SYNTHESIS OF A THIINO[2,3,4-d,e]PHTHALAZINE

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Abstract – The reaction of 5-(1,2-dibromo-2-phenylethenyl)-phthalazine (16) with Na₂CS₃ gives 5-phenylthiino[2,3,4-d,e]phthalazine (17).

Introduction
We have described¹ a route (Scheme 1) in which 2-(1,2-dibromoalkenyl)quinoxalines (1) are reacted with disodium trithiocarbonate² resulting in cyclising ring closures giving thieno[2,3-b]quinoxalines (2), with the loss of both bromine atoms. We proposed¹ a mechanism for the process which involved initial addition of trithiocarbonate to the double bond reflecting both the electron-withdrawing nature of the halogens and conjugation with the ring imine.

![Scheme 1](image)

On the basis of the mechanism proposed,¹ we speculated³ that there are two essential criteria for a successful thiophene-cyclisation: (1) there must be a ring imine, in conjugation with the dibromoalkene, in order to encourage correctly oriented dithiocarbonate addition and (2) there must be ring imine to encourage a subsequent intramolecular cyclising sulfur addition; both of these requirements are present in the quinoxaline series as (N-1–C-2) and (C-3–N-4) respectively. Confirmation for these ideas came when we attempted a ring closure with the dibromoalkenylquinoline (3) – no ring closure occurred, only elimination

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of bromine was observed on treatment of 3 with disodium trithiocarbonate giving 4 (Scheme 2).

The requirements for success in this process were further delineated when we found that neither the dibromoalkenylpyrazine (5) nor the dibromoalkenylpyrimidine (7) allowed the thiophene ring closing process, once again exposure to disodium trithiocarbonate resulting only in bromine elimination, giving 6 and 8 respectively (Scheme 3). We concluded that a second fused aromatic ring (present in 1 but not in either 5 or 6) is also a necessary requirement for the success of these ring closing processes.

![Scheme 2](image)

![Scheme 3](image)

**Results and discussion**

We have now turned to examine the possibility of extrapolating the process to the formation of six-membered sulfur-containing rings. We prepared dibromoalkenylisoquinoline (10) hoping that reaction with trithiocarbonate would yield the tricyclic system
(11), but instead only elimination to the alkyne (9) was observed (Scheme 4). As in the previous work\textsuperscript{1,3} the dibromoalkene (10) was prepared by bromine addition to alkyne (9).\textsuperscript{4}

With all the results described above in mind, we examined the possibility of forming a six-membered ring in a comparable fashion, but using a dibromoalkenylphthalazine (16) as our substrate, the heterocyclic ring now having an additional electron-withdrawing component, compared with the isoquinoline situation, in the second imine unit at C-3–N-4.

Our route to the substrates (1, 3, 5, 7, and 10), involved in each case the Pd(0)-catalysed coupling of a heteroaryl halide with an alkyne followed by bromine addition. Relatively few methods are available for the synthesis of halogenated phthalazines: 5-bromophthalazine was unknown when we began this work, however 5-chlorophthalazine (which would be unsuitable for the coupling step) had been prepared, along with several other phthalazines, by a process involving reaction of arylaldehyde azines with a mixture of aluminum chloride and aluminum bromide.\textsuperscript{5}

Reaction of 2-bromobenzaldehyde (12) with hydrazine gave crystalline, yellow azine (13). Application of Robev’s method\textsuperscript{5} produced the desired 5-bromophthalazine (14), though only in 13% yield after purification; an alternative route will be required for future work. Coupling with phenylethyne was efficient, giving the alkyne (15) in 76% yield, as was addition of bromine producing the desired cyclisation substrate (16) (Scheme 5).
After some experimentation to find suitable conditions, we were gratified to find that the interaction of the dibromoalkenylphthalazine (16) with disodium trithiocarbonate led to the target tricyclic compound (17), a crystalline material, in 50% yield. In support of the structural assignment, 17 showed two singlets in its $^1$H NMR spectrum, at $\delta$ 9.55 and 9.98, corresponding to H-6 and H-1 respectively, and had the appropriate molecular composition, now having one sulfur and no bromine atoms. This compound (17) is the first example of this tricyclic ring system.
Following our earlier mechanistic speculation we propose the sequence shown in Scheme 6 to rationalise the formation of 17. Thus, addition to the dibromoalkene unit, taking advantage of conjugation to the imine (intermediate (18)), then intramolecular sulfur addition forming the six-membered ring, is followed by successive losses of two mol equivalents of HBr. It is interesting that the only substantial structural difference between 16, in which the cyclisation is successful, and 10, for which no ring closure as observed, is the presence in 16 of a second imine unit – we suggest that this provides sufficient extra electron withdrawal to allow the nucleophilic sulfur addition.

EXPERIMENTAL

General
See reference 1.

8-(1,2-Dibromohex-1-en-1-yl)-7-methoxyisoquinoline (10)
A solution of Br₂ (0.032 mL, 0.61 mmol) in CH₂Cl₂ (1.25 mL) was added dropwise to a stirred solution of 8-(hex-1-yn-1-yl)-7-methoxyisoquinoline (9) (135 mg, 0.56 mmol) in CH₂Cl₂ (2.5 mL). The resultant mixture was stirred for 2 h at rt. Addition of 10% sodium metabisulphite and CH₂Cl₂ followed by separation, drying, and evaporation of the organic phase under reduced pressure gave a yellow oil. Purification by column chromatography over silica gel, eluting with petroleum ether/EtOAc (1:1) gave 8-(1,2-dibromohex-1-en-1-yl)-7-methoxyisoquinoline (10) (77 mg, 34%) as a brown solid, mp 131-132 °C, ¹H-NMR (300 MHz, CDCl₃) δ 1.06 (3H, t, J = 7.3 Hz), 1.57 (2H, m), 1.80 (2H, m), 3.02 (2H, m), 7.51 (1H, d, J = 9.2 Hz), 7.64 (1H, br s), 7.88 (1H, d, J = 9.2 Hz), 8.52 (1H, br s), 9.13 (1H, br s); ¹³C-NMR (300 MHz, CDCl₃) δ 13.9, 21.7, 29.7, 39.9, 56.7, 109.1, 118.0 (2 x C), 123.5, 128.5, 129.4 (2 x C), 130.9, 141.2, 149.1, 153.9; MS (CI) m/z 402, 400, 398 (M+1, 19, 37, 19), 240 (100); HRMS: Found: M⁺, 396.9682, C₁₆H₁₇N₂O⁷Br₂ requires M 396.9677.

2-Bromobenzaldehyde azine (13)
To a stirred mixture of powdered hydrazine sulfate (2.4 g, 13 mmol), water (18 mL) and aq. ammonia (saturated, 2.4 mL) was added 2-bromobenzaldehyde (7.6 g, 41 mmol) dropwise during 1 h. The solid produced was filtered off, washed with water and recrystallised from n-hexane/toluene (3:1) to give the azine (13) (6.3 g, 85%), as yellow needles, mp 170-171 °C, νₚₑₑₓₚ (film) 1587 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 9.06 (2H, s, 2xCH=N), 8.25 (2H, dd, J = 7.2, 1.8 Hz, 2xArH), 7.66 (2H, dd, J = 7.8, 1.4 Hz, 2xArH), 7.43 (2H, bd, J = 7.3 Hz, 2xArH), 7.35 (2H, dd, J = 7.4, 1.8 Hz, 2xArH); MS (CI) m/z 369, 367, 365 (M+1, 55, 100, 56%), 287 (25), 285 (20), 206 (45); Anal. Calcd for C₁₄H₁₀N₂Br₂: C, 45.9; H, 2.7; N, 7.7; Found: C, 45.9; H, 2.6; N, 7.6,
5-Bromophthalazine (14)
A mixture of 2-bromobenzaldehyde azine (13) (2.4 g, 2 mmol), aluminum chloride (16 g, 120 mmol) and aluminium bromide (14.7 g, 22 mmol) was heated at 180-185 °C under N2 for 30 min. Following addition of H2O (125 mL) to the cooled mixture, then aq. HCl (5%, 15 mL), the mixture was filtered. The filtrate was made alkaline using aq. KOH (15%) and then extracted thoroughly with toluene. The organic extract was dried and evaporated leaving crude material (0.61 g) which was purified by column chromatography over silica eluting with EtOAc/petroleum ether (4:1) giving 5-bromophthalazine (14) (0.25 g, 13%), mp 118-119 °C, νmax (film) 1553 cm⁻¹; 1H-NMR (300 MHz, CDCl3) δ 9.89 (1H, s, H-4), 9.52 (1H, br s, H-1), 8.18 (1H, dd, J = 7.6, 1.0 Hz, H-8), 7.98 (1H, d, J = 8.1 Hz, H-6), 7.80 (1H, t, J = 7.7 Hz, H-7); MS (CI) m/z 211, 209 (M+1, 89, 100%), 131 (20); Anal. Calcd for C8H5N2Br: C, 45.9; H, 2.4; N, 13.4, Found: C, 45.0; H, 2.2; N, 13.0.

5-Phenylethynylphthalazine (15)
A mixture of 5-bromophthalazine (14) (209 mg, 1.0 mmol), phenylethyne (0.13 mL, 1.2 mmol), bis(triphenylphosphine)palladium(II) chloride (1.8 mg), copper(I) iodide (8 mg), and Et3N (2 mL) were heated together at 62 °C for 24 h. After evaporation of the Et3N, the residue was treated with aq. HCl (1M, 20 mL) and extracted with CH2Cl2. The dried extract was evaporated and the residue purified by column chromatography over silica, elution with EtOAc/petroleum ether (4:1) giving the alkyne (15) (176 mg, 76%), mp 106-108 °C, λmax 320 nm; 1H-NMR (300 MHz, CDCl3) δ 10.08 (1H, br s, H-4), 9.58 (1H, d, J = 1.5 Hz, H-1), 8.12 (1H, dd, J = 6.2, 2.3 Hz, H-8), 7.95 (2H, m, ArH), 7.70 (2H, m, ArH), 7.46 (3H, m, ArH); MS (CI) m/z 231 (M+1, 100%); Anal. Calcd for C16H10N2: C, 83.5; H, 4.3; N, 12.1, Found: C, 82.2; H, 4.4; N, 11.8, M+ 230.0847.

5-(1,2-Dibromo-2-phenylethenyl)phthalazine (16)
A solution of Br2 in CH2Cl2 (0.12 mL in 10 mL, 3 mL) was added Dopwise to a stirred solution of 5-phenylethynylphthalazine (92 mg, 0.4 mmol) in CH2Cl2 (5 mL). The resultant mixture was stirred for 3 h at rt then aq. sodium metabisulfite (20%, 10 mL) was added, the layers separated and the CH2Cl2 layer dried and evaporated leaving crude material (120 mg). Purification by column chromatography over silica, eluting with EtOAc/CH2Cl2 (1:3) gave the dibromide (16) (60 mg, 59%), mp >230 °C decomp, 1H-NMR (300 MHz, CDCl3) δ 9.82 (1H, d, J = 1.2 Hz, H-4), 9.65 (1H, d, J = 1.5 Hz, H-1), 9.65 (1H, d, J = 1.5 Hz, H-1), 8.05 (3H, m, ArH), 7.70 (2H, m, ArH), 7.55 (3H, m, ArH); MS (CI) m/z 391 (M+1, 10%), 231 (16%); Anal. Calcd for C16H10N2Br2: Br, 41.0, Found: Br, 41.1, M+ 387.9214, C16H10N2Br2 requires M 387.9212.
5-Phenylthiino[2,3,4-d,e]phthalazine (17)
An aqueous solution of Na$_2$CS$_3^2$ (33%, 2 mL) was added dropwise to a solution of 5-(1,2-dibromo-2-phenylethenyl)phthalazine (16) (60 mg) in MeOH/THF (16:1, 8.5 mL) with stirring at 62 °C. After a further 18 h at reflux, the solvent was evaporated, the residue treated with H$_2$O and organic material extracted into CH$_2$Cl$_2$. The dried organic extract was evaporated leaving crude product (50 mg) which was purified by column chromatography over silica when elution with Et$_2$O/CH$_2$Cl$_2$ (1:1) gave the tricycle (17) (20 mg, 50%), mp >215 °C, $\lambda_{max}$ 266, 334 nm; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 9.98 (1H, s, H-1), 9.55 (1H, s, H-6), 8.20 (2H, m, ArH), 7.75 (3H, m, ArH), 7.42 (3H, m, ArH); MS (Cl) m/z 263 (M+1, 100%); Found M+: 262.0565, C$_{16}$H$_{10}$N$_2$S requires M 262.0565.

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REFERENCES