-derived Dyes

Dye	*Molarity (mmol)*	*Crude yield (g/%)*	*Purification method*	*Pure yield (g/%)*	*%s*	*Appearance*	*m.p. (°C)*
1	10	3.34/87	$\Delta\alpha\alpha$	0.21/5	–	dark green crystalline powder	228–230
2 (3-CO_2Me)	10	3.66/91	$\eta^d\eta^d\alpha\alpha$	0.51/13	38/35	shiny green leaflets	246–246.5
2 (3-CO_2Me-4-Me)	5.0	1.53/74	$\eta^d\eta^d\alpha^d\alpha\alpha\eta\alpha$	0.35/17	23	shiny yellow–green crystals	226.5–227
2 (3-CO_2Et)	5.0	1.75/84	$\eta^d\eta^d\eta^d\alpha\alpha\eta\alpha\alpha$	0.86/41	49	fine blue needles	202.5
2 (3-CO_2Bu)	5.0	1.94/87	$\Delta\eta$	0.22/10	71/62	fine blue needles	162–162.5
2 (3-NO_2)	9.0	2.31/66	$\eta^d\eta^d\alpha\eta\eta\beta\beta$	0.25/7	11	shiny blue leaflets	225–225.5
3	144	46.14/93	$\eta\eta\eta\eta\eta$	0.71/1	36/33	dark blue crystalline powder	215–216
4 (3-CO_2Me)	10	4.39/78	$\eta^d\eta\eta\gamma\delta\eta$	1.68/30	67/52	shiny green fibrous solid	167–168
4 (3-NO_2)	10	2.76/50	$\eta^d\eta^d\eta^d\eta^d\delta\eta$	0.40/7	16/8	green crystalline solid	164–165
5 (4-Me-5-NO_2)	7.5	2.74/88	$\varepsilon\varepsilon$	1.94/62	71	very dark red crystalline clumps	143–144
5 (5-NO_2)	7.5	2.70/90	$\eta\eta$	0.98/33	51/46	shiny purple leaflets	203–203.5
5 (4-NO_2)	0.35	0.13/95	$\lambda\theta$	0.07/50	54	shiny dark red crystals	101.5–102

[d]denotes digestion treatment.

significant reduction in melting point to 143–144°C; this change may have arisen through a similar effect as the dye has two groups on the heterocyclic ring *ortho* to the azo group. The equivalent introduction in **2** (3-CO_2Me) did not cause a large effect because the methyl group is not *ortho* to the azo link. Consequently, while the melting point was lowered (to 226.5–227°C), the reduction was much smaller.

It has been noted that increasing the chain length in 5-alkylthienyl-2-azo dyes reduces the melting point,[24] presumably by making packing less efficient; similarly, lengthening the ester group of **2** (3-CO_2Me) causes a reduction in melting point from 246–246.5°C to 202.5°C for the ethyl analogue, and to 162–162.5°C for the butyl ester.

2.3.2. ^{13}C NMR spectra

The ^{13}C NMR spectral data of **2** (3-CO_2Et) and **3** are shown in Fig. 4. The chemical shifts are consistent with those previously reported for *N*-2-cyanoethyl-*N*-ethyl-*m*-toluidine-based thienylazo[24] and phenylazo[25] dyes; the number of observed peaks in the spectrum of **3** was one lower than expected. (The low solubility of **2** (3-NO_2) defeated attempts to obtain the spectrum of this dye.)

3. EXPERIMENTAL

Chromatography, thermal analysis and FTIR spectroscopy were performed as described previously.[23] Melting points were determined using an Electrothermal melting point apparatus and were uncorrected. ^1H NMR spectra quoted to one decimal place were obtained using a Perkin–Elmer 60 MHz machine and to two places on a Jeol 200 MHz machine, which was also used

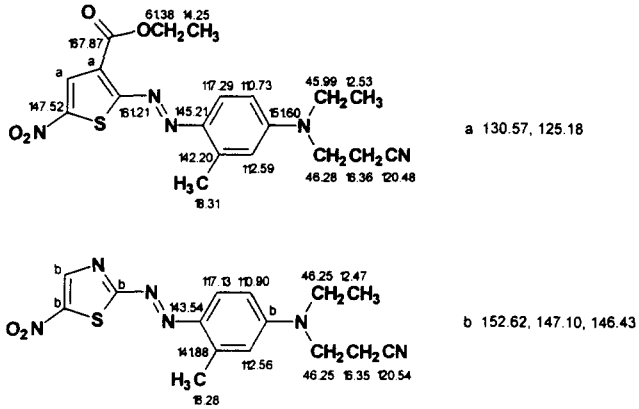


Fig. 4. ^{13}C NMR chemical shifts of the dyes **2** (3-CO_2Et) and **3** in deuterochloroform.

to record ^{13}C NMR spectra. Microanalyses were carried out in the Department of Chemistry at the University of Leeds.

3.1. Preparative details of the intermediates

Commercial samples of 2-amino-5-nitrothiazole (YCL) and 2-amino-3,5-dinitrothiophene (ICI) were used without further purification, and after refinement by Soxhlet extraction with acetone, respectively. All other diazo components were prepared as detailed below. The coupling components were industrial samples as described previously.[23]

3.1.1. 5-Acetyl-2-amino-3-nitrothiophene

Mixed acid, prepared from fuming nitric ($d = 1.50$, 6.3 g) and sulphuric (98%, 7.0 g) acids, was added to a solution of 2-acetyl-5-chlorothiophene[1,26] (11.13 g, 0.07 mol) in sulphuric acid (98%, 21 ml) over 35 min at 3–6°C. The chocolate-brown mixture was stirred for 5 min before cautiously pouring into ice. The precipitate was filtered off and washed neutral with water to give 5-acetyl-2-chloro-3-nitrothiophene as a lemon-yellow powder (14.03 g, 97% crude yield, m.p. 67.5–84°C). Recrystallisation (ethanol, cyclohexane, ethanol/charcoal) raised the melting point to 80.5–83.5°C, lit.[15] 85–87°C, lit.[14] 84–86°C.

Methanol (260 ml) and aqueous ammonia (33%, 45 ml) were heated to reflux and 5-acetyl-2-chloro-3-nitrothiophene (13.3 g, 0.065 mol) was added. After refluxing for 70 min, the brown liquor was allowed to cool and then refrigerated overnight. Filtration yielded a purple crystalline powder (7.10 g, 59% crude yield) which was recrystallised (methanol/charcoal) to give dark yellow needles of 5-acetyl-2-amino-3-nitrothiophene (5.20 g, m.p. 227.5–230°C, lit.[1] 227–228°C, lit.[14] 224–226°C).

3.1.2. 2-Amino-3-methoxycarbonyl-5-nitrothiophene

Methyl cyanoacetate (99%, 25.02 g, 0.25 mol) and 1,4-dithiane-2,5-diol (97%, 23.54 g, 0.15 mol) were mixed with methanol (50 ml) and triethylamine (12.5 ml) added over 13 min with stirring. The temperature rose to 57°C over the first few minutes, but was soon lowered by external water-cooling. The temperature of the stirred mixture was raised to 40°C over 1 h and maintained at this temperature for a further 2 h to give a clear yellow-orange liquid. This was refrigerated overnight and the stocky cream-coloured crystals (26.98 g, 69% crude yield based on diol, m.p. 79–80°C, lit.[27] 77–78°C) of 2-amino-3-methoxycarbonylthiophene were filtered off and water-washed. (Much less pure material (8.72 g, 22% crude yield) could be obtained by dilution of the filtrate with water, giving a combined crude yield of 91%.)

Crude 2-amino-3-methoxycarbonylthiophene (15.72 g, 0.10 mol) and acetic anhydride (50 ml) were refluxed for 5 min and refrigerated overnight. The solid (17.88 g, 90% crude yield) obtained after the hydrolysis of the anhydride was recrystallised (methanol) to give light brown crystals (17.16 g, m.p. 99.5–101°C, lit.[27] 98°C) of 2-acetylamino-3-methoxycarbonylthiophene.

To a solution of 2-acetylamino-3-methoxycarbonylthiophene (16.00 g, 0.08 mol) in sulphuric acid (98%, 80 ml), prepared by addition of the solid over 20 min under 10°C, a mixture of fuming nitric acid ($d = 1.5$, 8.0 g) and sulphuric acid (98%, 16 ml) was added dropwise over 50 min at 3–6°C. The reaction mixture was stirred for 5 min and poured cautiously into ice (*ca.* 2 litres) and the greenish–yellow suspension neutralised. The solid [12.15 g, 62% crude yield, m.p. 154–159°C (dec.)] was collected, recrystallised from methanol/DMF (4:1) and washed with ice-cold methanol to give 2-acetylamino-3-methoxycarbonyl-5-nitrothiophene (9.77 g, m.p. 162–163.5°C). Two further recrystallisations furnished analytically pure material, m.p. 164.5–166°C. Microanalysis found C, 39.4; H, 3.15; N, 11.4; S, 12.95% ($C_8H_8N_2O_5S$ requires C, 39.3; H, 3.3; N, 11.5; S, 13.1%). ^{1}H NMR DMSO-d_6: 2.5 (3H, s, $COCH_3$), 4.0 (3H, s, CO_2CH_3), 8.3 (1H, s, H_{ring}), 11.5–11.6 (1H, s, NH).

2-Acetylamino-3-methoxycarbonyl-5-nitrothiophene (9.38 g, 0.038 mol) in methanol (470 ml) and sulphuric acid (98%, 4.7 ml) were refluxed for 30 h. The dark yellow suspension was rotary-evaporated almost to dryness and water added to the residue, which was filtered and water-washed neutral. The collected solid (7.65 g, 98% crude yield) was crystallised (methanol/DMF, 9:1), affording 2-amino-3-methoxycarbonyl-5-nitrothiophene as dark yellow, fine needles (6.72 g, 87% purified yield, m.p. 230–231°C, lit.[17] 227°C) of analytical purity. Microanalysis found C, 35.5; H, 2.8; N, 13.95; S, 15.9% ($C_6H_6N_2O_4S$ requires C, 35.6; H, 3.0; N, 13.9; S, 15.9%). ^{1}H NMR (DMSO-d_6): 3.85 (3H, s, CH_3), 8.1 (H, s, H_{ring}), 8.7–9.2 (2H, broad s, NH_2, disappears on addition of D_2O).

3.1.3. 2-Amino-3-methoxycarbonyl-4-methyl-5-nitrothiophene

Diethylamine (5 ml) was added to a stirred mixture of 2,5-dimethyl-1,4-dithiane-2,5-diol (98%, 5.00 g, 0.027 mol), methyl cyanoacetate (99%, 6.01 g, 0.060 mol) and methanol (20 ml) under 30°C over 15 min (external water-cooling) to give a pale yellow clear liquid. The mixture temperature was raised to 35–40°C over 10 min and maintained for 150 min. A crystalline solid was observed after 10 min, the reaction mixture at completion consisting of a dark red liquid replete with this solid. After refrigerating overnight, filtering and washing with ice-cold methanol followed by water, 2-amino-3-methoxycarbonyl-4-methylthiophene was obtained as a pink crystalline solid (7.04 g, 76% crude yield) of m.p. 111–112°C. Lit.[27] 75% yield, m.p. 110–111°C.

The crude product (6.00 g) was acetylated in a similar manner to that used in Section 3.1.2 giving 2-acetylamino-3-methoxycarbonyl-4-methylthiophene as a cream-coloured material (7.16 g, 96% crude yield, m.p. 111–112°C, lit.[27] 109–111°C).

Crude 2-acetylamino-3-methoxycarbonyl-4-methylthiophene (6.00 g, 0.028 mol) was nitrated by a similar procedure to that employed in Section 3.1.2, giving a golden yellow powder (4.44 g, 61% crude yield), which was recrystallised (methanol/DMF, 6:1), furnishing 2-acetylamino-3-methoxycarbonyl-4-methyl-5-nitrothiophene as a sandy-coloured solid of m.p. 177–178°C, lit.[27] 176–178°C.

Dissolution of 2-acetylamino-3-methoxycarbonyl-4-methyl-5-nitrothiophene (3.50 g, 0.014 mol) in methanol (280 ml) and sulphuric acid (98%, 2.8 ml), followed by stirring and refluxing for 24 h produced a dark yellow suspension, which was refrigerated overnight. The solid was collected and washed twice with ice-cold methanol, yielding a dark yellow crystalline powder (2.56 g, 87% crude yield). Two recrystallisations (2-ethoxyethanol) gave analytically pure 2-amino-3-methoxycarbonyl-4-methyl-5-nitrothiophene in the form of yellow–brown crystals (1.83 g, 62% purified yield) with a violet reflex. DSC showed a sharp endotherm at 263.2°C. Microanalysis found C, 38.75; H, 3.6; N, 12.85; S, 14.7% ($C_7H_8N_2O_4S$ requires C, 38.9; H, 3.7; N, 13.0; S, 14.8%). ^{1}H NMR (DMSO-d_6): 2.68 (3H, s, CH_3), 3.73 (3H, s, CO_2CH_3), 8.63 (2H, broad s, NH_2).

3.1.4. 2-Amino-3-ethoxycarbonyl-5-nitrothiophene

Triethylamine (5 ml) was added over 10 min to an externally water-cooled mixture of 1,4-dithiane-2,5-diol (97%, 8.63 g, 0.055 mol), ethyl cyanoacetate (98%, 11.54 g, 0.10 mol) and methanol (20 ml) such that its temperature remained below 30°C. The suspension was stirred at 40°C for 2 h and the now dark yellow clear liquid was ice-cooled, treated with a few lumps of ice to induce crystallisation and refrigerated for several hours. Filtering and washing with ice-cold methanol gave 2-amino-3-ethoxycarbonylthiophene as a white crystalline solid (8.47 g, 50% crude yield, m.p. 46–47°C).

Crude 2-amino-3-ethoxycarbonylthiophene (6.00 g, 0.035 mol) was acetylated as in Section 3.1.2 yielding 2-acetylamino-3-ethoxycarbonylthiophene as a cream-coloured powder (6.42 g, 86% crude yield, m.p. 71–72°C). The crude product (6.00 g) was nitrated as in Section 3.1.2 to give a pale greenish–yellow solid (4.67 g, 64% crude yield, m.p. 135–137°C) which was recrystallised twice (ethanol/DMF, 10:1) furnishing straw-coloured needles of 2-acetylamino-3-ethoxycarbonyl-5-nitrothiophene, m.p. 143.5–145°C, lit.[17] 144°C.

A stirred mixture of 2-acetylamino-3-ethoxycarbonyl-5-nitrothiophene (2.80 g, 10.8 mmol), ethanol (60 ml) and sulphuric acid (98%, 0.6 ml) was refluxed for 49 h. Neutralisation (aqueous NaOH) of the cooled mixture and

rotary evaporation followed by water-washing of the collected solid produced a dark yellow crystalline powder (2.23 g, 95% crude yield, m.p. 228–229.5°C). Two recrystallisations (aqueous 2-ethoxyethanol) gave analytically pure 2-amino-3-ethoxycarbonyl-5-nitrothiophene as fine yellow needles of m.p. 236.5°C, lit.[17] 240–242°C. Microanalysis found C, 38.75; H, 3.45; N, 13.05; S, 14.9% ($C_7H_8N_2O_4S$ requires C, 38.9; H, 3.7; N, 13.0; S, 14.8%). ^{1}H NMR (DMSO-d_6): 1.24 (3H, t, CH_3), 4.18 (2H, q, CH_2), 7.85 (1H, s, H_{ring}), 8.59 (2H, broad s, NH_2).

3.1.5. 2-Amino-3-butoxycarbonyl-5-nitrothiophene

A mixture of 2-amino-3-methoxycarbonyl-5-nitrothiophene (3.50 g, 17 mmol), 1-butanol (225 ml) and titanium isopropoxide (97%, 2.82 g, 9.6 mmol) was stirred and heated to reflux for 24 h under nitrogen. The solvent was removed by rotary evaporation, the yellow–brown solid treated with boiling ethanol (120 ml), filtered hot and the volume reduced to 20 ml, followed by standing overnight to crystallise. The yellow–brown crystals (3.33 g, 79% crude yield, m.p. 131.5–132°C) were collected and washed with a little ethanol. Further recrystallisation (ethanol) gave analytically pure material (m.p. 132–133°C, lit.[17] 136–139°C). Microanalysis found C, 44.0; H, 4.95; N, 11.5; S, 13.3% ($C_9H_{12}N_2O_4S$ requires C, 44.25; H, 4.95; N, 11.5; S, 13.1%). ^{1}H NMR (DMSO-d_6): 0.89 (3H, t, $CH_2CH_2CH_2CH_3$), 1.34 (2H, m, $CH_2CH_2CH_2CH_3$), 1.59 (2H, m, $CH_2CH_2CH_2CH_3$), 4.13 (2H, t, CO_2CH_2), 7.84 (1H, s, H_{ring}), 8.61 (2H, broad s, NH_2).

3.1.6. 2-Acetylamino-3-cyano-5-nitrothiophene

1,4-Dithiane-2,5-diol (97%, 3.00 g, 19 mmol), malononitrile (99%, 2.61 g, 39 mmol) and ethanol (60 ml) were stirred together and diethylamine (98%, 3.18 g, 44 mmol) in ethanol (3 ml) was added over 10 min under 5°C. The stirred mixture was heated to 30–35°C over 20 min and kept at this temperature for 1 h to give a clear brown solution. Dilution of the liquid with water and refrigeration gave solid which was collected and water-washed, yielding shiny beige leaflets (2.68 g, 57% crude yield, m.p. 103.5–104°C, lit.[27] 104–105°C) of 2-amino-3-cyanothiophene.

Acetic anhydride (7 ml) and 2-amino-3-cyanothiophene (2.48 g, 20 mmol) were stirred together and refluxed for 10 min. After refrigerating overnight, shiny, light brown crystals (2.89 g, 87% crude yield, m.p. 210–211°C) were collected and water-washed. Two recrystallisations (*ca.* 5:1 ethanol:DMF) furnished analytically pure 2-acetylamino-3-cyanothiophene as buff crystals of m.p. 210–211°C, lit.[16] 194°C. Microanalysis found C, 50.35; H, 3.5; N, 16.75; S, 19.2% ($C_7H_6N_2OS$ requires C, 50.6; H, 3.6; N, 16.9; S, 19.3%). FTIR (KBr)/cm^{-1}: 3277 (NH), 2219 (C≡N), 1694 (C=O).

A suspension of 2-acetylamino-3-cyanothiophene (2.40 g, 14 mmol) in acetic acid (99%, 18 ml) and acetic anhydride (18 ml) was treated with a mixture of HNO_3 (2.00 g, $d = 1.50$), acetic anhydride (2.6 ml) and acetic acid (99%, 2.6 ml) at 35–40°C over 30 min. The dark orange suspension was poured onto ice and neutralised (aqueous NaOH); the solid (2.12 g, 88% crude yield, m.p. 228–232°C) was filtered and water-washed. Two recrystallisations (ethanol) produced 2-acetylamino-3-cyano-5-nitrothiophene (m.p. 232–232.5°C) of analytical purity. Microanalysis found C, 39.8; H, 2.35; N, 20.05; S, 15.25% ($C_7H_5N_3O_3S$ requires C, 39.8; H, 2.4; N, 19.9; S, 15.2%). FTIR (KBr)/cm^{-1}: 2240 (C≡N), 1704 (C=O).

3.1.7. 2-Amino-3-carbamyl-5-nitrothiophene

3.1.7.1. Acetyl chloride (12.66 g, 0.161 mol) was added over 50 min at 3–6°C to a solution of 2-amino-3-carbamylthiophene[22] (20.76 g, 0.146 mol) in pyridine (250 ml). After stirring for 1 h at 0°C and quenching with ice/water, the mixture was rotary evaporated to dryness. The solid was water-washed to give 2-acetylamino-3-carbamylthiophene as a grey powder (22.54 g, 84% crude yield, m.p. 217–218°C). DSC showed an endotherm at 217.9–218.3°C.

Mixed acid, prepared from sulphuric acid (98%, 18 ml) and nitric acid ($d = 1.5$, 10.0 g), was added over 45 min to a solution of 2-acetylamino-3-carbamylthiophene (15.00 g, 0.081 mol) in sulphuric acid (98%, 100 ml) at 3–5.5°C. The mixture was stirred at 5°C for 10 min before pouring into ice (1.5 litres) to a give a greenish suspension. After neutralisation (aqueous NaOH), a yellow solid (11.41 g, 61% crude yield) was filtered off and recrystallised (aqueous ethanol, twice) to give analytically pure 2-acetylamino-3-carbamyl-5-nitrothiophene as lustrous yellow needles of m.p. 253.5–254°C (dec.). Microanalysis found C, 36.4; H, 2.9; N, 18.3; S, 13.95% ($C_7H_7N_3O_4S$ requires C, 36.7; H, 3.1; N, 18.3; S, 14.0%). FTIR (KBr)/cm^{-1}: 3466, 3444, 3351, 3171 (NH); 1698, 1663 (NH and C=O).

A mixture of 2-acetylamino-3-carbamyl-5-nitrothiophene (0.54 g, 2.4 mmol), ethanol (40 ml) and sulphuric acid (98%, 0.4 ml) was stirred and heated to reflux. The refluxing was continued for 20 h. Cooling and neutralising (aqueous NaOH) brought about precipitation of a dark yellow solid (0.33 g, 75% crude yield), which was collected and oven-dried (60°C). Two recrystallisations from aqueous 2-ethoxyethanol furnished analytically pure 2-amino-3-carbamyl-5-nitrothiophene as a dark yellow crystalline powder. Microanalysis found C, 32.4; H, 2.6; N, 22.6; S, 16.9% ($C_5H_5N_3O_3S$ requires C, 32.1; H, 2.7; N, 22.45; S, 17.1%). DSC indicated purity, showing a sharp endotherm at 273.2°C. FTIR (KBr)/cm^{-1}: 3436, 3382, 3273 (NH); 1655 (C=O).

3.1.7.2. Acetic anhydride (200 ml) and 2-amino-3-carbamylthiophene (17.40 g, 0.12 mol) were stirred and heated to reflux for 1.75 h, rotary evaporated to dryness and water-washed giving a light grey–brown solid

(20.02 g, 73% crude yield) which was recrystallised (ethanol/DMF) affording 2-acetylamino-3-(*N*-acetyl)carbamylthiophene as an off-white solid (m.p. 220–222°C). DSC indicated reasonable purity, showing a major endotherm at 220.0–222.4°C, with a minor one at 177.3°C. ^{1}H NMR ($CDCl_3$): 2.35, 2.65 (3H, s, CH_3), 6.95, 7.3 (1H, d, H_{ring}), 8.8, 11.8 (s, Ar*N*H*C*OCH_3 and Ar*C*O*N*H*C*OCH_3).

The product (6.45 g, 28.5 mmol) was nitrated in a similar manner to that in Section 3.1.7.1, giving a yellow solid (7.19 g, 93% crude yield). Three recrystallisations (ethanol/DMF, 1:1) furnished 2-acetylamino-3-(*N*-acetyl)-carbamyl-5-nitrothiophene as analytically pure pale yellow crystals of m.p. 243.5–244°C (dec.). Microanalysis found C, 40.1; H, 3.45; N, 15.6; S, 11.85% ($C_9H_9N_3O_5S$ requires C, 39.8; H, 3.3; N, 15.5; S, 11.8%).

A mixture of ethanol (350 ml), sulphuric acid (98%, 3.5 ml) and 2-acetylamino-3-(*N*-acetyl)carbamyl-5-nitrothiophene (4.61 g, 17 mmol) was stirred and refluxed for 24 h. After cooling, the solution was neutralised (aqueous NaOH) to give a dark yellow suspension. The solid (2.98 g, 94% crude yield) was recrystallised (aqueous 2-ethoxyethanol) yielding material identical to the 2-amino-3-carbamyl-5-nitrothiophene obtained in Section 3.1.7.1.

3.1.8. 3-Amino-2-methoxycarbonyl-4-methyl-5-nitrothiophene

A solution of 3-amino-2-methoxycarbonyl-4-methylthiophene (2.57 g, 15 mmol) in pyridine (10 ml) was treated with acetyl chloride (1.57 g, 20 mmol) over 30 min at under 4°C to give a cream-coloured suspension. After stirring at this temperature for 20 min, the solid (1.20 g, m.p. 117.5–118.5°C) was collected and combined with that (1.58 g, m.p. 116–116.5°C) obtained from dichloromethane extracts of the filtrate to give crude 3-acetylamino-2-methoxycarbonyl-4-methylthiophene as a white solid (2.78 g, 87% crude yield).

Mixed acid, prepared from nitric acid (d = 1.5, 0.75 g) and sulphuric acid (98%, 1.5 ml), was added dropwise over 15 min to a solution of 3-acetylamino-2-methoxycarbonyl-4-methylthiophene (1.50 g, 7.0 mmol) in sulphuric acid (98%, 7.5 ml) at 2–5.5°C. The clear yellow liquid was stirred at 2–3°C for 30 min before pouring cautiously into ice (*ca.* 100 ml) to give a very pale yellow suspension, which was filtered and the collected solid water-washed neutral and oven-dried (60°C). The solid (1.57 g, 87% crude yield, m.p. 174–176°C) was recrystallised from methanol yielding analytically pure pale yellow needles (1.26 g, 70% purified yield, m.p. 175.5–176.5°C) of 3-acetylamino-2-methoxycarbonyl-4-methyl-5-nitrothiophene. Microanalysis found C, 41.6; H, 3.7; N, 10.85; S, 12.4% ($C_9H_{10}N_2O_5S$ requires C, 41.85; H, 3.9; N, 10.85; S, 12.4%). ^{1}H NMR (DMSO-d_6): 2.05 (3H, s, NHCOC*H*$_3$), 2.33 (3H, s, CH_3), 3.80 (3H, s, CO_2CH_3). FTIR (KBr)/cm^{-1}: 3271 (NH); 1721 (ester C=O); 1674 (amide C=O).

The product (0.80 g, 3.1 mmol) was hydrolysed as in Section 3.1.2 furnishing a bright orange powder (0.59 g, 88% crude yield, m.p. 119–120°C). Recrystallisation (methanol) produced bright orange–red crystals (0.55 g, 82% purified yield, m.p. 119.5–120°C) of analytically pure 3-amino-2-methoxycarbonyl-4-methyl-5-nitrothiophene. Microanalysis found C, 38.8; H, 3.7; N, 13.1; S, 14.55% ($C_7H_8N_2O_4S$ requires C, 38.9; H, 3.7; N, 13.0; S, 14.8%). ^{1}H NMR (DMSO-d_6): 2.38 (3H, s, CH_3), 3.77 (3H, s, CO_2CH_3), 6.71 (2H, s, NH_2). FTIR (KBr)/cm^{-1}: 3467, 3368 (NH); 1681 (C=O).

3.1.9. 3-Amino-2-methoxycarbonyl-4(5)-nitrothiophene

3-Amino-2-methoxycarbonylthiophene (2.77 g, 18 mmol) was dissolved in hot acetic anhydride (10 ml) and the solution refluxed for 15 min before refrigerating overnight. The acetic anhydride was hydrolysed, and the solid collected (3.14 g, 89% crude yield), water-washed and air-dried. A light beige crystalline solid (2.53 g, m.p. 97–97.5°C) was obtained by recrystallisation from methanol; the 3-acetylamino-2-methoxycarbonylthiophene was used without further purification.

Nitration of 3-acetylamino-2-methoxycarbonylthiophene (1.49 g, 7.5 mmol) was performed as in Section 3.1.8, producing 3-acetylamino-2-methoxycarbonyl-4(5)-nitrothiophene (1.52 g, 83% crude yield) as a yellow solid. The crude product (1.00 g, 4.1 mmol) was dissolved in methanol (40 ml) and H_2SO_4 (98%, 0.4 ml) before refluxing with stirring for 23 h. Dark red crystals (0.35 g, 42% crude yield, m.p. 169–171°C) were deposited on standing at room temperature overnight; recrystallisation (methanol) furnished analytically pure 3-amino-2-methoxycarbonyl-5-nitrothiophene (0.30 g, 36% pure yield, m.p. 170.5–171.5°C) as dark red crystals. Microanalysis found C, 35.65; H, 2.9; N, 13.95; S, 16.05% ($C_6H_6N_2O_4S$ requires C, 35.6; H, 3.0; N, 13.9; S, 15.9%). ^{1}H NMR (DMSO-d_6): 3.9 (3H, s, CH_3), 6.95 (2H, broad s, NH_2, intensity reduced on D_2O shake), 7.65 (1H, s, H_{ring}).

The filtrate was evaporated *in vacuo* to leave a dark yellow powder (0.46 g), which was applied onto alumina (10 g) by evaporation of dichloromethane (25 ml). The medium was placed onto a column of alumina and chromatographed, eluting with 1:1 dichloromethane:60–80° ligroin. The green–yellow first major fraction collected was evaporated to give analytically pure 3-amino-2-methoxycarbonyl-4-nitrothiophene (0.15 g, 18% pure yield, m.p. 119.5–120°C) as a bright yellow solid. Microanalysis found C, 35.8; H, 2.95; N, 13.65; S, 16.05% ($C_6H_6N_2O_4S$ requires C, 35.6; H, 3.0; N, 13.9; S, 15.9%). ^{1}H NMR (DMSO-d_6): 3.9 (3H, s, CH_3), 7.3 (2H, broad s, NH_2, intensity reduced on D_2O shake), 9.15 (1H, s, H_{ring}). The dark orange fraction eluted next furnished fine crimson crystals (0.26 g, 31% pure yield) of 3-amino-2-methoxycarbonyl-5-nitrothiophene, giving a combined pure yield of 67% for this isomer.

3.2. Preparative details of the dyes

The synthetic details for each dye are given in Table 1. The coupling conditions used were specific to each coupler (see Section 3.2.1). Also given in Table 1 are the crude yields, purification methods (see Section 3.2.2) and pure yields of the dyes, "%s" being the percentage yield of the purification process, i.e. the percentage amount of pure dye obtained from the crude dye used in the purification (a second figure represents the theoretical pure yield, i.e. the percentage amount of pure dye obtained if all the crude sample had been used in the purification process, extrapolated from the percentage yield of the purification process).

3.2.1. Diazotisation and coupling

Each diazo component was diazotised as follows: nitrosylsulphuric acid was prepared by adding sodium nitrite (10% excess) to sulphuric acid (98%, 0.4 ml per mmol of amine) at 20–30°C, heating to 60–65°C over 10 min with stirring and maintaining this temperature for up to 5 min to ensure complete dissolution. After allowing the solution to cool, a mixture of acetic and propionic acids (5:1, 0.64 ml per mmol of amine) was added under 30°C. The amine was added over 20–30 min under 5°C and the whole stirred at 0–5°C for 2–4 h.

For dyes derived from the toluidine coupler (**1**, **2**, **3** and **5**), a mixture of the coupling component (0.188 g per mmol of amine), water (4.9 ml per mmol of amine), hydrochloric acid (36%, 0.10 ml per mmol of amine) and ice (5 g per mmol of amine) was used. Addition of the diazonium mixture was made at 0–5°C and the whole stirred for at least 2 h before diluting or raising the pH to 4.5 (aqueous sodium hydroxide or sodium acetate) prior to filtering and water-washing neutral.

The dyes **4**, synthesised from the 5-acetylamino-2-methoxyaniline-based coupler, were prepared by dissolving the component (70%, 0.5 g per mmol of amine) in water (2.2 ml per mmol of amine), sulphuric acid (98%, 0.1 ml per mmol of amine) and ice (4.0 g per mmol of amine). The diazonium mixture was added over 5–10 min under 5°C and stirred at this temperature for 1–2 h before diluting and/or raising the pH to 6. The suspension was stirred overnight and filtered and the collected solid water-washed neutral.

Sulphamic acid was added to the coupler solution before addition of the diazonium mixture if it had not already been added at the end of the diazotisation.

3.2.2. Purification

The crude products were isolated as solids and purified as detailed in Table 1, by column chromatography (Δ, silica/85:15 toluene:ethyl acetate) and/or

recrystallisation with the following solvents: 2-ethoxyethanol (α), 2-methoxyethanol (β), aqueous 2-methoxyethanol (γ), ethyl acetate (δ), toluene/ethyl acetate (ε), toluene (η), toluene/80–100° ligroin (θ) and toluene/100–120 ligroin (λ). The purified dyes all gave satisfactory microanalyses.

4. CONCLUSIONS

Thienyl-2- and thienyl-3-azo dyes have been prepared in good yield from aminonitrothiophenes using conventional methods; the former were reddish-blue to green, whereas the latter were yellow to orange. Difficulties were encountered in the preparation of 3-cyano and 3-carbamyl-5-nitrothienyl-2-azo dyes; the nitrile function readily underwent hydration and the amide diazo component may have cyclised to a significant extent when diazotised. Certain trends in the melting points of the dyes could be correlated with molecular structure. ^{13}C NMR data for a 5-nitrothienyl-2-azo dye and its 5-nitrothiazolyl-2-azo analogue were found to be consistent with previously reported chemical shifts of thiophene-derived azo dyes.

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