Synthesis of 3,1-Benzoxazines, 3,1-Benzothiazines and 3,1-Benzoxazepines *via* *N*-Arylimino-1,2,3-dithiazoles

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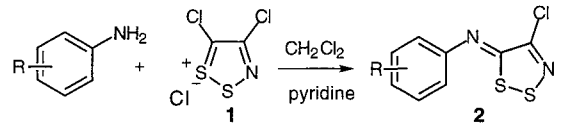
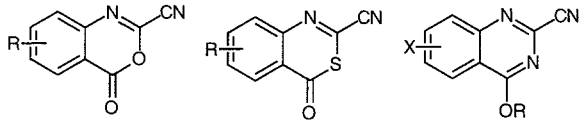
Abstract : *o*-Aminobenzyl alcohols are converted in two steps into 3,1-benzoxazines **7** and 3,1-benzothiazines **8**, and *o*-aminophenethyl alcohol is converted into 3,1-benzoxazepine **9**.

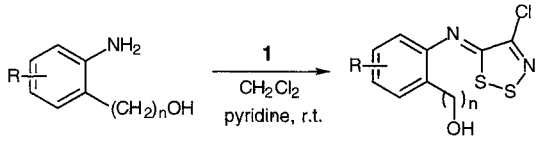
We have shown that 4,5-dichloro-1,2,3-dithiazolium chloride **1**, which is readily prepared from chloroacetonitrile and disulfur dichloride, reacts rapidly with anilines in the presence of pyridine to give very stable, pale yellow to orange, *N*-arylimines **2**.[1] We have studied the effect of varying substituents in the aniline ring.[1-3] Thus, neighbouring groups such as carboxylic acid and nitrile introduced into the *ortho* position of the *N*-aryl group of the imines **2** allowed formation of novel 3,1-benzoxazin-4-ones **3**,[3] 3,1-benzothiazin-4-ones **4**[3] and 4-alkoxyquinazolines **5**,[4] derivatives of which continue to be of interest because of their diverse biological activity [*e.g.* potent alternate inhibitors of human leucocyte elastase, herpes simplex (HSV-1) and C1 complex (C1r) serine proteases and porcine cyclic GMP phosphodiesterase].[5]





In this paper we report that introduction of a hydromethyl group into the *ortho* position of the iminodithiazole **2** allows access to the benzoxazine and benzothiazine rings (products **7** an **8**) in moderate to good yields. The dihydro-3,1-benzoxazepine **9** was also prepared in two steps from 2-aminophenethyl alcohol.

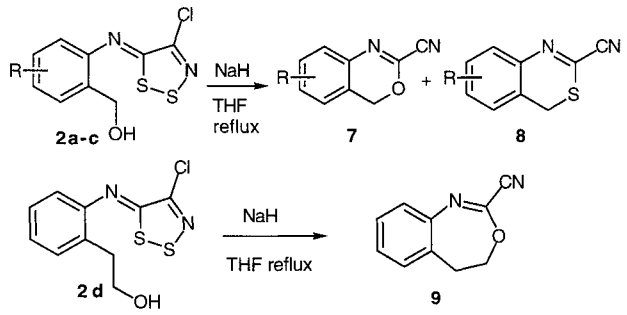
Primary aromatic amines **6**[6,7] were condensed with 4,5-dichloro-1,2,3-dithiazolium chloride **1** in dichloromethane at room temperature, followed by addition of pyridine, to give the iminodithiazoles **2a-d** in good yield (Scheme 1).[8]



Amine	n	R	Product	yield (%)	mp(C°)
6a	1	H	**2a**	60	142
6b	1	4-Me	**2b**	70	116
6c	1	5-Cl	**2c**	75	145
6d	2	H	**2d**	71	oil

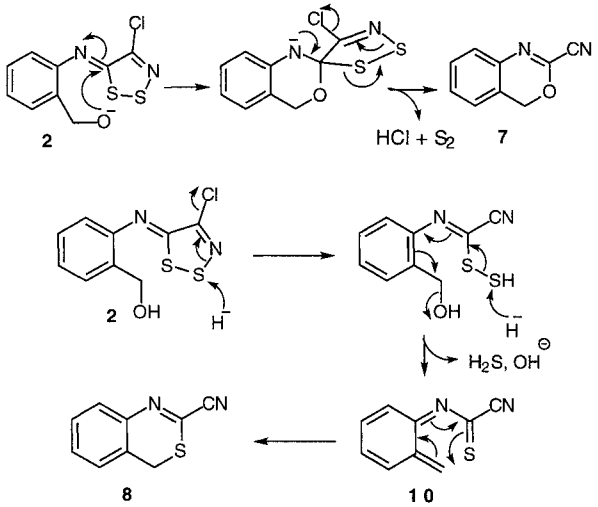
Scheme 1

A mixture of 2-cyanobenzoxazines **7** and 2-cyanobenzothiazines **8** (approximate ratio 8:1) was obtained by heating the starting imines **2a-c** in THF at reflux in the presence of 2 equiv. of sodium hydride for approximately 1 h (Scheme 2). Direct separation and purification of the two products was difficult and needed three recrystallizations. Treatment of the reaction mixture with an excess of *m*-chloroperbenzoic acid allowed an easier isolation of the benzoxazines **7** from the S-oxides of **8** by column chromatography (Table, method A).



Scheme 2

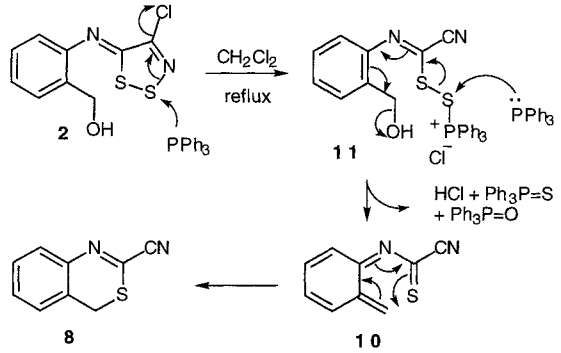
Mechanisms for the formation of **7** and **8** are proposed in Scheme 3. The oxygen-containing rings **7** and **9** are probably formed by cyclisation of the alkoxide from **2** onto the imine bond, followed by loss of singlet diatomic sulfur to generate the cyano group. The formation of the sulfur compounds **8** may involve opening of the dithiazole ring (see below) by hydride,[9] followed by elimination of H_2S and H_2O, as shown, to give the reactive intermediate **10** which cyclises to the stable product.



Scheme 3

The benzothiazine ring may also be obtained, in much better yield, by heating the imino-1,2,3-dithiazoles **2a-c** in dichloromethane at reflux in the presence of 2 equiv. of triphenylphosphine (Table, method B). As we

previously suggested for the synthesis of 2-cyano-3,1-benzothiazin-4-ones **4**,[3] initial attack by phosphorus on S-2 of the 1,2,3-dithiazole **2** will open the dithiazole ring with formation of the intermediate disulfide **11**. Attack by a second triphenylphosphine on the same sulfur results in elimination of $Ph_3P=S$ and $Ph_3P=O$ to give the reactive intermediate **10** which cyclises to the stable benzothiazine **8** in good yield (Scheme 4).



Scheme 4

Table. Synthesis of benzoxazines **7**, benzothiazines **8** and benzoxazepine **9** from imines **2**.[10]

Starting imines	Method[a]	Product	Yield of product[b] (%)
2a	A	**7a**	44 (55 : 5)
2a	B	**8a**	58
2b	A	**7b**	54 (60 : 10)
2b	B	**8b**	65
2c	A	**7c**	30 (44 : 6)
2c	B	**8c**	80
2d	A	**9**	50

[a] Method A : NaH (2 equiv.), THF reflux; method B : PPh_3 (2 equiv.), CH_2Cl_2 reflux. [b] In brackets : yields of compounds (**7** : **8**) after a rapid separation by column chromatography and before treatment of the mixture by MCPBA (determined by ^{1}H-NMR spectroscopy).

In conclusion, these reactions provide a simple route to benzo fused derivatives of 2-cyanooxazines and 2-cyanothiazines. Functional groups at the 2-position of these ring systems are not common and 2-cyano groups are very rare. To our knowledge 2-cyano-3,1-benzoxazepines have not been reported before.

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(6) Starting amines are commercially available excepted for the 5-chloro derivative **6c** which was synthesized by reduction of 2-amino-4-chlorobenzoic acid by the procedure described in ref. 7.

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(9) A similar mechanism was suggested for reduction by HCl/ $NaBH_3CN$; Lee H.; Kim, K. *Heteroatom. Chem.* **1993**, *4*, 263.

(10) All compounds were fully characterized by spectroscopy and elemental analysis; selected data for new compounds **2a**, **2b** and **2d**; **7a** and **7c**, **8a**, **8c** and **9**.

4-Chloro-5-(2-hydroxymethylphenylimino)-5H-1,2,3-dithiazole **2a**: orange needles, mp 142°C, IR (KBr), ν 3200 (OH), 2926, 2863, 1698, 1600, 1568, 1480, 1450, 1364, 1224, 1186, 1144, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$+ D_2O): δ 4.74 (s, 2H, CH_2OH), 7.25-7.45 (m, 4H, Harom); ^{13}C-NMR ($CDCl_3$): δ 63.40, 115.76, 127.36, 128.83, 129.11, 135.01, 147.41, 148.46, 153.43; MS (EI) m/z 258 (M^+, 22%), 194 (M^+-S_2, 25), 159 (M^+-[S_2,Cl], 55), 132 (M^+-[S_2-N=C-Cl], 100). HRMS: calcd. for $C_9H_7ClN_2OS_2$: 257.9688, found 257.9680.

4-Chloro-5-(4-methyl-2-hydroxymethylphenylimino)-5H-1,2,3-dithiazole **2b**: yellow needles, mp 144°C, IR (KBr), ν 3253 (OH), 2936, 1610, 1591, 1481, 1230, 1141, 1109, 1046, 1017 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$+ D_2O): δ 2.38 (s, 3H, CH_3), 4.72 (s, 2H, CH_2OH), 7.18-7.34 (m, 3H, Harom); ^{13}C-NMR ($CDCl_3$): δ = 21.71, 63.98, 116.08, 129.42, 130.30, 135.86, 138.09, 144.76, 149.10, 156.25; MS (EI) m/z = 272 (M^+, 23%), 208 (M^+-S_2, 14), 173 (M^+-[S_2,Cl], 49), 146 (M^+-[S_2-N=C-Cl], 100). HRMS: calcd. for $C_{10}H_9ClN_2OS_2$: 271.9844, found 271.9838.

4-Chloro-5-(5-chloro-2-hydroxymethylphenylimino)-5H-1,2,3-dithiazole **2c**: yellow needles, mp 116°C, IR (KBr), ν 3289 (OH), 2905, 1602, 1557, 1537, 1505, 1478, 1393, 1220, 1143, 1036 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$+ D_2O): δ = 4.75 (s, 2H, CH_2OH), 7.307 (dd, 1H, J = 2.1 and 8.3 Hz, Harom), 7.38 (d, 1H, J = 2.1 Hz, Harom), 7.46 (d, 1H, J = 8.3 Hz, Harom); ^{13}C-NMR ($CDCl_3$): δ = 62.89, 116.55, 127.31, 130.61, 133.50, 134.76, 148.68, 149.09, 159.35; MS (EI) m/z 292 (M^+, 24%), 228 (M^+-S_2, 34), 193 (M^+-[S_2,Cl], 51), 166 (M^+-[S_2-N=C-Cl], 100). HRMS: calcd. for $C_9H_6Cl_2N_2OS_2$: 291.9298, found 291.9300.

4-Chloro-5-[2-(2-hydroxyethyl)phenylimino]-5H-1,2,3-dithiazole **2d**: orange oil; IR (neat), ν 3381, 2927, 1588, 1570, 1481, 1447, 1264, 1223, 1146, 1043 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$+ D_2O): δ 2.95 (t, 2H, J = 6.28 Hz, CH_2CH_2OH), 3.85 (t, 2H, J = 6.28 Hz, CH_2CH_2OH), 7.15-7.35 (m, 4H, Harom); ^{13}C-NMR ($CDCl_3$): δ 35.82, 63.83, 116.27, 127.55, 128.49, 131.74, 132.93, 148.49, 149.82, 158.53.

4H-3,1-Benzoxazine-2-carbonitrile **7a**: colourless needles, mp 89°C; IR (KBr), ν 2888, 2244 (CN), 1626, 1601, 1487, 1463, 1250, 1183, 1006 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 5.40 (s, 2H, CH_2O), 6.97 (dd, 1H, J = 1.8 and J = 8.6 Hz, Harom), 7.23 (dd, 1H, J = 1.8 and J = 8.6 Hz, Harom), 7.30 (m, 2H, Harom); ^{13}C-NMR ($CDCl_3$) : δ = 67.96, 112.01, 122.26, 124.65, 126.44,

130.10, 130.32, 136.44, 136.9; MS (EI) m/z 158 (M^+, 100%), 132 (M^+-CN, 20), 103 (M^+-1-[O-C-CN], 58). HRMS: calcd. for $C_9H_6N_2O$: 158.0480, found 158.0487.

*6-Methyl-4*H-*3,1-benzoxazine-2-carbonitrile* **7b**: white needles, mp 124°C (Lit.[9] : 121-123°C).

*7-Chloro-4*H-*3,1-benzoxazine-2-carbonitrile* **7c**: pale yellow needles, mp 94°C; IR (KBr), ν 2923, 2244 (CN), 1627, 1593, 1458, 1376, 1249, 1178, 1122, 1078 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.39 (s, 2H, CH_2O), 6.93 (d, 1H, J = 8 Hz, Harom), 7.27 (dd, 1H, J = 2.4 and J = 8 Hz, Harom), 7.30 (d, 1H, J = 2.4 Hz, Harom); ^{13}C-NMR ($CDCl_3$): δ 67.24, 111.24, 120.02, 125.22, 126.13, 129.65, 135.23, 136.81, 137.62; MS (EI) m/z 192 (M^+, 55%), 166 (M^+-CN, 17), 157 (M^+-Cl, 45). HRMS: calcd. for $C_9H_5ClN_2O$: 192.0090, found 192.0090.

*4*H-*3,1-Benzothiazine-2-carbonitrile* **8a**: colourless needles, mp 86°C; IR (KBr), ν 2923, 2232 (CN), 1574, 1525, 1455, 1306, 1159, 1111, 1075 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 2H, CH_2S), 7.14 (m, 1H, Harom), 7.40 (m, 3H, Harom); ^{13}C-NMR ($CDCl_3$): δ 27.98, 114.04, 117.78, 127.48, 128.14, 129.39, 131.12, 135.33, 142.34; MS (EI) m/z 174 (M^+, 100%), 148 (M^+-CN, 3). HRMS: calcd. for $C_9H_6N_2S$: 174.0251, found 174.0260.

*6-Methyl-4*H-*3,1-benzothiazine-2-carbonitrile* **8b**: white needles, mp 102°C (Lit.[9] : 105°C).

*7-Chloro-4*H-*3,1-benzothiazine-2-carbonitrile* **8c**: pale yellow needles, mp 149°C; IR (KBr), ν 2971, 2235 (CN), 1562, 1530, 1470, 1421, 1124, 1077 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.03 (s, 2H, CH_2S), 7.09 (d, 1H, J = 8.3 Hz, Harom), 7.37 (dd, 1H, J = 2 and J = 8.3 Hz, Harom), 7.40 (d, 1H, J = 2 Hz, Harom); ^{13}C-NMR ($CDCl_3$): δ 27.62, 113.74, 116.15, 127.96, 128.45, 130.77, 134.94, 137.12, 143.11; MS (EI) m/z 208 (M^+, 61%), 182 (M^+-CN, 3), 173 (M^+-Cl, 100). HRMS: calcd. for $C_9H_5ClN_2S$: 207.9862, found 207.9873.

3,1-Benzoxazepine-2-carbonitrile **9**: white needles, mp 80°C; IR (KBr), ν 2923, 2243 (CN), 1660, 1597, 1484, 1455, 1266, 1225, 1180 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.19 (t, 2H, J = 4.4 Hz, CH_2), 4.53 (t, 2H, J = 4.4 Hz, CH_2O), 7.12 (dd, 1H, J = 1.5 and J = 8 Hz, Harom), 7.20 (dt, 1H, J = 1.5 and J = 8 Hz, Harom), 7.28 (dt, 1H, J = 1.5 and J = 8 Hz, Harom), 7. 39 (dd, 1H, J = 1.5 and J = 8 Hz, Harom); ^{13}C-NMR ($CDCl_3$): δ 36.84, 53.50, 73.05, 113.22, 128.01 , 128.98, 129.98, 130.74, 135.93, 140.97; MS (EI) m/z 172 (M^+, 100%), 142 (M^+- CH_2O, 85), 118 (M^+- [O-C-CN], 78). HRMS: calcd. for $C_{10}H_8N_2O$: 172.0636, found 172.0630.