Cyclisation chemistry of 4H-1,2,6-thiadiazines

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3,5-Dichloro-4H-1,2,6-thiadiazine-4-one \(1 \) condenses rapidly at room temperature with 1,2-diaminobenzene, 2-aminophenol and sodium 2-aminophenoxide to give, respectively, the purple thiadiazinoquinoline 4a, red thiadiazinobenzothiazine 4b and orange thiadiazinobenzoxazine 4c in almost quantitative yield. The 10H-tautomer 4a is spectroscopically almost identical with the purple 10-methyl derivative 11 formed by condensation of 1 with N-methyl-1,2-diaminobenzene and by the methylation of 4a. The chlorine substituent in these tricyclic thiadiazine compounds is readily displaced by nucleophiles, to give the 4-ethoxy derivative 21. The dicyanomethylene compound 2, analogous to 1, reacts in the same way as 1 with 2-aminophenol to give 4b (87%), but its reaction with 1,2-diaminobenzene is more complex since, in addition to the analogous formation of 4a, there is now the possibility of another cyclisation in the intermediate 16 which leads to the tetracyclic compound 14 and its substitution product 15. This difference in reaction pathway between 1 and 2 is further illustrated by their condensation with 1,8-diaminonaphthalene: 1 is converted into 19 by simple displacement of chlorine, whilst 2 gives, almost quantitatively, the product 20 of cyclisation onto the neighbouring cyano group.

We have recently described some chemistry of the readily available 3,5-dichloro-4H-1,2,6-thiadiazine-4-one \(1 \) \(^{1,2} \) and the related new thiadizaine \(2 \) \(^{2,3} \) directed towards the synthesis of their amino derivatives required as monomers for conjugated polymers incorporating the repeat unit 3. The chlorine atoms in 1 and 2 are readily displaced by nucleophiles such as thiophenols and amines. We now describe the reactions of 1 and 2 with 1,4- and 1,5-bis-nucleophiles which provide a ready source of new, colourful poly cyclic ring systems.

Results and discussion

Cyclisations with 3,5-dichloro-4H-1,2,6-thiadiazine-4-one 1

Thiadiazinone 1 reacted smoothly with ethanolic solutions of 1,2-diaminobenzene and 2-aminophenol at room temperature to give purple 4-chloro-10H-1,2,6-thiadiazino[3,4-b]quinoxaline 4a [\(\lambda_{\text{max}} 548 \text{ nm (log } \varepsilon 3.58)\)], and the red 4-chloro[1,2,6]thiadiazino[3,4-b][1,4]benzothiazine 4b [\(\lambda_{\text{max}} 463 \text{ nm (log } \varepsilon 3.66)\)] respectively. The reactions were rapid and at relatively high concentrations (1 mmol of 1 and 2 mmol of the amine in \(ca. 10 \text{ ml EtOH}\) were complete within one hour; the new tricyclic products separated from the reaction mixture and recrystallisation gave analytically pure 4a (96%) and 4b (95%) in very high yields.

In view of the earlier work \(^{1,2} \) we propose that the first step is nucleophilic displacement of chlorine followed by cyclic dehydration as shown in Scheme 1. This is supported by treatment of thiadiazinone 1 with the mono-Boc derivative 5 of 1,2-diaminobenzene, under the same conditions, to give the analogous first product 6 in good yield (76%); deprotection of 6 with 3 M HCl in ethyl acetate\(^6 \) gave the cyclised product 4a (72%) directly (Scheme 2). The ready cyclisation appears to drive the reactions cleanly to completion since the analogous reaction of thiadiazinone 1 with 1,4-diaminobenzene, and its mono-Boc derivative,\(^6 \) gave the secondary amines 7a (20%) and 7b (38%) respectively in much lower yield. The Boc derivative 7b was hydrolysed with HCl as before to give 7a (93%).

![Scheme 1](image)

![Scheme 2](image)

Thiadiazinone 1 reacted slowly with 2-aminophenol (2 equiv. in boiling EtOH) to give the analogous secondary amine 8 (86%), where the amino group had preferentially displaced...
chlorine (Scheme 3). It is notable that even in boiling EtOH the uncyclised product 8 gave no sign of cyclodehydrating to give the thiadiazinobenzoxazine 9 with its higher energy S\(^\text{V}\) sulfur-dimide structure. However thiadiazinone 1 reacted rapidly and virtually quantitatively with the sodium salt of 2-aminophenol, in THF at room temperature in one hour, to give orange virtually quantitatively with the sodium salt of 2-aminophenol, diimide structure. However thiadiazinone

The spectral data of the three tricyclic compounds 4 are in good agreement with the proposed structures with sulfur in the S\(^\text{IV}\) oxidation state though, in principle, there is another regioisomer possible in each case with S\(^\text{V}\) sulfur, such as 9. In the formation of 4b and 4c the reagents 2-aminothiophenol and sodium 2-aminothiophenoxide would be expected to effect displacement of chlorine through the more nucleophilic sulfur and oxygen functions. However a further ambiguity arises in the 1,2-diaminobenzene reaction; by analogy with structures 4b and c, 4a is written with the amino hydrogen located at N-10 rather than N-1 or N-5, though delocalisation around the tricyclic system could possibly reduce the energy difference between these tautomers. Structure 4a was shown to be correct for the major tautomer (the only one observed) by comparison with the N-methylated derivative, 4-chloro-10-methyl-10\(^\text{H}\)thiadiazinoquinoxaline 11 which was prepared in two ways. The first involved reacting thiadiazinone 1 with N\(^\text{Me}\)-1,2-diaminobenzene, where it was expected that the greater nucleophilicity of the secondary amine would result in formation of isomer 10 which would cyclise to the N-10 methylated derivative 11 (Scheme 4). This reaction gave a

monomethylated purple product (70%) whose spectral data supported structure 11. No other isomeric product was observed, but a small amount (15%) of a yellow, highly fluorescent compound was obtained and identified as the tetracyclic

A comparison of the spectral data, particularly the UV and \(^{13}\)C NMR spectra, for compound 4a and its methylated derivative 11 showed that they were almost identical, in agreement with the 10\(^\text{H}\) structure 4a being the tautomer isolated.

Cyclisations with 3,5-dichloro-4-dicyanomethylene-1,2,6-thiadiazine 2

An ethanolic solution of the dicyanomethylene compound 2 and 2-aminothiophenol gave the tricyclic thiadiazine 4b (87%), identical with the product from thiadiazinone 1, presumably by the same mechanism but with the expulsion of malononitrile upon cyclisation (Scheme 5). The reaction of 2 with 1,2-diaminobenzene was more complex however (Scheme 6, Table 1). Two major products, thiadiazinoquinoxaline 4a and 4-chloro-5-cyano[1,2,6]thiadiazino[3',4':5,4]pyrrolo[1,2-a]-benzimidazole 14, and a minor product 15 were isolated. Compound 4a was identical with that described above (Scheme 1). Attempts to improve the yields (Table 1) of 4a and 14 were unsuccessful, though we noted that an excess of 1,2-diaminobenzene reduced the yield of 14 whilst one equiv. actually improved the yield; this suggests that cyclisation onto the nitrile to yield 14 is acid catalysed.

Compound 14 was obtained as bright red needles (the kinetic polymorph from rapid crystallisation from 1,2-dichloroethane)
or as deep red prisms (the thermodynamic polymorph from slow crystallisation from 1,2-dichloroethane), both with mp 254–256 °C. The bright red needles darkened in colour on heating above 145 °C. Microanalysis and HRMS gave the molecular formula as C_{14}H_{12}ClN_{3}S, indicating the loss of the elements of NH_{2}Cl in its formation. The 14C NMR spectra showed twelve separate resonances indicating an unsymmetrical molecule, and the signal at 112.3 ppm supported the presence of a cyanide indicated by IR stretching at 2230 cm \(^{-1}\); no amine stretching was observed. On this basis structure 14 was proposed and this was confirmed by X-ray crystallography.\(^{8}\) An attempted independent synthesis of 14 from thiadiazine 1 and 2-benzimidazolylacetonitrile gave only a trace ( TLC) of the desired compound.

A probable route to the tetracyclic compound 14 is shown in Scheme 7. After displacement of chlorine by 1,2-diamino-

<table>
<thead>
<tr>
<th>Compound 2/ mmol</th>
<th>1,2-Diamino- benzene (equiv.)</th>
<th>Reaction time/h</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.24</td>
<td>1</td>
<td>48</td>
<td>22 4a(^{a}) 34(^{b}) Trace</td>
</tr>
<tr>
<td>0.22</td>
<td>2</td>
<td>12</td>
<td>— 42 19 —</td>
</tr>
<tr>
<td>0.26</td>
<td>3</td>
<td>36</td>
<td>— 23 Trace —</td>
</tr>
</tbody>
</table>

\(^{a}\) Yields calculated assuming 2 equiv. of amine required for the formation of 4a. \(^{b}\) Yields take into account the recovered starting material 2.

Conclusion

We have shown that a variety of highly coloured, stable polycyclic 1,2,6-thiadiazines can be readily prepared from the

Cyclisations with 1,8-diaminonaphthalene

With these mechanisms in mind, we decided to treat the thiadiazines 1 and 2 with a bis-amine that could not form a 6-membered cyclic intermediate necessary for generation of the very stable products like 4a; we chose 1,8-diaminonaphthalene which would have to form a less favourable 7-membered ring when cyclising onto C-4 of the thiadiazine ring. Reaction of the thiadiazine 1 with 1,8-diaminonaphthalene gave only the initial product 19 in moderate yield (46%), with no sign of cyclodehydration (Scheme 8). Since the analogous cyclisation
monocyclic thiadiazines 1 and 2. By variation of the C-4 substituent and the heteroatom at position 10 of the tricyclic compounds 4 a wide range of potential new chromophores could be produced. Whilst the highly coloured compounds are not suitable for use as non-linear optical materials, simple oxidation of the sulfur to its dioxide would give compounds similar to the sulfone 22, the only other reported example of these ring systems, which has been investigated as an optical dye.  

Experimental

General experimental details have been described before. Compounds 1 and 2 were prepared by the literature methods. Additionally 250 MHz 1H NMR and 62.9 MHz 13C NMR were recorded on a Bruker WM250 machine.

4-Chloro-10H-[1,2,6]thiadiazino[3,4-b]quinazoline 4a

Method 1. To a stirred solution of 3,5-dichloro-4H-1,2,6-thiadiazino-4-one 1 (182 mg, 1.0 mmol) in EtOH (7 ml) at ca. 20 °C 1,2-diaminobenzene (216 mg, 2.0 mmol) was added in one portion. The mixture became purple and after 1 h a deep purple precipitate had formed. This was filtered off (215 mg, 91%) and the addition of a little water to the filtrate gave a second purple precipitate (12 mg, 5%). The precipitates (identical by TLC) were combined and crystallisation gave the title compound 4a (227 mg, 96%) as purple-red needles, mp >280°C. By variation of the C-4 substituent and the heteroatom at position 10 of the tricyclic compounds 4 a wide range of potential new chromophores could be produced. While the highly coloured compounds are not suitable for use as non-linear optical materials, simple oxidation of the sulfur to its dioxide would give compounds similar to the sulfone 22, the only other reported example of these ring systems, which has been investigated as an optical dye.  

4-Chloro-10H-[1,2,6]thiadiazino[3,4-b][1,4]benzothiazine 4b

Method 1. To a stirred solution of 3,5-dichloro-4H-1,2,6-thiadiazino-4-one 1 (182 mg, 1.0 mmol) in EtOH (7 ml) at ca. 20 °C 2-aminothiazoline (1.0 mmol) was added in one portion. The mixture rapidly became red and after 1 h a red precipitate had formed. This was filtered off and crystallisation gave the title compound 4b (645 mg, 85%) as orange-red needles, mp 149–152 °C (from EtOH) (Found: C, 42.6; H, 1.3; N, 16.5. Calc. for C27H19ClN5S, 456.0553). (ii) To a stirred solution of 3-[2-(N-tert-butoxycarbonylamino)anilino]-5-chloro-1,2,6-thiadiazino-4-one 6 (21 mg, 0.06 mmol) in ethyl acetate (1 ml) at ca. 20 °C, was added 3 M HCl. After 6 h the mixture was diluted with ethyl acetate (5 ml), treated with aqueous sodium bicarbonate and the organic layer was separated, dried and the volatiles were removed. Flash chromatography (EtOAc) of the residue gave the title compound 4a (10 mg, 72%) identical with that prepared above.

4-Chloro-1,2,6-thiadiazino[3,4-b][1,4]benzoxazine 4c

To a solution of 2-aminophenol (981 mg, 9 mmol) in THF (60 ml) at ca. 20 °C, under nitrogen, excess of NaH (380 mg of 60% mineral suspension) was added. This solution (0.15 M, 8 ml, 1.20 mmol) was added slowly to a stirred solution of 3,5-dichloro-4H-1,2,6-thiadiazino-4-one 1 (211 mg, 1.16 mmol) in THF (5 ml) at ca. 20 °C, under nitrogen. The mixture became orange and after 1 h no starting material remained (TLC). The mixture was diluted with DCM (30 ml) and washed with water (5 × 10 ml). The organic fraction was dried, filtered, and the volatiles were removed. Crystallisation of the residue gave the title compound 4c (272 mg, 99%) as orange prisms, mp 158–163 °C (from EtOH) (Found: C, 45.3; H, 1.6; N, 17.6. Calc. for C17H14ClN5S, requires C, 45.6; H, 1.7; N, 17.7%).
3-(Aminoanilino)-5-chloro-1H,2,6-thiadiazin-4-one 7a

Method 1. (i) To a stirred solution of 3,5-dichloro-1H,2,6-thiadiazin-4-one 1 (419 mg, 2.29 mmol) in DCM (20 ml) at ca. 20 °C 4-(N-tert-butoxycarbonylamino)aniline* (478 mg, 2.29 mmol) was added in one portion and after 2 h pyridine (186 µl, 2.30 mmol) was added. After further 1 h the orange coloured mixture was adsorbed onto silica and flash chromatography (DCM) followed by recrystallisation gave the 3-(4-(N-tert-butoxycarbonylamino)anilino)-3-chloro-1H,2,6-thiadiazin-4-one 7b (310 mg, 38%) as orange crystals, mp 184–185 °C (from EtOH); m(w) (EtOH)/nm 245 (log ε 2.97), 319 (3.16), 336 (3.16); m(w)(Nujol)/cm–1 3380 and 3300 (NH), 1728, 1632m, 1596m, 1557m, 1525s, 1508s, 1318m, 1249m, 1229m, 117m, 1159m, 889m, 837m; δ 250 MHz; CDCl3) 8.22 (1H, br, NH), 7.56 (2H, d, J 8.8 Hz, Ar H), 7.40 (2H, d, J 8.8 Hz, Ar H), 6.51 (1H, br, NH), 1.53 (9H, s, Bu). δ 62.9 MHz; CDCl3) 156.7, 152.7, 149.9, 141.1, 135.8, 132.0, 120.9, 119.4, 80.8 [C(Chl)]. 28.4 (CH2); m(w) (EtOH) 354 (M+2, 2%), 298 (M+2, Ba 3), 280 (12), 254 (24), 253 (308), 196 (38), 178 (13), 165 (4), 160 (11), 152 (43), 134 (32), 118 (5), 108 (50), 91 (50), 86 (16), 57 (Bu), (88) (Found: M+, 354.0550. C13H11ClN3O3S requires M+, 354.0553). (ii) To a stirred solution of 3-[4-(N-tert-butoxycarbonylamino)anilino]-3-chloro-1H,2,6-thiadiazin-4-one 7b (52 mg, 0.15 mmol) in ethyl acetate (5 ml) at 20 °C, was added 3 M HCl. After consumption of the starting material (TLC) the volatiles were removed. Flash chromatography (EtO)/residue gave the title compound 7a (35 mg, 93%) as a red solid, mp 214–215 °C; m(w)(EtOH)/nm 240 (log ε 3.74), 322 (3.92), 340 (3.92); m(w)(Nujol)/cm–1 3426, 3320, and 3340s (NH), 1616s, 1596s, 1586m, 1505w, 1175m; δ 270 MHz; DMSO-d6) 7.33 (2H, d, J 8.6 Hz, Ar H), 6.54 (2H, d, J 8.6 Hz, Ar H), 5.04 (2H, br, NH2); m(w) (EtOH) 254 (M+, 100%), 165 (24), 160 (17), 133 (64), 132 (9), 118 (22), 107 (38), 80 (13), 65 (7) (Found: M+, 254.00014. C13H11ClN3O3S requires M+, 254.0029). 3-Chloro-5-(2-hydroxyanilino)-1H,2,6-thiadiazin-4-one 8

To a stirred solution of 3,5-dichloro-1H,2,6-thiadiazin-4-one 1 (523 mg, 2.86 mmol) in EtOH (10 ml) at 20 °C 2-aminophenol (625 mg, 5.73 mmol) was added in one portion. The mixture was heated at reflux for 72 h and then cooled to ca. 20 °C. The volatiles were removed and flash chromatography (EtO)/residue gave the title compound 8 (626 mg, 86%) as orange crystals, mp 230–231 °C (from MeOH) (Found: C, 42.2; H, 2.2; N, 16.1. C12H9ClN3O3S requires C, 42.3; H, 2.4; N, 16.4%; m(w)(Nujol)/cm–1 3400–3200br (Ar OH), 3346m (Ar NH), 3019w (Ar CH), 1607m, 1557w; δ 500 MHz; DMSO-d6) 10.30 (1H, br, OH), 9.25 (1H, br, NH), 8.05 (1H, dd, J 4.1, 8.0 Hz, Ar H). 7.00–6.97 (1H, m, Ar H), 6.91 (1H, dd, J 1.5, 8.0 Hz, Ar H), 7.07 (1H, d, J 1.5, 7.8 Hz, Ar H), 10.17 (1H, d, J 7.8 Hz, Ar H); m(w) (EtOH) 313 (30), 255 (1), 175 (4), 163 (8), 134 (9), 119 (22), 107 (38), 80 (14), 67 (7) (Found: M+, 254.00014. C12H9ClN3O3S requires M+, 254.0029).
9-Chloro-8-cyano[1,2,6]thiadiazino[3',4':5,4']pyrrolo[1,2-e]-perimidine 20

To a stirred solution of (3,5-dichloro-4H-1,2,6-thiadiazin-4-ylidene)propanedinitrile 2 (57.5 mg, 0.25 mmol) in EtOH (4 ml) at ca. 20 °C, 1,8-diaminonaphthalene (39.5 mg, 0.25 mmol) was added in one portion. After 12 h at ca. 20 °C filtration gave a black precipitate which on crystallisation gave the title compound 20 (68 mg, 81%) as deep green needles, mp >300 °C (from glacial acetic acid) (Found: C, 57.1; H, 2.1; N, 20.7. C_{12}H_{8}ClN_{3}S requires C, 57.3; H, 1.8; N, 20.9%). \( \lambda_{\text{max}} \) (DCM)/nm 274 (log e 4.84), 326 (4.00), 387 (4.35), 406 (4.37), 431 (3.94), 457 (3.86), 491 (3.60), 568 (3.60), 609 (3.75), 662 (3.77), 722 (3.54); \( \nu_{\text{max}} \) (Nujol)/cm\(^{-1} \) 3103w and 3062w (Ar CH), 2231 (1135), 1652w, 1523s, 1570s, 1527s, 1494w, 1455s, 1417s, 1387s, 1235s, 1221m, 1184m, 1166s, 1132s, 1124m, 1058m, 1005m, 904s, 827s, 810m, 793m, 770m, 708s, 663m, 622s; \( \nu_{\text{max}} \) (EtOH) 335 (M^+ , 100%), 299 (M^+ – HCl, 29), 267 (6), 212 (5), 167.5 (M^+ – 8), 162 (12), 151 (10), 140 (7), 113 (8), 91 (4), 69 (55) (Found: M^+ , 335.0027. C_{12}H_{8}ClN_{3}S requires M^+, 335.0032). The use of two equivalents of 1,8-diaminonaphthalene, under similar conditions, gave the title compound 20 in 96% yield.

4-Piperidino[1,2,6]thiadiazino[3,4-f]-[1,4]benzothiazine 21

To a solution of 4-chloro[1,2,6]thiadiazino[3,4-f]-[1,4]benzothiazine 4b (126.5 mg, 0.50 mmol) in DCM (5 ml) at ca. 20 °C piperidine (99 µl, 1 mmol) was added in one portion. The mixture was refluxed for 1 h after which time TLC indicated a new product and no starting material. The mixture was diluted with DCM (20 ml), washed with water (3 x 5 ml) and the organic fraction was filtered, washed and the volatiles were removed. Crystallisation of the residue gave the title compound 21 (149 mg, 99%) as red prisms, mp 101–103 °C (from EtOH-water; \( \lambda_{\text{max}} \) (DCM)/nm 240 (log e 4.24), 269 (3.93), 389 inf (4.14), 382 (3.82), 492 (3.90); \( \nu_{\text{max}} \) (Nujol)/cm\(^{-1} \) 3030w (Ar CH), 1586m, 1515s, 1505s, 1461w, 1287m, 1257s, 1275m, 1227m, 1203s, 1133m, 1125m, 1036m, 1062w, 968m, 955m, 916s, 883m, 855m, 815s, 804m, 790m, 760s, 793m, 721s, 625s, 601s; \( \delta_{\text{H}} \) (CDCl\(_3\)) 7.25–7.21 (1H, m, Ar CH), 7.15–7.09 (2H, m, Ar H), 6.92–6.89 (1H, m, Ar H), 3.57 [4H, br s, 2(CH\(_2\)N\(_2\)) ], 1.69 [6H, br s, 3(CH\(_2\)) ]; \( \delta_{\text{C}} \) (CDCl\(_3\)) 149.3 (C–N), 144.4 (C–N), 139.9 (C–N), 135.7, 130.2 (Ar CH), 129.7, 128.2 (Ar CH), 127.5 (Ar CH), 125.4 (Ar CH), 48.0 (CH\(_2\)N\(_2\)), 25.7 (CH\(_2\)CH\(_2\)N\(_2\)), 24.8 (CH\(_2\)CH\(_2\)CH\(_2\)N\(_2\)) \( \nu_{\text{max}} \) (EtOH) 302 (M^+ , 41%), 267 (4), 236 (3), 220 (6), 186 (3), 161 (26), 134 (2), 108 (6), 84 (CH\(_2\)N\(_2\)) (100) (Found: M^+, 302.0600. C_{12}H_{8}ClN_{3}S requires M^+, 302.0660).

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