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New and Improved Syntheses of Arylazoxycyanides

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Two new approaches to the synthesis of arylazoxycyanides are reported. The most efficient conditions found involve either oxidation of an azocyanide with hydrogen peroxide/formic acid or nitrene insertion into an arylnitroso derivative using cyanamide and NBS.

Arylazoxycyanides have proved to be interesting and potentially useful compounds in a number of different medical and agrochemical applications. The functional group also occurs in Nature, the best known example being calvatic acid, which has been isolated from three different natural sources, *Calvatia craniformis*[1], *Lycoperdon pyriforme*[2] and *Calvatia lilacina*[3]. In addition to antibiotic and general cytotoxicity,[4] arylazoxcyanides also appear to exhibit a variety of more selective forms of biological action including inhibition of tubulin binding,[5] glutathione transferase,[6] ornithine decarboxylase,[7] and as labels for the α_1-adrenoreceptor.[8] Our own research has shown that some

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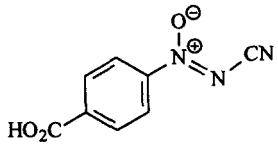
arylazoxycyanides show potent fungicidal activity against commercially important crop diseases.[9]



Calvatic Acid

Syntheses of arylazoxycyanides have involved two basic approaches: formation of an azo- intermediate and subsequent oxidation or nitrene insertion into a nitroso intermediate. In the original isolation papers, the synthesis of calvatic acid was reported by both of these approaches.[1,3] Our need for rapid access to arylazoxycyanides for an analogue programme and for large scale syntheses for field screening, prompted us to explore new methodology for the synthesis of these compounds which we report herein.

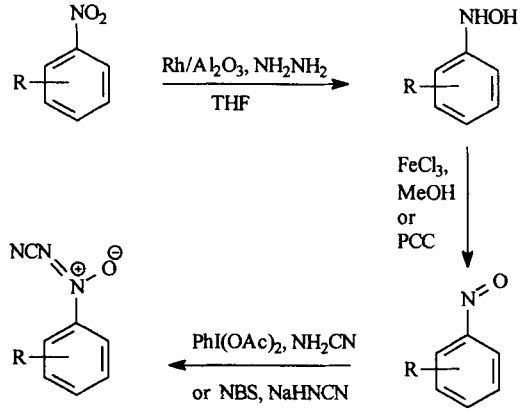
RESULTS AND DISCUSSION

Nitrene Insertion Routes to Azoxycyanides

Gasco *et al.* reported the synthesis of calvatic acid and its *o*-isomer from the corresponding nitrobenzaldehydes by photolysis, to give an intermediate nitroso-compound, and subsequent insertion of cyanonitrene, generated from cyanamide and iodosobenzene diacetate.[3,10] This provided a useful starting point for the synthesis of calvatic acid analogues. However, although iodosobenzene diacetate could be successfully used to prepare kilo quantities of various arylazoxycyanides, the cost of this stoichiometric reagent was prohibitive. Similarly the photolytic methodology used to prepare the nitroso intermediates was unsuitable for rapid or large scale syntheses of these compounds.

An alternative protocol, outlined in **Scheme 1**, was therefore devised. Arylnitroso derivatives cannot generally be prepared by reduction of

nitrobenzenes, due to over reduction, and so a two step procedure was used to prepare these compounds involving reduction of a nitrobenzene to the hydroxylamine and then oxidation back to the nitroso level. In most cases it was possible to prepare aryl hydroxylamines from nitrobenzenes by catalytic transfer hydrogenation using rhodium on alumina and hydrazine hydrate as the hydrogen source,[11] however this protocol failed when the substrate carried functional groups such as esters, which were sensitive to hydrazine. In these cases tin (II) chloride was used as a stoichiometric reductant.[12] Oxidation of the hydroxylamine to the nitroso level could be carried out using either ferric chloride[13] or PCC.[14]



Scheme 1

At the time that this work was in progress, Zlotin and co-workers reported an alternative oxidant for the generation a nitrene from cyanamide.[15] In this work, dibromoisocyanurate (DBI) was used to generate the nitrene, presumably by way of dibromocyanamide. This procedure worked satisfactorily in our hands, but still required preparation of DBI from cyanuric acid. We also found that on a large scale, DBI tended to liberate elemental bromine which, in turn, oxidized the nitroso substrate back to the nitro oxidation level, contaminating the final azoxycyanide product. We therefore looked for other brominating agents and

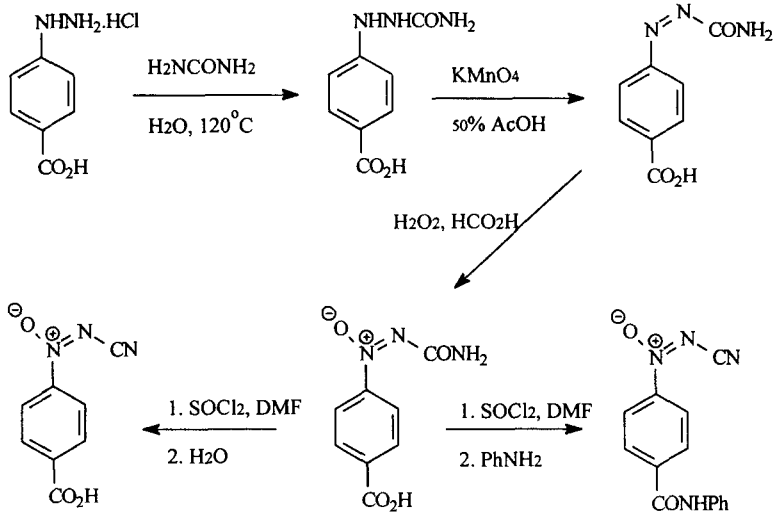
found that, in contrast to the literature report,[15] NBS in conjunction with the sodium salt of cyanamide (either as a solid, aqueous solution or generated *in situ*) gave excellent yields in the final coupling . This reagent system did not liberate elemental bromine and was also commercially available on a scale suitable for our needs. It was also possible to substituted NCS in the system with equally satisfactory results. This constitutes a new and efficient synthesis of arylazoxycyanides.

Oxidation of Azo Intermediates

Umezawa and co-workers reported the synthesis of calvatic acid from hydrazinobenzoic acid (**Scheme 2**). We were able to adapt this process for our own purposes firstly by replacing potassium permanganate with DDQ and an organic solvent in the oxidation step and, secondly, by recognizing that the final dehydration step with thionyl chloride would give rise to an acid chloride intermediate. This could be utilized in the synthesis of analogues of calvatic acid by quenching *in situ* with amines or alcohols. For the compounds required for this study, aniline was used to quench the mixture to give the amide product.[16]

Although this approach gave a useful method for the synthesis of close analogues of calvatic acid, four synthetic steps were still required to accomplish a conceptually simple task. The principle reason for taking a roundabout approach to the synthesis lay in the relative difficulty of oxidising azocyanides directly. The preparation of azocyanides by modified diazonium chemistry has been known for many years.[17] However these compounds are not particularly stable and are less easily raised to the azoxy oxidation state than the azoamides used in the calvatic acid synthesis above. Presumably the increased electronwithdrawing effect of the cyanide group *vis-a-vis* the amide group makes the azo double bond less susceptible to electrophilic oxidation.

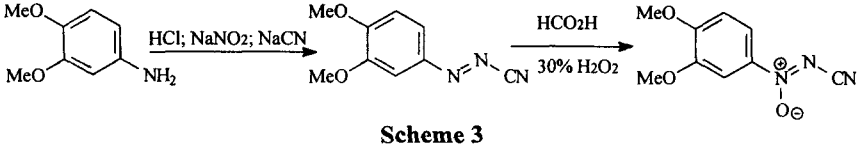
Oxidations of some azocyanides to azoxycyanides have been achieved under forcing conditions. Gasco *et al* reported such a synthesis using 85% hydrogen peroxide and trifluoroacetic acid.[4c] These conditions were clearly



Scheme 2

unsuitable for the larger scale work which we envisioned. In a number of experiments it was found that less concentrated forms of hydrogen peroxide with trifluoroacetic acid were ineffective in oxidizing azocyanides. Similarly 85% hydrogen peroxide in conjunction with acetic acid was ineffective. Surprisingly, and fortuitously, we discovered that formic acid in combination with 30% hydrogen peroxide was an effective oxidizing medium, giving azoxycyanides in good yields (**Scheme 3**). Any yield loss was generally attributed to the instability of the azocyanide intermediate, rather than the oxidative process.

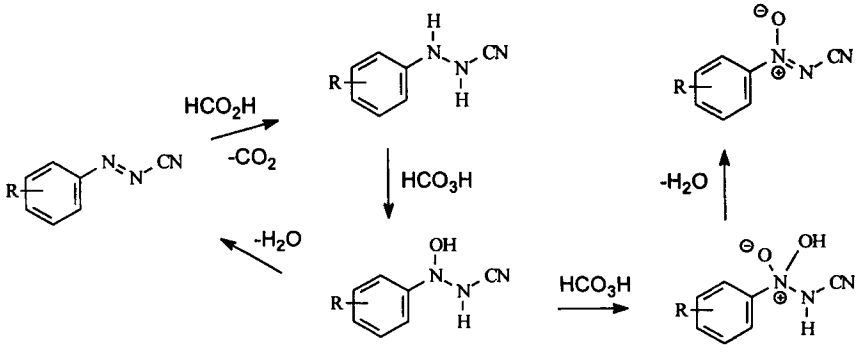
Oxidation of azo-double bonds by peroxy acids is generally understood to involve nucleophilic attack by nitrogen at oxygen. Since, in these examples, the nature of the nucleophile and the solvent remains constant, the observed reactivity



Scheme 3

must arise solely from the change in electrophile. It has been shown recently that the bond dissociation energies of performic, peracetic and pertrifluoroacetic acids are unaffected by the alkyl substitution pattern and are essentially the same,[18] and thus that the relative reactivity of these peroxy acids depends primarily on the relative stabilities of the anions generated in the reaction.[19] On the basis of this argument, pertrifluoroacetic acid would be expected to be the most powerful oxidant, as is generally observed. It therefore seems likely that this particular oxidation with performic acid follows a different mechanism.

Unlike acetic and trifluoroacetic acids, formic acid can act as a reducing agent with the liberation of carbon dioxide as is observed in the Eschweiler-Clarke reductive amination. It is therefore possible that formic acid could act in the same way in this reaction, bringing about a reduction of the diazo- bond to a hydrazine (**Scheme 4**). Oxidation and elimination of water would lead back to the starting azocyanide. However if the oxidized intermediate underwent a second oxidation, the elimination of water would lead to an azoxycyanide.



Scheme 4

CONCLUSION

Several new approaches to the synthesis of arylazoxycyanides have been described herein, giving more efficient and rapid access to this class of compound.

The syntheses have advantages over the currently available methodology both in terms of overall efficiency, cost and the mildness of the reagents employed.

EXPERIMENTAL

3,4-Dimethoxy-1-azoxycyanobenzene (oxidation of Arylazocyanide).

3,4-Dimethoxyaniline (3.8 g, 25 mmol) was dissolved in methanol (20 ml). Hydrochloric acid (20 ml, 20% w/w) was added and the solution was diazotised by the addition of sodium nitrite (3.8 g, 55 mmol). Ethyl acetate (70 ml) was added and the reaction mixture was cooled to -10°C. After the addition of sodium cyanide (2.5 g, 51 mmol) dissolved in water (5 ml), the reaction mixture was stirred for 30 minutes. The organic layer was separated dried over sodium sulphate and evaporated to dryness. The resulting brown-orange solid was recrystallized from petroleum ether/dichloromethane to give the 3,4-dimethoxy-1-azocyanobenzene (2.6 g, 55%).

3,4-Dimethoxy-1-azocyanobenzene (2.0 g, 10 mmol) was suspended in a mixture of formic acid (30 ml) and hydrogen peroxide (10 ml, 30% w/w). The mixture was heated to 60°C for 24 hours and then cooled in an ice bath. The resulting orange crystals were collected and washed with water to give 3,4-dimethoxy-1-azoxycyanobenzene (1.56 g, 72%). M.p. 157°C, m/e (M^+): 207. Analysis: Found: C, 52.5; H, 4.4; N, 20.0;$C_9H_9N_3O_3$ requires C, 52.5; H, 4,4; N, 20.2%.

4-N-Phenylamido-1-azoxycyanobenzene (Nitrene insertion with iodosobenzenediacetate)

4-N-Phenylamidonitrobenzene (10 g, 41 mmol) was dissolved in THF (1000 ml) with Rh/carbon (0.2 g, 5%). The mixture was treated with hydrazine hydrate (2.4 ml) dropwise at ambient temperature. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The product (4-N-phenylamidohydroxylaminobenzene, 9.0 g) was dissolved in methanol (30 ml) and added to a solution of ferric chloride hexahydrate (7.2 g, 26 mmol) in

methanol/water (300 ml, 1:2) at room temperature. The precipitate was collected to give crude 4-N-phenylamidonitrosobenzene as a yellow solid (7.2 g) and used directly in the next step. 4-N-Phenylamidonitrosobenzene in DMF (100 ml) at 0°C was treated with cyanamide (1.3 g, mmol) and then dropwise with iodosobenzenediacetate (7.2 g, mmol) in chloroform (100 ml). The reaction mixture was stirred for 12 hours at ambient temperature. The resultant brown solid was washed with chloroform to yield a yellow solid (1.2 g), m.p. 220-225°C. Analysis (of recrystallized sample): Found: C, 63.8; H, 3.8: N, 19.8. $C_{14}H_{10}N_4O_2$ requires C, 63.2; H, 3.8; N 21.1%.

4-N-Phenylamido-1-azoxycyanobenzene (DMF/$SOCl_2$ Dehydration)

4-Carboxy-1-azoxyformamide (1.85 g, 0.009 mol) was dissolved in dry THF (40 ml) at 40°C and thionyl chloride (2.8 g, 1.8 ml, 0.024 mol) was added dropwise. The reaction mixture was stirred for three hours at 40°C before being quenched with aniline (3 ml, 2.9 g, 0.03 mol) and then stirred for a further 20 minutes at 40°C. The reaction mixture was then poured into water and the yellow precipitate collected, to give a product identical to authentic material. Yield: 0.9 g (38%).

4-N-Phenylamido-1-azoxycyanobenzene (Nitrene Insertion with NBS)

4-(N-Phenylamido)nitrosobenzene (2.7 g, 11.9 mmol) was suspended in DMF (65 ml). NBS (2.17 g, 12.2 mmol) was added in one portion. The reaction mixture was treated in portions with monosodium cyanamide (1.18 g, 18. 4 mmol). After 30 minutes at ambient temperature, the mixture was poured on water (700 ml) and the yellow solid filtered, washed with water and dried to give 4-(N-phenylamido)-1-azoxycyanobenzene (2.41g, 76%). M.p. 220-225°C.

4-(N-Acetylamino)-1-azoxycyanobenzene (Nitrene Insertion with NCS)

4-(N-Acetylamino)-1-nitrosobenzene (1.64 g, 10.0 mmol) was dissolved in DMF (20 ml) and treated with monosodium cyanamide (1.0 g, 15.6 mmol). NCS (1.33 g, 10.0 mmol) was added and the mixture stirred for 24 hours at ambient temperature. The mixture was poured on ice-water (100 ml) and the precipitate

filtered off to give 4-(N-acetylamino)-1-azoxycyanobenzene as a yellow powder (1.2 g, 59%). M.p. 240-242°C.

Calvatic Acid

4-Hydrazinobenzoic acid hydrochloride (14 g, 0.074 mol) and urea (5.2 g, 0.086 mol) in water (100ml) were heated under reflux for 12 hours and then acidified with 2N hydrochloric acid. The precipitate was collected and dried to give 4-semicarbazido-benzoic acid (12 g, 83%). Found: C, 49.3; H, 4.7: N, 21.4. $C_8H_9N_3O_3$ requires C, 49.2; H, 4.7; N, 21.5%. M^+ (CI): 196 ($M^+ + H$). ^1H n.m.r. (DMSO) 8.15 (1H, s, NH), 7.88 (1H, s, NH), 7.70 and 6.65 (4H, AB, C_6H_4), 5.98 (2H, s, NH_2).

4-Semicarbazidobenzoic acid (2.0 g, 8.6 mmol) was suspended in THF (25 ml) and water (2.5 ml) and DDQ (2.27 g, 0.01 mol) was added. The solution turned red, became homogeneous and a precipitate then formed. After 1 hour the precipitate was collected, washed with ethyl acetate and dried to give 4-azoamidobenzoic acid (1.82 g, 90%). Found: C, 49.7; H, 3.8; N, 21.7. $C_8H_7N_3O_3$ requires C, 49.7; H, 3.7, N, 21.8%. M^+ (CI): 194 ($M^+ + H$). ^1H n.m.r. (DMSO): 8.10 and 7.82 (4H, AB, C_6H_4), 7.85 (2H, m, NH_2).

4-Azoamidobenzoic acid (5 g, 0.026 mol) was suspended in acetic acid (100 ml) and was treated with hydrogen peroxide (30%, 50 ml). No reaction occurred until formic acid (100 ml) was added and the mixture was heated to 80°C to 2 hours. The mixture was then cooled and the precipitate collected, washed with ether and dried to give 4-azoxyamidobenzoic acid (3.85 g, 71%).Found C, 46.7; H, 3.5; N, 20.0. $C_8H_7N_3O_4$ requires C, 45.9; H, 3.4: N, 20.1%. M^+ (CI): 210 ($M^+ + H$). ^1H n.m.r. (DMSO): 8.20 and 8.08 (4H, AB, C_6H_4), 7.78 (2H, s, NH_2).

4-Azoxyamidobenzoic acid (2.0 g, 0.01 mol) was dissolved in dry DMF (40 ml) under N_2 at 40°C. Thionyl chloride (2.8 g, 1.8 ml, 0.024 mol) was added dropwise. After 1 hour the mixture was allowed to cool and the solution poured into water. The precipitate was collected and the product washed with ether and

dried to give calvatic acid (0.95 g, 50%). Found: C, 49.9; H, 3.1; N, 21.8. $C_8H_5N_3O_3$ requires C, 50.3; H, 2.6; N, 22.0%. M^+ (CI): 192 ($M^+ + H$). ^1H n.m.r. (DMSO): 8.58 and 8.10 (2H, AB, C_6H_4).

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REFERENCES

1. Umezawa, A.; Takeuchi, T.; Iinuma, H.; Ito, M.; Ishizuka, M.; Kurakata, Y.; Nakamura, T.; Obayahi, A.; Tanabe, O. *J. Antibiot.*, **1975**, *28*, 87.

2. Okuda, T.; Nakayama, N.; Fujiwara, A. *Trans.Mycol.Soc., Japan,* **1982**, *23*, 225.

3. Gasco, A.; Serafino, A.; Mortarini, V.; Menziani, E. *Tetrahedron Lett.*, **1974**, *38*, 3431.

4. Fruttero, R.;Calvino,R.; Di Stilo, A ; Gasco, A.; Galatulas, I.; Bossa, R. *Pharmazie*, **1988**, *48*, 7; Mortarini, V.; Rua, G.; Gasco, A.; Bianco, M.A.; SanFilippo, A. *Eur. J. Med.- Chim Ther.*, **1977**, *12*, 52.

5. Miglietta,A.; Chiarpotto, E.; Olivero, A.; Gadoni, E.; Gabriel, L. *Research Comm. In Chem. Path. and Pharm.*, **1987**, *56*, 265; Gadoni, E.; Miglietta, A,; Olivero, A.; Gabriel. L. *Biochem. Pharmacol.*, **1989**, *38*, 1121; Miglietta, A.; Gadoni, E.; Olivero, A.; Gabriel, L.; Calvino, R. *Med. Sci. Res.*, **1988**, *16*, 267; *Med. Sci. Res.*, **1988**, *16*, 471; Gadoni, E.; Gabriel, L..; Olivero, A.; Bocca, C.; Miglietta, A. *Cell Biochem.Funct.*, **1995**, *13*, 231.

6. Caccurai, A.; Ricci, G.; Desideri, A.; Buffa, M.; Fruttero, R.; Gasco, A; Ascenzi, P. *Biochem. Molecular Biol. Internat.*, **1994**, *32*, 819.

7. Brossa, O.; Gadoni, E.; Olivero, A.; Seccia, M.; Miglietta, A.; Gabriel, L.; Gravela, E. *Res. Comm. Chem. Path. Pharm.* **1990**, *70*, 143.

8. Sorba, G.; Di Stilo, A.; Medana, C.; Cena, C.; Gasco, A.; Orsetti. M. *Bioorg. Medic. Chem.***1995**, *3*, 173.

9. Pearson, M.; Gray, A.C.G.; Naisby, T.W.; Wood, W.W.; Turner, S.J.; Machin, T.M. *EP 371560*; Wood, W.W.; Naisby, T.W.; Gray, A.C.G. *EP 411716*;

Wood, W.W.; Naisby, T.W.; Gray, A.C.G.; *EP 411719*; Wood, W.W.; Naisby, T.W.; Simon, W.E.J. *EP 518436*: Simon, W.E.J.; *EP 645373*; Simon, W.E.J. *WO 9412470*; Simon, W.E.J. *EP 644184*: Simon, W.E.J. *EP 645384*.

10. Fruttero, R.; Mulatero, G.; Calvino, R.; Gasco. A. *J.Chem.Soc., Chem. Commun.*, **1984**,323.

11. Entwistle, I.D.; Gilkerson, T.; Johnstone, R.A.W.; Telford, R.P.; *Tetrahedron*, **1978**, *34*,213.

12. Walser, A.; Zenchoff, G.; Fryer, R. *J.Med.Chem.*, **1976**, *19*, 1378.

13. Oxley, P.W.; Adger, B.M.; Sasse, M.J.; Forth, M.A. *Org. Synth.*, **1988**, *67*, 187.

14. Wood, W.W.; Wilkin, J.A. *Synth. Commun.*, **1992**, *22*, 1683.

15. Zlotin, S.G.; Airapetova, N.V.; Vinogradova, E.A.; Podgurskii, A.I.; Strelenko, Yu.A.;Luk'yanov, O.A. *Izvest. Akad.Nauk. SSSR. Ser. Khim.*, **1990**, 2821 (English transl: **1991**,2560).

16. Wood, W.W. EP 518439.

17. LeFevre and Northcott, *J.Chem.Soc.*, 1949, 333 *et loc.cit.*

18. Bach, R.D.; Ayala, P.Y.; Schlegel, H.B. *J.Am.Chem.Soc.*, **1996**, *118*, 12758.

19. Bach, R.D.; Winter, J.E.; McDouall, J.J.W. *J.Am.Chem.Soc.*, **1995**, *117*, 8586.

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