N-(Cyanothioformyl)indoline; a new indoline ring forming reaction

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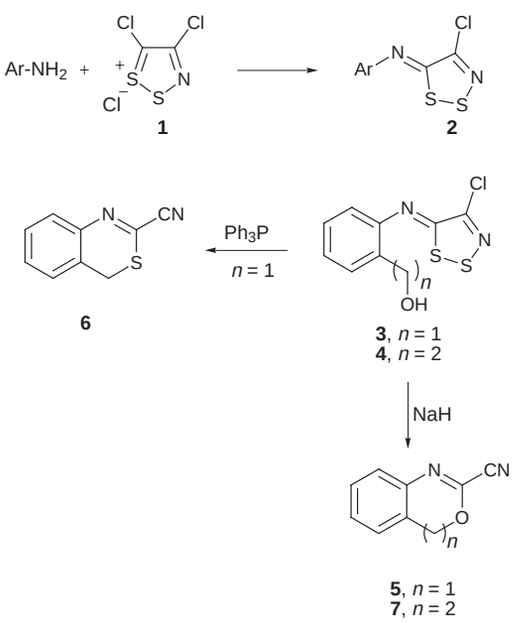
Conversion of 2-hydroxymethyl- and 2-hydroxyethylaniline with Appel salt **1** into the arylimines **3** and **4** is accompanied by formation of the chloromethyl and chloroethyl derivatives **8** and **9**. Triphenylphosphine converts compound **8** into the benzothiazine **6** but the chloroethyl compound **9** gives *N*-(cyanothioformyl)indoline **10** (55%) rather than the analogous benzothiazepine **12**. Indoline **10** is also formed from **9** with sodium hydride (45%), and from the hydroxyethyl compound **4** with mesyl chloride and triethylamine (65%) or with excess of Appel salt **1** (38%). ^{1}H and ^{13}C NMR spectra show that the indoline exists in solution as two rotamers **10a** and **10b**. Indoline **10** is converted into the known cyanoformylindoline **13** by the nitrile oxide method, and is prepared independently from indoline and 4-chloro-5*H*-1,2,3-dithiazole-5-thione. Mechanisms are proposed for the new reactions.

5-(*N*-Arylimino)-4-chloro-5*H*-1,2,3-dithiazoles **2** are stable crystalline solids readily prepared in high yield from anilines and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) **1**, itself readily available from chloroacetonitrile and disulfur dichloride.[1] These iminodithiazoles **2** are reactive towards both inter- and intra-molecular nucleophilic attack at S-1, S-2 and C-5 of the ring, the driving force being regeneration of the latent cyano group.[2] As a result, the iminodithiazoles **2** have proved to be highly versatile intermediates in heterocyclic synthesis.[3] We have recently shown that introduction of a hydroxymethyl group into the *ortho* position of the *N*-aryl group, giving **3**, provides access to the benzoxazine **5** and benzothiazine **6** rings in moderate to good yields.[4] We also described the synthesis of the dihydro-3,1-benzoxazepine **7** which was prepared in two steps from 2-aminophenethyl alcohol *via* **4** (Scheme 1).[4]



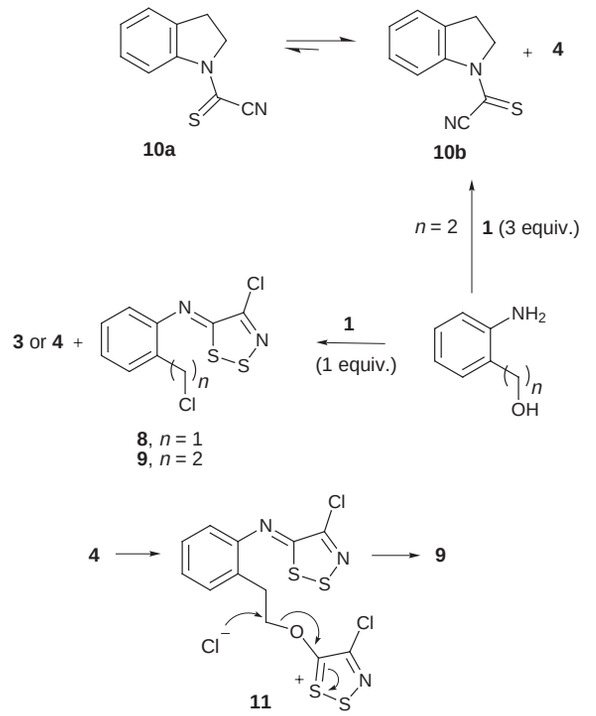
Scheme 1

Results and discussion

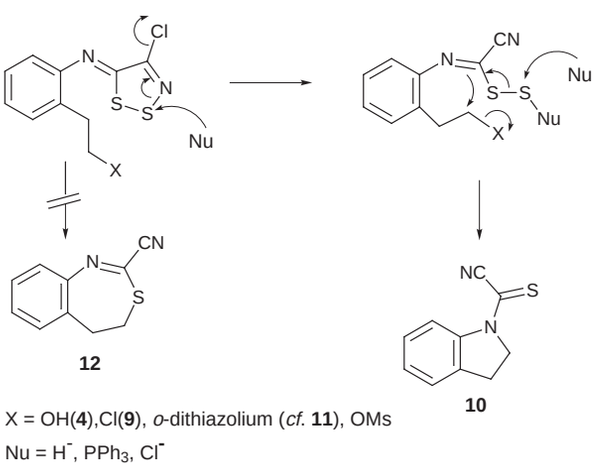
The primary aromatic amines were condensed with dithiazolium chloride **1** (1 equiv.) at room temperature followed by the addition of pyridine to give iminodithiazoles **3** and **4** in good yield. In the preparation of these imines, by-products were isolated in low yield and identified as the chloro derivatives **8** (10%) and **9** (20%) respectively (Scheme 2). Formation of these chlorides could involve activation of the hydroxy group of **3** and **4** by reaction with dithiazolium chloride **1** (to give, for example, **11** from **4**) followed by nucleophilic displacement by chloride (*cf.* ref. 5). Heating the imines **3** and **4** in THF at reflux with 2 equiv. of sodium hydride for approximately 1 h gave the oxygen-containing rings **5** and **7** (Scheme 1). The benzothiazine **6** was prepared by heating imine **3** in dichloromethane at reflux with 2 equiv. of triphenylphosphine.[4]

As with the hydroxymethyl compound **3**, the chloromethyl compound **8** and triphenylphosphine in dichloromethane at room temperature gave the benzothiazine **6** (60%). The analogous chloroethyl imine **9** was treated in the same way in the expectation of producing the benzothiazepine **12** (Scheme 3). A yellow crystalline product, mp 148 °C, with the required formula $C_{10}H_8N_2S$ was isolated (55%). However, this differed markedly from the benzoxazepine **7** in that the ^{1}H and ^{13}C NMR spectra were more complex; many of the signals were twinned suggesting the presence in solution of two rotamers which could not be separated by chromatography (see Experimental section).

Since the thiazepine **12** was expected to be formed by opening of the dithiazole ring and intramolecular displacement of chlorine by sulfur, the most likely alternative structure would be *N*-(cyanothioformyl)indoline **10** where cyclisation has occurred through nitrogen, rather than sulfur, to give a 5 membered ring (see Scheme 3 below). Furthermore the indoline could exist in

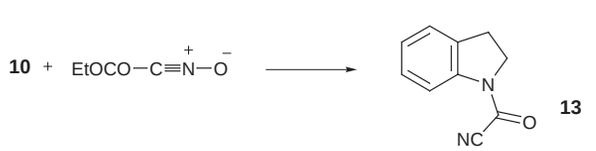


Scheme 2



Scheme 3

two interconvertible geometrical isomers because of hindered rotation of the polarised, planar thioamide function.[6] The ^{1}H NMR spectrum showed two isomers to be present in a 1 : 1 ratio in DMSO, and in a 1 : 3 ratio in $CDCl_3$. We assume that in the latter the major species is likely to be the less hindered rotamer **10b** (Scheme 2). The proposed indoline structure **10** was unknown but the analogous *N*-cyanoformylindoline **13** has been made by conversion of indoline into its *N*-isonitrosoacetyl derivative with trichloroacetaldehyde and hydroxylamine followed by dehydration with thionyl chloride.[7] We therefore applied the simple and reliable nitrile oxide method for converting thiocarbonyl groups[8] on our product **10** (Scheme 4). Treatment of **10** with ethyl chlorooximidoacetate and triethylamine in THF rapidly gave an almost quantitative yield of the known cyanocarbonyl compound **13** which showed the same characteristic twinning of the ^{1}H and ^{13}C NMR signals as did **10**. This conversion adds yet another thiocarbonyl function to those that are cleanly oxidised by the nitrile oxide method.[8]



Scheme 4

Finally the structure of **10** was confirmed by an independent synthesis by the method which Lee and Kim have described for *N*-alkyl- and *N,N*-dialkylcyanothioformamides.[6] This involved the treatment of indoline with 4-chloro-5*H*-1,2,3-dithiazole-5-thione[1] in dichloromethane at room temperature for 12 h to give **10** (30%), with a very similar ^{1}H NMR spectrum in $CDCl_3$ indicating the same mixture of isomers as before.

Some other reactions that could yield either the indoline **10** or the thiazepine **12** were investigated; in all cases only the former was isolated, in contrast with the analogous oxygenated compounds which gave only the benzoxazepine **7** and not the cyanoformylindoline **13**. Firstly, when 2-aminophenethyl alcohol was treated with an excess of reagent **1** (3 equiv.) in dichloromethane at room temperature, the indoline **10** was formed in low yield (12%), possibly *via* the bis-dithiazolo intermediate **11** (Scheme 2). This yield increased to 38% if the reaction mixture was heated under reflux for 3 h. The chloroethyl compound **9** was not isolated in these experiments; any **9** that was formed was probably also converted into the indoline. Next, the alcohol **4** was treated with methanesulfonyl chloride and triethylamine in cold THF and the mesylate rearranged spontaneously to the indoline **10** in 65% yield (Scheme 3). We have shown that the heterocyclic ring of *N*-aryliminodithiazoles **2** is readily opened by sodium hydride,[4] and so finally we treated chloroethyl compound **9** with sodium hydride (2 equiv.) in THF at room temperature and this also gave the indoline **10** (45%).

These reactions are probably all proceeding by the same general mechanism (Scheme 3) involving initial nucleophilic attack at S-2 of the dithiazole ring, followed by cleavage of the disulfide bond to generate the cyanothioformanilide anion (*cf.* ref. 2) which displaces the leaving group X through nitrogen, rather than the more usual sulfur, to give the highly favoured 5-membered ring.

Thus *N*-arylimino-1,2,3-dithiazoles **2** derived from 2-chloroethylaniline, 2-hydroxyethylaniline and its mesylate readily undergo opening of the dithiazole ring followed by cyclisation in a new indoline forming reaction.

Experimental

IR spectra were recorded on a Perkin-Elmer Paragon 1000PC instrument. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL JNM LA400 spectrometer (Laboratoire Commun d'Analyse, Université de La Rochelle-France); chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard.

Mass spectra were recorded on a Varian MAT311 in the Centre Régional de Mesures Physiques de L'Ouest (C.R.M.P.O.), Université de Rennes-France. Chromatography was carried out on silica gel 60 at medium pressure. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} aluminium backed plates. Light petroleum refers to the fraction bp 40–60 °C.

1,2,3-Dithiazoles 3, 4, 8 and 9: general procedure

4,5-Dichloro-1,2,3-dithiazolium chloride (0.208 g, 1 mmol) was added to the aniline derivative (1 mmol) in dichloromethane (10 ml) and stirred at room temperature until the amine was consumed (TLC). Then pyridine (0.17 ml, 2 mmol) was added and the mixture stirred for a further 1 h, filtered, and the crude product obtained by evaporation of the solution was purified by column chromatography to give the following compounds.

From 2-aminobenzyl alcohol. Elution with light petroleum–dichloromethane (8 : 2) gave 4-chloro-5-(2-chloromethyl-

phenylimino)-5*H*-1,2,3-dithiazole **8** as a red oil (10%) (Found: 275.9352. $C_9H_6Cl_2N_2S_2$ requires M^+ 275.9349); ν_{max}(film)/cm^{-1} 1687, 1660, 1498, 1115, 832, 768 and 671; δ_H (400 MHz, $CDCl_3$) 4.70 (2H, s, CH_2), 7.21 (1H, dd, *J* 1.2 and 7.8 Hz, H_{arom}), 7.24–7.30 (1H, m, H_{arom}), 7.40–7.46 (1H, m, H_{arom}) and 7.55 (1H, dd, *J* 1.5 and 7.6 Hz, H_{arom}); *m*/*z* 276 (M^+, 22%), 227 ($M^+ - CH_2Cl$, 2) and 116 ($M^+ - CNS_2Cl_2$, 100), and 4-chloro-5-(2-hydroxymethylphenylimino)-5*H*-1,2,3-dithiazole **3** as orange needles (60%), mp 142 °C, identical with that previously described.[4]

From 2-aminophenethyl alcohol. Elution with light petroleum–ethyl acetate (8:2) gave 4-chloro-5-[2-(2-chloroethyl)phenylimino]-5*H*-1,2,3-dithiazole **9** as a red oil (20%) (Found: 289.9524. $C_{10}H_8Cl_2N_2S_2$ requires M^+ 289.9506); ν_{max}(film)/cm^{-1} 2957, 1685, 1600, 1181, 1063 and 849; δ_H (400 MHz, $CDCl_3$) 3.13 (2H, t, *J* 7.3 Hz, CH_2) 3.74 (2H, t, *J* 7.3 Hz, CH_2), 7.20–7.28 and 7.34–7.40 (4H, m, H_{arom}); δ_C (100 MHz, $CDCl_3$) 35.42, 49.94, 115.95, 126.70, 128.44, 131.20, 131.47, 146.59, 148.59 and 182.83; *m*/*z* 290 (M^+, 9%), and 188 ($M^+ - Cl_2S_2$, 100), and 4-chloro-5-[2-(2-hydroxyethyl)phenylimino]-5*H*-1,2,3-dithiazole **4** as a brown oil (71%), identical with that previously described.[4]

4*H*-3,1-Benzothiazine-2-carbonitrile 6

The imine **8** (0.276 g, 1 mmol) was stirred with triphenylphosphine (0.524 g, 2 mmol) in dichloromethane at room temperature for 1 h, followed by column chromatography, to give the title compound (0.105 g, 60%) as colourless needles, mp 86 °C, identical with that previously described.[4]

N-(Cyanothioformyl)indoline 10

From 2-aminophenethyl alcohol. To a solution of 2-aminophenethyl alcohol (2 mmol) in dichloromethane (10 ml) was added 4,5-dichloro-1,2,3-dithiazolium chloride **1** (6 mmol). The mixture was stirred at room temperature for 10 min after which pyridine (4 mmol) was added to give a red solution. This was stirred for a further 3 h at reflux, filtered, and the crude product obtained by evaporation of the solution was purified by column chromatography with light petroleum–ethyl acetate (9:1) as eluent.

From 4-chloro-5-[2-(2-chloroethyl)phenylimino]-5*H*-1,2,3-dithiazole 9. A solution of 4-chloro-5-[2-(2-chloroethyl)phenylimino]-5*H*-1,2,3-dithiazole **9** (1 mmol) and triphenylphosphine (2 mmol) in dichloromethane (7 ml) was stirred at room temperature for 2 h. The mixture obtained was filtered and the crude product purified by column chromatography with light petroleum–dichloromethane (8:2) as the eluent.

From 4-chloro-5-[2-(2-hydroxyethyl)phenylimino]-5*H*-1,2,3-dithiazole 4. During 15 min a solution of mesyl chloride (2 mmol) in THF was added dropwise to a cooled (−30 °C) solution of the imine **4** (1 mmol) and triethylamine (2.8 mmol) in THF (10 ml). After a further 20 min stirring, aqueous ammonium chloride was added to give an acidic pH. The aqueous phase was washed three times with ethyl acetate (10 ml). The combined extracts were washed with water and brine and then dried. The crude product obtained was purified by column chromatography with light petroleum–dichloromethane (9:1) as the eluent. *N*-(Cyanothioformyl)indoline **10** was obtained as yellow needles (38, 55 and 65% respectively), mp 148 °C (from ethanol) (Found: C, 64.09; H, 4.25; N, 14.76. $C_{10}H_8N_2S$ requires C, 63.83; H, 4.26; N, 14.89%); ν_{max}(KBr)/cm^{-1} 2935, 2236 (CN), 1499, 1462, 1329, 1277, 1160 and 776; δ_H (400 MHz, $CDCl_3$) 3.24 (2H^a, t, *J* 7.6 Hz, CH_2), 3.33 (2H^b, t, *J* 7.6 Hz, CH_2), 4.46 (2H^a, t, *J* 7.6 Hz, CH_2), 4.67 (2H^b, t, *J* 7.6 Hz, CH_2), 7.24–7.39 (6H^{a+b}, m, H_{arom}), 8.23 (1H^a, d, *J* 8.3 Hz, H_{arom}) and 9.11–9.15 (1H^b, m, H_{arom}); δ_C (100 MHz, $CDCl_3$) 26.00, 27.35, 52.52, 54.68, 56.61, 112.69, 112.97, 114.74, 119.21, 125.50, 126.47, 127.28, 128.29, 128.41, 135.34, 135.45, 140.86, 142.17, 155.96 and 158.44; *m*/*z* 188 (M^+, 100%) and 118 ($M^+ - CSCN$, 35).

N-(Cyanoformyl)indoline 13

At 0 °C, triethylamine (0.34 ml, 2.4 mmol) was added dropwise to a solution of indoline **10** (0.09 g, 0.48 mmol) and ethyl chlorooximidoacetate (0.29 g, 1.9 mmol) in dry THF (5 ml). The mixture was stirred for 15 min at 0 °C and a further 15 min at room temperature. The reaction mixture was filtered through Celite and the solvent removed *in vacuo*. The crude product was purified by colum chromatography (light petroleum–ethyl acetate, 8:2) to give the title compound (0.078 g, 95%) as colourless needles, mp 98–100 °C (lit.[7] mp 104 °C) (from ethanol); ν_{max}(KBr)/cm^{-1} 2229 (CN), 1658 (C=O), 1597, 1481, 1410, 1317 and 1102; δ_H (400 MHz, $CDCl_3$) 3.14 (2H^b, t, *J* 8.5 Hz, CH_2), 3.28 (2H^a, t, *J* 8.5 Hz, CH_2), 4.16 (2H^b, t, *J* 8.5 Hz, CH_2), 4.37 (2H^a, t, *J* 8.5 Hz, CH_2), 7.11–7.32 (6H^{a+b}, m, H_{arom}), 7.89 (1H^b, d, *J* 8.2 Hz, H_{arom}) and 8.02 (1H^a, d, *J* 8.2 Hz, H_{arom}); δ_C (100 MHz, $CDCl_3$) 26.53, 27.58, 48.34, 49.20, 111.00, 113.34, 117.79, 125.20, 126.18, 126.64, 128.02, 132.53, 133.53, 140.34 and 140.58.

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