

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

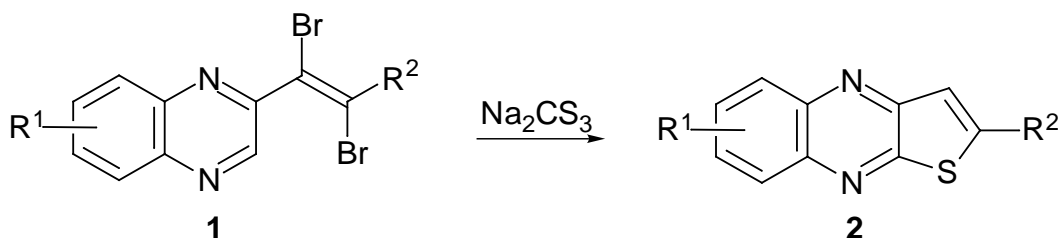
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Abstract – The reaction of 5-(1,2-dibromo-2-phenylethenyl)-phthalazine (**16**) with Na₂CS₃ gives 5-phenylthiino[2,3,4-*d,e*]phthalazine (**17**).

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.



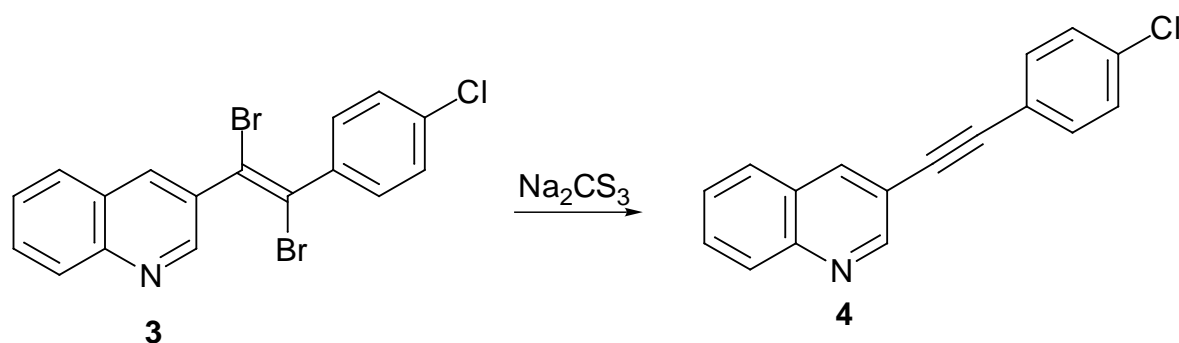
Scheme 1

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

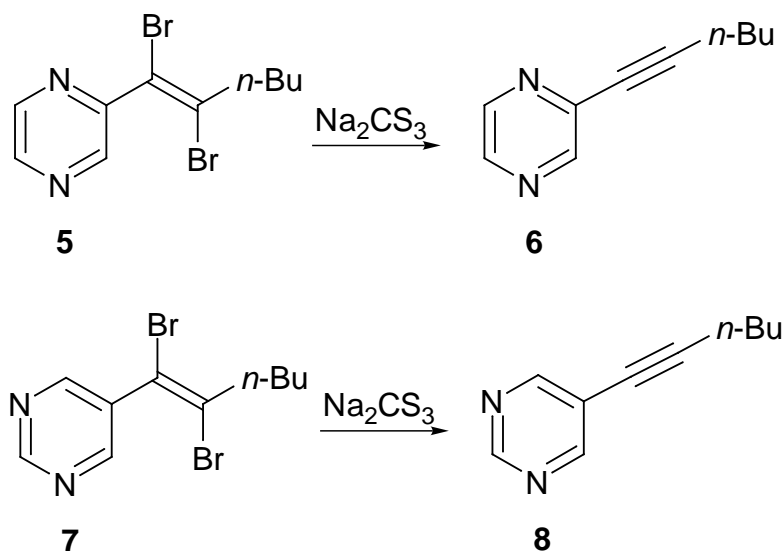
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of bromine was observed on treatment of **3** with disodium trithiocarbonate giving **4** (Scheme 2).

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



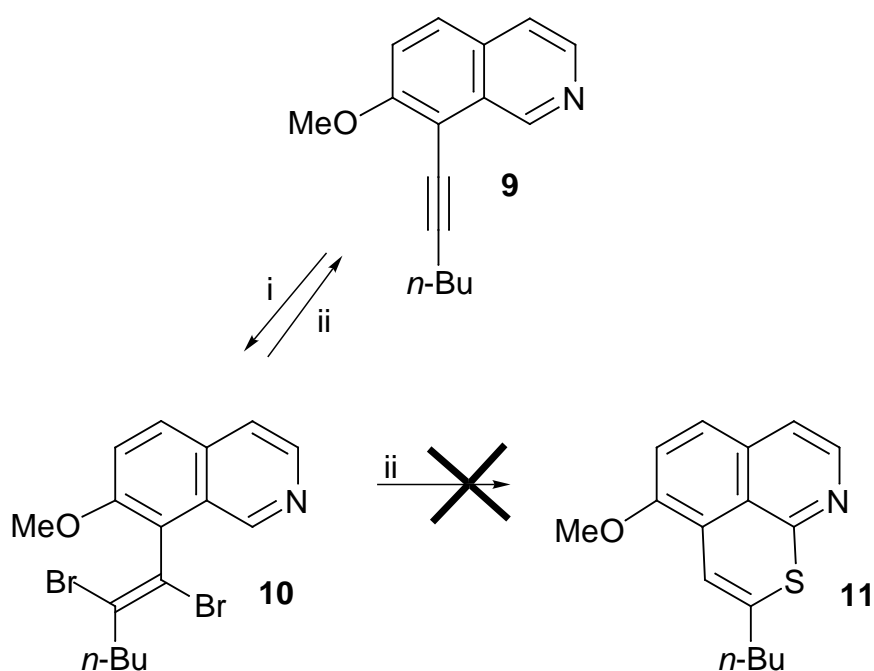
Scheme 3

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^{1,3} the dibromoalkene (10) was prepared by bromine addition to alkyne (9).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.

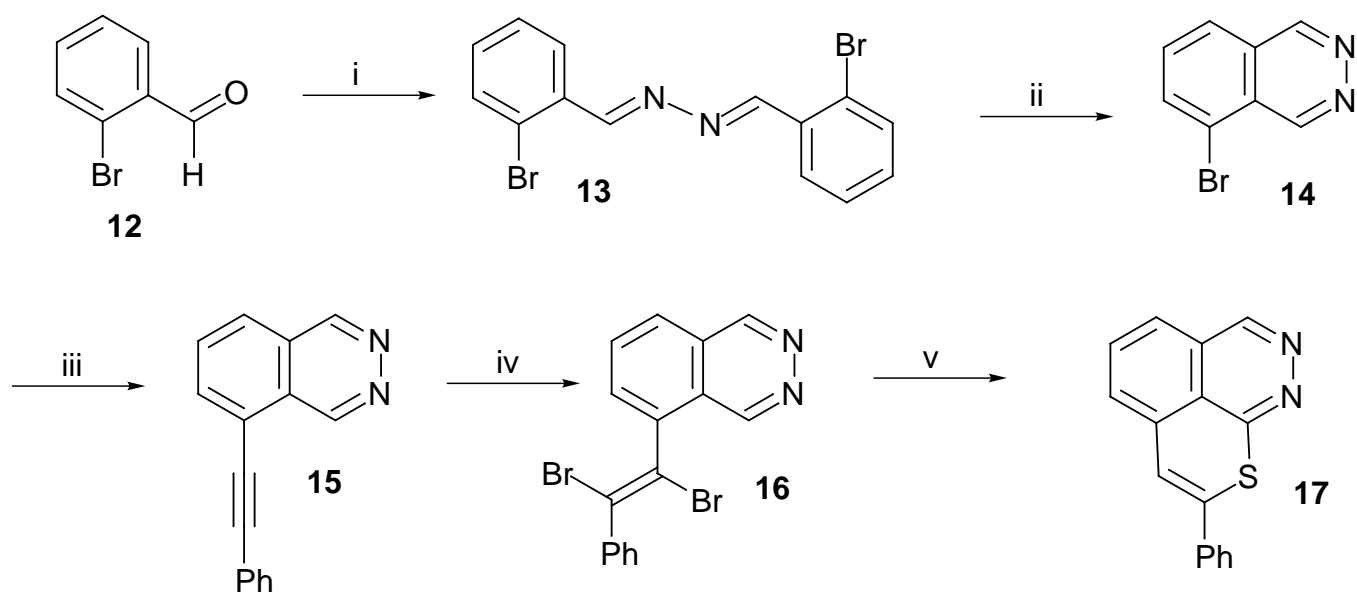


Scheme 4

Reagents: i, Br₂, CH₂Cl₂, rt (34%); ii, Na₂CS₃, MeOH, reflux (ca. 100%).

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.⁵

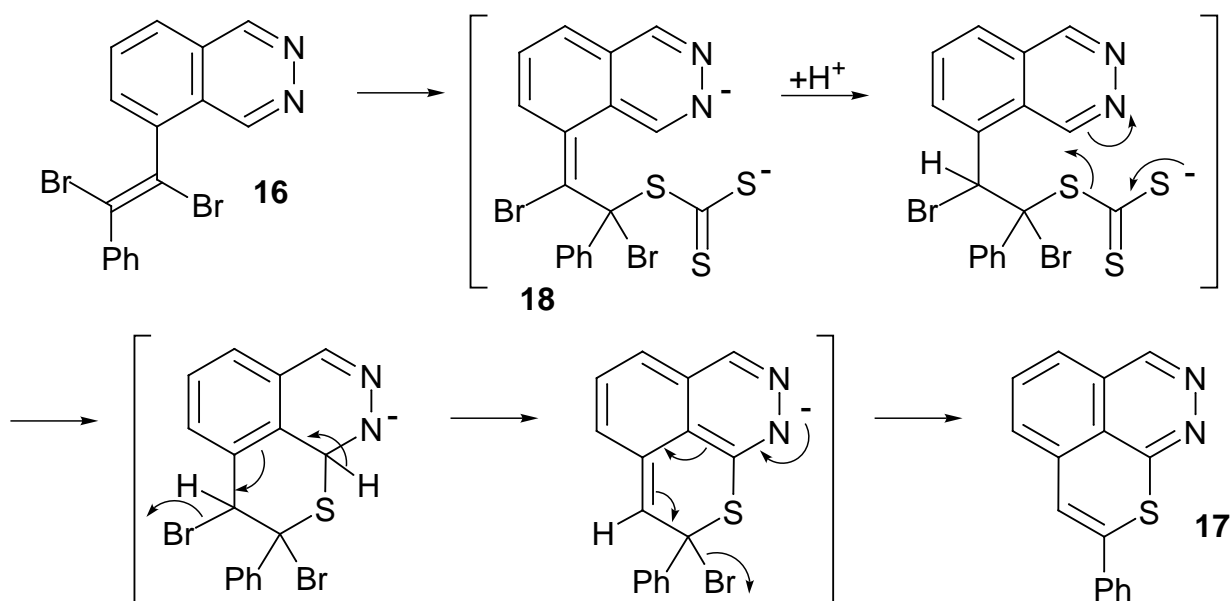
Reaction of 2-bromobenzaldehyde (**12**) with hydrazine gave crystalline, yellow azine (**13**). Application of Robev's method⁵ produced the desired 5-bromophthalazine (**14**), though only in 13% yield after purification; an alternative route will be required for future work. Coupling with phenylethyne was efficient, giving the alkyne (**15**) in 76% yield, as was addition of bromine producing the desired cyclisation substrate (**16**) (Scheme 5).



Scheme 5

Reagents: i, $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{SO}_4$, aq. NH_3 , rt (85%); ii, AlCl_3 , AlBr_3 , $185\text{ }^\circ\text{C}$, N_2 (13%); iii, $\text{PhC}\equiv\text{CH}$, $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, CuI , Et_3N , $62\text{ }^\circ\text{C}$ (76%); iv, Br_2 , CH_2Cl_2 , rt (59%); v, aq. Na_2CS_3 , MeOH , reflux (50%).

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 ^1H NMR spectrum, at δ 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.



Scheme 6

Following our earlier mechanistic speculation¹ 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**)⁴ (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, C₁₆H₁₇N₂O⁷⁹Br₂ 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, ν_{\max} (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, ν_{\max} (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, λ_{\max} 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, M 230.0842, 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 dropwise 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 Et₂O/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), 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, C₁₆H₁₀N₂⁷⁹Br₂ requires M 387.9212.

5-Phenylthiino[2,3,4-*d,e*]phthalazine (17)

An aqueous solution of Na_2CS_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_2O and organic material extracted into CH_2Cl_2 . The dried organic extract was evaporated leaving crude product (50 mg) which was purified by column chromatography over silica when elution with $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ (1:1) gave the *tricycle* (**17**) (20 mg, 50%), mp >215 °C, λ_{max} 266, 334 nm; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 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 (CI) m/z 263 ($\text{M}+1$, 100%); Found M^+ : 262.0565, $\text{C}_{16}\text{H}_{10}\text{N}_2\text{S}$ requires M 262.0565.

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