

Intramolecular Diazo Coupling of 2-Aminophenylthiophenes. The Formation of Isomeric Thieno[*c*]cinnolines

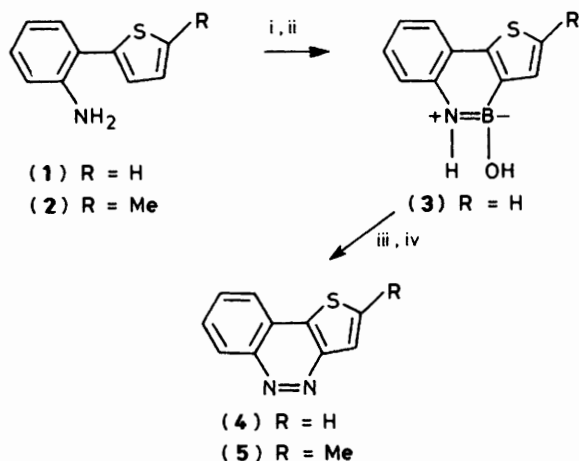
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Thieno[2,3-*c*]- (4) and thieno[3,2-*c*]-cinnolines (7) have been obtained by diazotisation and internal coupling of the corresponding 2-(*o*-aminophenyl)thiophenes. By the same reaction 3-(*o*-aminophenyl)-2,5-dimethylthiophene gives 1,3-dimethylthieno[3,4-*c*]cinnoline (9).

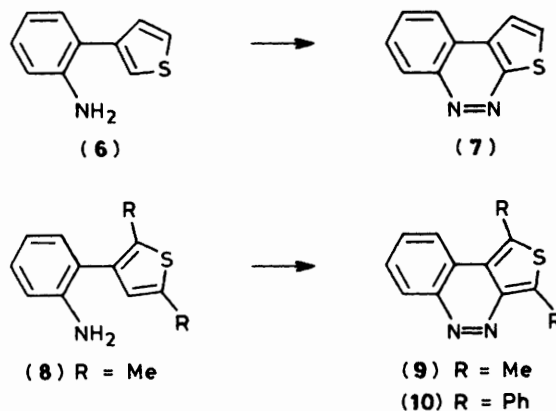
Thiophene undergoes electrophilic substitution much more readily than benzene, and yet it and its monomethyl derivatives are insufficiently reactive to undergo diazo-coupling, even with the relatively electrophilic 2,4-dinitrobenzenediazonium cation.¹ Surprisingly, they undergo Gomberg arylation in acetic acid solution at 0 °C to give 2-(2,4-dinitrophenyl)thiophenes. More reactive thiophenes, bearing an aryl or several alkyl groups, undergo diazo-coupling at vacant ring positions, although in the case of polymethyl derivatives coupling at a 2-methyl substituent to give a 2,4-dinitrophenylhydrazone becomes the main reaction.² In connection with our synthesis of benzo[3,4]cyclobuta[1,2-*b*]thiophene³ we prepared thieno[3,2-*c*]cinnoline (4) from 2-(*o*-aminophenyl)thiophene (1) via the azaborine (3), a sequence (see Scheme) analogous to the

more reactive α -position to give thieno[2,3]cinnoline (7), while 3-(*o*-aminophenyl)-2,5-dimethylthiophene (8), in which the α -position is blocked, couples at the remaining vacant ring position to give 1,3-dimethylthieno[3,4-*c*]cinnoline (9).



Scheme. Reagents: i BCl_3 , xylene, reflux; ii H_2O ; iii NaNO_2 , HCl ; iv NaOAc

conversion of 2-aminobiphenyl into benzo[*c*]cinnoline described by Dewar and Poesche.⁴ We now find that diazonium salts from (*o*-aminophenyl)thiophenes undergo spontaneous intramolecular cyclisation in aqueous solution, a reaction which has only been observed previously in the benzo[*b*]-thiophene⁵ series. Thus (1) may be converted directly into (4), albeit in low yield. The yields obtained in these reactions reflect the reactivity of the ring position at which the intramolecular coupling takes place. For example, cyclisation of the diazonium salt from (1), which involves attack at a less reactive β -position of the thiophene nucleus, takes place more readily when a methyl group is introduced at position 5. As expected, 3-(*o*-aminophenyl)thiophene (6) couples regioselectively at the



Thus certain derivatives of all three thieno[*c*]cinnoline ring systems are readily constructed by this direct diazotisation procedure and the method is obviously capable of extension. As far as we are aware there have been only two previous reports on the formation of members of these ring systems. The diphenyl derivative (10) was prepared in low yield by the reaction of 3,4-dibenzoylcinnoline with ammonium sulphide⁶ and a compound, considered to be methyl 2,3-dihydro-3-iminothieno[3,2-*c*]cinnoline-2-carboxylate on the basis of ^1H n.m.r. data, was obtained from the reaction of 4-chlorocinnoline-3-carbonitrile with methyl thioglycollate.⁷

^1H N.m.r. Spectra.—Assignments in the proton spectra of the thieno[*c*]cinnolines were based on those found for benzo[*c*]cinnoline,⁸ the resonances for protons 6-H and 9-H of the benzene rings being at lowest field in each case. In the spectra of (4) and (7) the protons of the thiophene rings show as clearly defined doublets, while in (5) 3-H appears as a poorly resolved quartet owing to coupling with the protons of the adjacent methyl group. A small, long-range coupling between the protons of the two methyl groups is also apparent in the spectrum of (9).

Experimental

^1H N.m.r. spectra were obtained on a Jeol JNM FX200 spectrometer. Samples were run as solutions in deuteriochloro-

form at ambient temperature and chemical shifts are recorded as p.p.m. downfield from internal tetramethylsilane. I.r. spectra were run as Nujol mulls. Mass spectra were obtained on an AEI MS902 instrument operated at 70 eV and a source temperature of 200 °C. Flash chromatography⁹ was carried out on Merck Kieselgel 60, 230–400 mesh. The following starting materials were prepared by literature routes: 3-iodothiophene¹⁰ and 3-iodo-2,5-dimethylthiophene.¹¹

2-(*o*-Nitrophenyl)thiophene.—*o*-Nitroaniline (7.6 g), thiophene (350 ml), and pentyl nitrite (9.6 g) were warmed under reflux until a vigorous reaction set in with evolution of gas. After the initial reaction had subsided the solution was refluxed for 2 h; the excess of thiophene and low-boiling products were then removed under reduced pressure. Distillation of the residue gave a fraction, b.p. 128–131 °C/0.3 Torr which gave 2-(*o*-nitrophenyl)thiophene as pale yellow needles (6.55 g, 58%), m.p. 50–51 °C (from MeOH) (lit.,¹² m.p. 51–52 °C).

2-(*o*-Aminophenyl)thiophene (1).—A mixture of the above nitro compound (1.07 g), reduced iron (1.5 g), and ammonium chloride (1.4 g) in ethanol (30 ml) and water (15 ml) was refluxed for 2 h. The hot solution was filtered and both the filtrate and the solid residues were extracted with dichloromethane. Evaporation of the dried (K₂CO₃) extracts gave the amine (0.87 g, 95%) as a pale yellow oil which on low-temperature crystallisation formed buff needles, m.p. 31–32 °C (from MeOH) (lit.,¹² m.p. 35–36 °C).

Diazotisation of 2-(*o*-aminophenyl)thiophenes.—The amount of solvent (propanoic acid) was varied, according to the solubility of the starting material; the following procedure is typical. A stirred solution of 2-(*o*-aminophenyl)thiophene (0.7 g) in hydrochloric acid (15 ml), propanoic acid (5 ml), and sulphuric acid (0.7 ml) was diazotised at 0–3 °C by the addition of sodium nitrite (0.5 g) in water (5 ml). After 1 h a cold solution of sodium acetate (7.0 g) in water (25 ml) was added dropwise, then stirring was continued at 0–3 °C for a further 30 min and at room temperature for 24 h. The mixture was neutralised with sodium carbonate and extracted with dichloromethane to yield brown tarry material which was flash chromatographed on silica, using dichloromethane–ethyl acetate (3:1) as eluant. The main band afforded thieno[3,2-*c*]cinnoline (4) (0.093 g, 13%) as orange crystals, m.p. 133–134 °C (from cyclohexane), identical with a sample prepared *via* the azaborine (3) (Found: C, 64.4; H, 3.2; N, 14.85; S, 17.5%; *M*⁺, 186.023. C₁₀H₆N₂S requires C, 64.5; H, 3.2; N, 15.05; S, 17.2%; *M*, 186.025); δ_H 7.77 (d, *J*_{2,3} 5.37 Hz, 2-H), 7.83 (2 H, m, 7-H, 8-H), 8.07 (m, 9-H), 8.11 (d, *J*_{2,3} 5.37 Hz, 3-H), and 8.69 (m, 6-H).

2-Methylthieno[3,2-*c*]cinnoline (5).—By a sequence similar to that used for the preparation of (1) 2-methylthiophene was converted in 29% yield into 2-methyl-5-(*o*-nitrophenyl)thiophene, b.p. 126–130 °C/0.1 Torr, yellow plates, m.p. 28–30 °C (from MeOH) and thence in 70% yield into 2-(*o*-aminophenyl)-5-methylthiophene (2), b.p. 122–128 °C/0.1 Torr; *v*_{max}. 3 350 and 3 450 cm⁻¹ (NH). Diazotisation of the amine by the method outlined above gave 2-methylthieno[3,2-*c*]cinnoline (5) (36%) as orange needles, m.p. 115–116 °C (from cyclohexane) (Found: C, 65.85; H, 4.1; N, 13.75; S, 16.2. C₁₁H₈N₂S requires C, 66.0; H, 4.0; N, 14.0; S, 16.0%); δ_H 2.75 (3 H, d, *J*_{3,Me} 1.02 Hz, Me), 7.74 (q, *J*_{3,Me} 1.02 Hz, 3-H), 7.80 (2 H, m, 7-H, 8-H), 7.99 (m, 9-H), and 8.65 (m, 6-H).

3-(*o*-Nitrophenyl)thiophene.—Copper bronze (8.3 g) was added in portions during 5 min to a mixture of 1-bromo-2-nitrobenzene (3.0 g) and 3-iodothiophene (4.7 g) at 170–180 °C (bath). The bath temperature was raised and maintained at

200–210 °C for 3 h. On cooling, the products were extracted into hot acetone and the extracts filtered through Celite and evaporated to give a brown oil which was flash chromatographed on silica with light petroleum b.p. (40–60 °C)—dichloromethane 3:1 as eluant. The main band gave 3-(*o*-nitrophenyl)thiophene as an orange oil which slowly crystallised. It formed pale yellow prisms, m.p. 39–40 °C (from hexane) (Found: C, 58.8; H, 3.4; N, 7.0%; *M*⁺, 205. C₁₀H₇NO₂S requires C, 58.5; H, 3.45; N, 6.8%; *M*, 205).

3-(*o*-Aminophenyl)thiophene (6).—Reduction of 3-(*o*-nitrophenyl)thiophene by the method used for the 2-isomer gave the amine (91%) as a pale pink oil which slowly crystallised. It formed colourless prisms, m.p. 39–40 °C (from hexane) (Found: C, 68.3; H, 5.0; N, 7.8%; *M*⁺, 175. C₁₀H₉NS requires C, 68.5; H, 5.2; N, 8.0%; *M*, 175); *v*_{max}. 3 350 and 3 450 cm⁻¹ (NH).

Thieno[2,3-*c*]cinnoline (7).—Diazotisation of 3-(*o*-aminophenyl)thiophene in the usual manner gave, after dichloromethane extraction, a solid which afforded the cinnoline (69%) as pale orange needles, m.p. 138–139 °C (from cyclohexane) (Found: C, 64.2; H, 2.95; N, 14.8; *M*⁺, 186. C₁₀H₆N₂S requires C, 64.5; H, 3.2; N, 15.05%; *M*, 186); δ_H 7.85 (2 H, m, 7-H, 8-H), 7.89 (d, *J*_{1,2} 5.86 Hz, 2-H), 7.99 (d, *J*_{1,2} 5.86 Hz, 1-H), 8.26 (m, 9-H), and 8.68 (m, 6-H).

2,5-Dimethyl-3-(*o*-nitrophenyl)thiophene.—A crossed Ullman reaction between 1-bromo-2-nitrobenzene (4.0 g) and 3-iodo-2,5-dimethylthiophene (7.15 g, 1.5 equiv.) was carried out as described for the preparation of 3-(*o*-nitrophenyl)thiophene. Flash chromatography gave the nitro compound as an orange oil (3.48 g, 75%) (Found: C, 61.5; H, 4.55; N, 5.8%; *M*⁺, 233. C₁₂H₁₁NO₂S requires 61.8; H, 4.75; N, 6.0%; *M*, 233).

3-(*o*-Aminophenyl)-2,5-dimethylthiophene (8).—Reduction of the above nitro compound by the method used for 2-(*o*-nitrophenyl)thiophene gave the amine (99%) as a pale yellow oil (Found: C, 70.5; H, 6.3; N, 6.4%; *M*⁺, 203. C₁₂H₁₃NS requires C, 70.9; H, 6.4; N, 6.4%; *M*, 203); *v*_{max}. 3 380 and 3 470 cm⁻¹ (NH).

1,3-Dimethylthieno[3,4-*c*]cinnoline (9).—Diazotisation of the amine (8) in the usual manner gave, after dichloromethane extraction and crystallisation from aqueous ethanol (charcoal), the cinnoline (54%) as orange needles, m.p. 112–117 °C. Further crystallisation from hexane gave material, m.p. 123–126 °C (Found: C, 67.0; H, 4.6; N, 13.2; *M*⁺, 214. C₁₂H₁₀N₂S requires C, 67.3; H, 4.7; N, 13.1%; *M*, 214); δ_H 2.93 (3 H, q, *J*_{Me,Me} 0.52 Hz, 3-Me), 3.12 (3 H, q, *J*_{Me,Me} 0.52 Hz, 1-Me), 7.70 (2 H, m, 7-H, 8-H), 8.18 (m, 9-H), and 8.54 (m, 6-H).

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