3,1-Benzoxazin-4-ones, 3,1-Benzothiazin-4-ones and *N*-Arylcyanothioformamides

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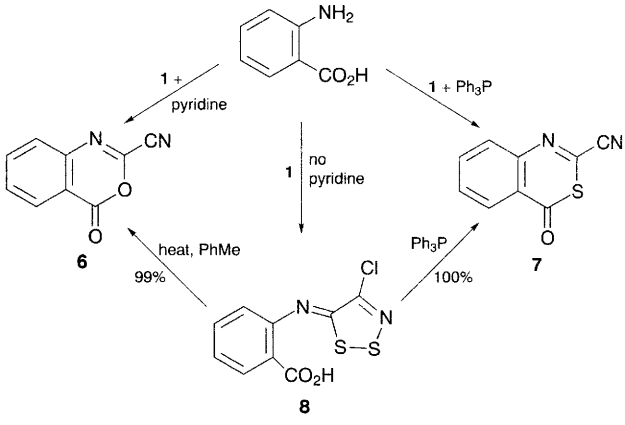
Anthranilic acid and 4,5-dichloro-1,2,3-dithiazolium chloride **1** give the delicate dithiazoloimino carboxylic acid **8** which on mild thermolysis gives 2-cyano-3,1-benzoxazin-4-one **6** and with triphenylphosphine gives 2-cyano-3,1-benzothiazin-4-one **7**, both quantitatively; in general *N*-aryliminodithiazoles **2** with triphenylphosphine give the corresponding cyanothioformanilides **3**, providing a route to these compounds from anilines in two mild steps.

Aromatic amines condense readily with 4,5-dichloro-1,2,3-dithiazolium chloride **1**[1] in dichloromethane (DCM) at room temperature, followed by the addition of pyridine to give the stable, crystalline iminodithiazoles **2**.[1,2] With triphenylphosphine (2 equiv.) in moist DCM at room temperature, these imines **2** give the *N*-arylcyanothioformamides **3** together with triphenylphosphine oxide and sulfide. Thus, methyl anthranilate and dithiazolium chloride **1** gave the imine **4** (72%), and if triphenylphosphine was added to the reaction mixture instead of pyridine, the cyanothioamide **5** (51%) was formed.†

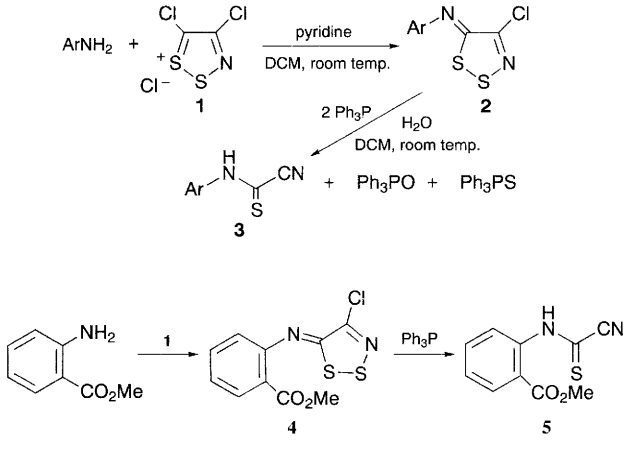
Anthranilic acid, however, behaved differently to all the other anilines investigated. With dithiazolium chloride **1**, as above, it did not give the analogous imine (**8**, see below) but rather 2-cyano-3,1-benzoxazin-4-one **6** (46%), and with triphenylphosphine it gave 2-cyano-3,1-benzothiazin-4-one **7** (69%). But when an excess of anthranilic acid (4 equiv.) was treated with dithiazolium chloride **1** without the addition of the usual base (pyridine), the delicate imino derivative **8** of the free carboxylic acid could be isolated in 60% yield. Acid **8** is a yellow solid, mp 128 °C decomp., which is slightly unstable to storage at room temperature but keeps well in a dry inert atmosphere at 4 °C in the dark. On recrystallisation, and more rapidly on melting, it rearranges to the benzoxazinone **6**. When heated in boiling toluene it gave benzoxazinone **6** (99%) in virtually quantitative yield, and when treated with triphenylphosphine (2 equiv.) in DCM it gave benzothiazinone **7** quantitatively.

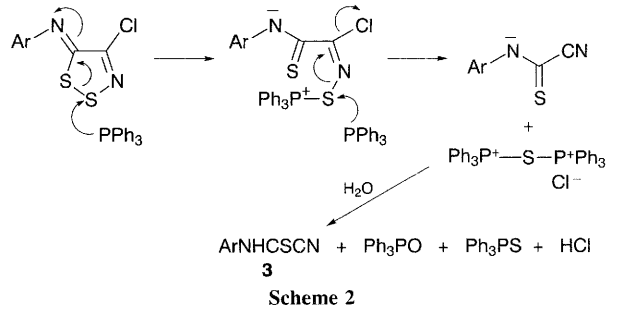
These heterocyclic-forming reactions of anthranilic acid extend to its benzo-substituted derivatives. Thus 4-chloro- and 4,5-dimethoxy-anthranilic acid with the dithiazolium salt **1**, but without additional base, gave the iminocarboxylic acids analogous to **8** in 85 and 53%, respectively. On heating in toluene, both gave the benzoxazinone analogous to **6** and, with triphenylphosphine, the benzothiazinone analogous to **7**. The benzothiazinones could be prepared more simply and in better yield in a one-pot procedure without isolation of the iminocarboxylic acid. These reactions provide a new and simple route to benzo-substituted 2-cyanooxazinones and 2-cyanothiazinones from the appropriate anthranilic acids. Whilst the 2-alkyl and aryl derivatives of these ring systems have been moderately well studied,[3] and continue to be of interest because of their diverse biological activity,[4] functional groups in the 2-position are less common and 2-cyano groups are rare, though 2-cyano-3,1-benzoxazin-4-one itself was recently prepared from *o*-isocyanatobenzoyl chloride and cyanotrimethylsilane.[5] 2-Cyano-3,1-benzothiazin-4-ones have not been reported before.

The above differences between anthranilic acid and its methyl ester can be rationalised mechanistically (Schemes 1–3). Thermolysis of the iminocarboxylic acid **8** probably proceeds by cyclisation to the spiro intermediate **9** and elimination from this of hydrogen chloride and disulfur to give the stable cyano heteroaromatic compound **6** (Scheme 1). The triphenylphosphine-induced conversion of imines **2** generally into the cyanothioformanilides **3** could result from attack of the phosphine on S(2) of the dithiazole ring with formation of the thioamide anion. Attack by a second phosphine on the same sulfur would give the stabilised cyanothioformamide anion and



Scheme 1

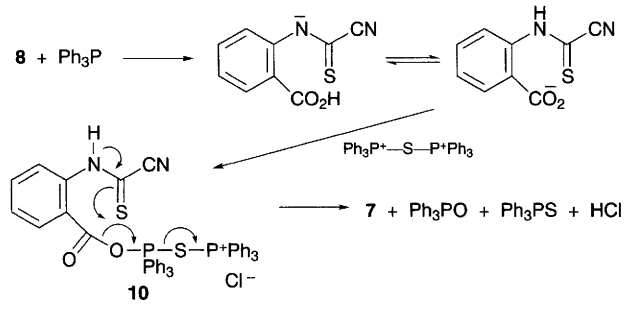




Scheme 2

Ph_3P^+–S–P^+Ph_3, hydrolysis of which would give all the observed products (Scheme 2). In exactly the same way the imine **8** from anthranilic acid would give the ionic species, shown in Scheme 3, which could combine to give **10** in which the carboxylic acid is now activated by the phosphonium salt; this then acts as a good leaving group to give the benzothiazinone **7** and the other observed products (Scheme 3). The pathways of Schemes 1 and 3 are not, of course, available to the methyl ester **4**.

Finally, we confirmed the utility of the very mild two-step procedure for the conversion of anilines into cyanothioformanilides **3**, with 3,4-dimethoxyaniline, 2-cyano-4,5-dimethoxyaniline, and methyl 2-amino-4,5-dimethoxybenzoate. Each of these, with the dithiazolium salt **1** and pyridine in DCM at room temperature, gave the corresponding iminodithiazole **2**



Scheme 3

which, with triphenylphosphine (2 equiv.) in moist DCM at room temperature for 3 h, gave the corresponding thioformanilide **3**, all in good yield.

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Footnote

† All compounds were fully characterised by spectroscopy and elemental analysis.

References

1 R. Appel, H. Janssen, M. Siray and F. Knoch, *Chem. Ber.*, 1985, **118**, 1632.
2 R. F. English, Ph.D. Thesis, University of London, 1989; C. W. Rees, *J. Heterocycl. Chem.*, 1992, **29**, 639.
3 M. Sainsbury, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 3, p. 995; W. Thiel, *J. Prakt. Chem.*, 1992, **334**, 92.
4 See *e.g.* A. Krantz, R. W. Spencer, T. F. Tam, T. J. Liak, L. J. Copp, E. M. Thomas and S. P. Rafferty, *J. Med. Chem.*, 1990, **33**, 464.
5 M. Takahashi and A. Hiratsuka, *Heterocycles*, 1989, **29**, 1349.