

## SYNTHESIS OF TETRACHLOROISOPHTHALO-[<sup>14</sup>C]-NITRILE

PETER E. DAVIES

Department of Zoology, University of Tasmania,  
Box 252C, G.P.O. Hobart, Tasmania, Australia, 7001

### SUMMARY

A low cost, high yield synthesis of tetrachloroisophthalo-[<sup>14</sup>C]-nitrile (TCIN) is described. Direct replacement of iodine in 3-iodobenzonitrile using <sup>14</sup>C-labelled cuprous cyanide, and vapour phase chlorination yields [<sup>14</sup>C]-TCIN, with maximum utilisation of the radiolabel. Alternative and unsuccessful routes are also briefly described.

**KEY WORDS:** Tetrachloroisophthalonitrile; Chlorothalonil; <sup>14</sup>C label; Synthesis

Tetrachloroisophthalonitrile (TCIN), or Chlorothalonil, is widely used as a broad-spectrum fungicide (1). TCIN labelled with <sup>14</sup>C was required for a study of its metabolism and ecological fate. The industrial approach to the synthesis of TCIN is by catalytic ammoxidation of m-xylene and subsequent chlorination, the whole process being performed in the vapour phase (2). This approach, already attempted at laboratory scale (3), is impracticable for the synthesis of [<sup>14</sup>C]-TCIN due mainly to the high cost of ring-labelled m-xylene.

It is known that TCIN readily undergoes nucleophilic attack at the chlorinated ring carbons adjacent to the nitrile functions (4, 5). Some hydrolysis of the nitrile functions to amide has been reported (5).

Generally, however, the nitrile functions are expected to be biologically stable. Hence,  $^{14}\text{C}$  labelling in these functions is a viable low cost route to generating labelled TCIN.

Several routes were attempted. Route 1 (Fig. 1) was unsuccessful due to the failure of formation of the bis-diazonium salt (IV). Hodgson and Heyworth (6) successfully generated isophthalonitrile by the analogous route, but at a yield of only 25.4 %. This was repeated and gave similar but variable yields. Chlorination of sites adjacent to the amine functions appears to inhibit formation of a stable bis-diazonium salt, although the high yield of bis-diazonium salt (82 %) generated from 4,6-diamino-m-xylene and a subsequent Sandmeyer generation of the di-cyano compound (no yield given) seems to preclude a direct steric effect (7).

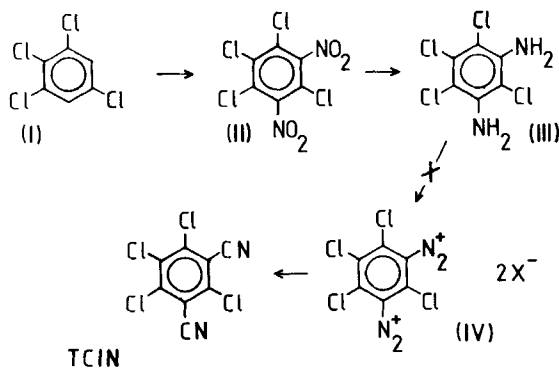


Fig. 1. Route 1

Secondary chlorination of the isophthalonitrile formed by the di-Sandmeyer reaction, as described by Hodgson and Heyworth (6), is possible but radiolabel loss and low reaction yield prohibit the use of this route. Route 2 (Fig. 2) involved an attempt at replacing Br with CN by direct nucleophilic replacement, using  $\text{CuCN}$ , in 1,3-dibromotetrachlorobenzene (V).

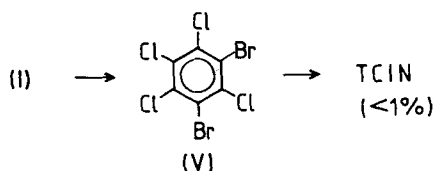


Fig. 2. Route 2

The cyanylation reaction was monitored by gas chromatography (Fig. 3), and showed significant production of the primary replacement product (Fig. 3, Va). However, it appears that the second bromine no longer competes successfully with the remaining chlorines for replacement. Several products are observed, probably with multiple replacement, and only a small fraction of the total is TCIN (< 1 % at 4 h).

Route 3 (Fig. 4) involved replacing halogen (Cl, Br, I) with CN from CuCN (9, 10) in 3-halogenated benzonitrile, and chlorinating in the vapour phase. The first step was successfully carried out for Br and I, with I giving the highest yields (Table 1). Reaction conditions were investigated (10, 11), and both N-methyl pyrrolidone (NMP) and dimethylformamide (DMF) were used as solvents. Catalysis of this reaction type has been reported (12, 13) but was not investigated.

TABLE 1. CN replacement yields

Solvent	Halogen		
	Cl	Br	I
DMF	N.R.	50%	-
NMP	-	65%	92%

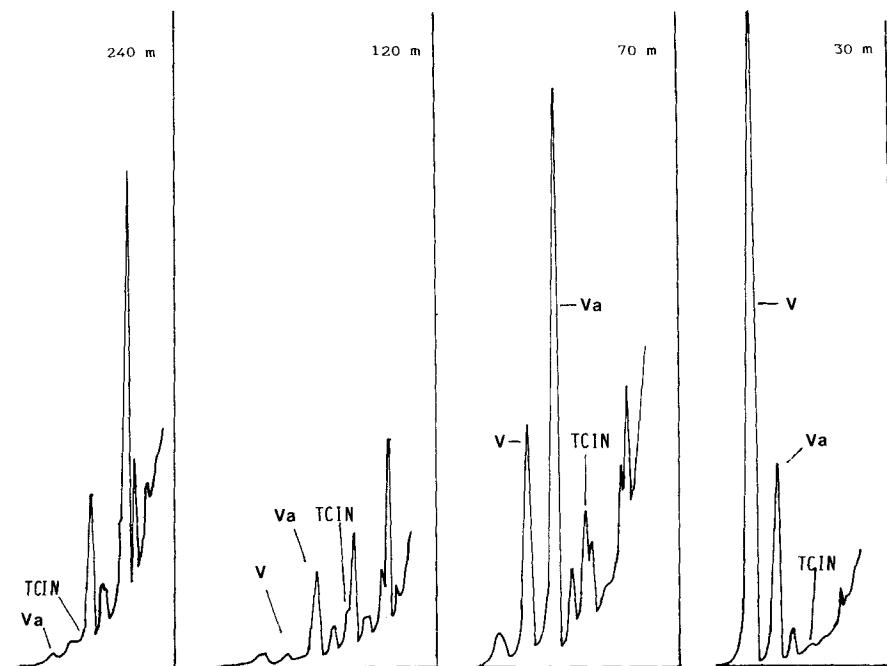


Fig. 3 : Gas chromatograms of the reaction between CuCN and 1, 3-dibromo-tetrachlorobenzene (V) in refluxing DMF at different times (min). Va is the mono replacement product.

Chlorination gave a gradual conversion of isophthalonitrile (VI) to TCIN in the vapour phase at temperatures between 250-300<sup>o</sup> C with high yields, although some form of catalysis is important (14). Attempts at chlorination in high boiling solvents were unsuccessful.

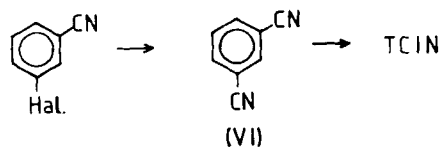


Fig. 4. Route 3

Synthesis of 3-iodobenzonitrile (IX) was as indicated in Fig. 5. CuCN was made fresh and dried in vacuo. After optimization, the reaction was repeated several times with [<sup>14</sup>C]-CuCN to give [cyano-<sup>14</sup>C] TCIN with activity of 0.733-0.762 mCi/mmol from [<sup>14</sup>C]-KCN of activity 57.8 mCi/mmol, which had been diluted with KCN to 1.18 %. This final product activity was 107-112 % of expected.

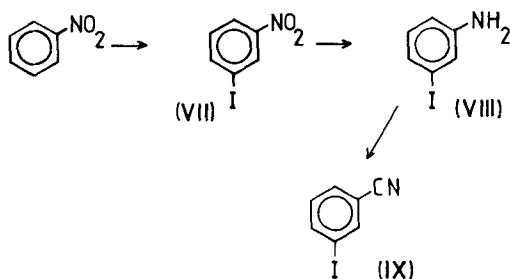


Fig. 5. Synthesis of IX

It should be noted in this context that <sup>14</sup>C labelling of CN functions can be carried out by a combination of thermal decomposition and neutron irradiation of Cu<sub>3</sub>N (20). Benzo-[<sup>14</sup>C]-nitrile has been prepared by this route (with ≈ 10 % radiochemical yield), although further substitution has not been attempted.

The use of Route 3, Hal. = I, with an overall radiochemical yield of 51 %, from a relatively cheap starting material is recommended for the synthesis of (cyano-<sup>14</sup>C) TCIN.

#### EXPERIMENTAL

[<sup>14</sup>C]-KCN (57.81 mCi/mmol) was obtained from Amersham International, Australia. NMP and DMF were freshly distilled and dried. Melting points were determined on a Yanagimoto Seisakusho micro-melting point apparatus, and are uncorrected. Preparative TLC was performed on Merck silica gel GF254. Infrared spectra were determined as mulls on a Beckman IR-33 spectrometer.

N.m.r. (H) spectra were performed at 100 MHz with a Jeol JNM-4H-100 spectrometer, tetramethylsilane as internal standard. E.I. Mass spectra were obtained on a Micromass 7070F double focusing mass spectrometer. G.C. analysis was performed on a Philips PV4000 series gas chromatograph, at conditions indicated, with an SE30 column, nitrogen gas as carrier.

#### 2, 4, 5, 6-Tetrachlorodiaminobenzene (III)

Produced by nitration of 1, 3, 4, 5-tetrachlorobenzene, by the method of Jackson and Carlton (15) with chloroform extraction and recrystallization from Lt. petrol (40-60<sup>0</sup>); 70 % yield. Quantitative reduction of the dinitro compound gave (III), by the method of Yakobson et al. (16).

#### Diazonium salt of (III). (IV)

Attempts at diazotisation by the method of Hodgson and Heyworth (6), and at making the fluoroborate salt under anhydrous conditions by the method of Doyle and Bryker (17) were unsuccessful.

#### 1, 3-Dibromotetrachlorobenzene (V)

Synthesized in 90 % yield by the method of Hugel et al. (8), as fine colourless needles, M.P. = 250-253<sup>0</sup> C.

#### Cyanylation of (V)

(V) was refluxed in dry DMF with fresh CuCN (1.15 molar ratio). Samples were taken at intervals over 4 h and worked up as in (11), Method C. The dried benzene layers were analyzed by G.C. (210<sup>0</sup> C), as in Fig. 3.

#### m-Iodoaniline (VIII)

Nitrobenzene was iodinated according to (18), to give a 47 % yield of an oil, 90% pure by G.C., (VII). Reduction by the method of Yakobson et al. (16) gave (VIII), as an oil, pure by G.C., in 80 % yield.

3-Iodobenzonitrile (IX)

(VIII) was subjected to a Sandmeyer reaction (6) to give 41 % (IX) as colourless needles (M.P. = 39-40° C, lit. 40° C), after preparative TLC (Rf 0.65, Lt. petrol-acetone, 8:1).

Isophthalonitrile (VI)

(IX), 229 mg, was dried in vacuo and dissolved in dry distilled NMP (7 ml). CuCN (produced by method of Chabannes *et al.* (19), 90 % yield, and dried by azeotropic benzene distillation in vacuo), 104 mg, was added and the whole refluxed under nitrogen for 2.5 h. The mixture was cooled, mixed with hot 30 % NaCN solution, diluted to 100 ml with cold water, and extracted with benzene (3 x 20 ml). The benzene layers were combined, extracted with 10 % NaCN (2 x 50 ml), water (3 x 50 ml) and then dried (Na<sub>2</sub>SO<sub>4</sub>, anhyd.). The benzene was evaporated to give 150 mg crude material which was subjected to TLC (Lt. petrol-acetone, 8 : 1.5). This gave 118 mg (VI) (92 % yield). M.P. = 162-164° C (lit. 162° C). M<sup>+</sup> = 128. N.m.r. (CDCl<sub>3</sub>), 7.6-8.1, multiplet.

The above reaction was performed with [<sup>14</sup>C]-KCN, diluted to 1.18 % by KCN, to produce [<sup>14</sup>C]-CuCN (90 % yield) and isophthalo-[<sup>14</sup>C]-nitrile in 75 % yield.

Tetrachloroisophthalonitrile

(VI), 100 mg, was dried in vacuo and introduced into a 100 ml thick-wall, round flask with a Rotaflo (R) tap adaptor, with 400 mg of preactivated charcoal as catalyst.

Fine charcoal was preactivated by heating in the above bulb filled with chlorine gas at 220° C for 2 h. After evacuation and refilling with chlorine the bulb was sealed and heated at 250-300° C by immersion in a Woods metal bath for 4.5 h. Cooling, evacuation, acetone extraction (3 x 20 ml) gave, on filtering, evaporation and vacuum drying, 160 mg of TCIN (95 %; 75 % yield). G.C. analysis was performed on cooled flask wall deposits during a trial run.

The same yield was obtained on performing the reaction with isophthalo-[<sup>14</sup>C]-nitrile from the previous reaction. Radioactivity = 0.733-

0.762 mCi/mmol; expected = 0.705 mCi/mmol. TCIN produced by this method, was identical by M.P., TLC, G.C. and M.S. with purified technical material.

#### ACKNOWLEDGEMENTS

I thank Dr. J.B. Bremner and Mr. C. Dragar for assistance in providing facilities and advice.

#### REFERENCES

1. The Pesticide Manual, British Crop Protection Council, 6th Edn. (1979)
2. U.S. patent : 3652637 (1972)
3. Siegel, M.R. - pers. comm..
4. Vincent, P.G. and Sisler, H.D. - *Physiol. Plant.* 21: 1249 (1968)
5. Szalkowski, M.B. and Stallard, D.E. - *J. Agric. Food Chem.* 25 (1): 208 (1977)
5. Hodgson, H.H. and Heyworth, F. - *J. Chem. Soc.* 1131 (1949)
7. Ruggli, P. and Caspar, E. - *Helv.* 18: 1418 (1935)
8. Hugel, G., Lever, M. and Fabre, C. - *Bull. Soc. Chim.* 836 (1954)
9. Bacon, R.G.R. and Hill, H.A.D. - *J. Chem. Soc.* 1097 (1964)
10. Newman, M.S. and Boden, H. - *Org. Chem.* 26: 2525 (1961)
11. Friedman, L. and Schechter, H. - *Org. Chem.* 26: 2522 (1961)
12. Cassar, L. and Ferrara, S., Foa, M. - *Adv. Chem. Ser.* 132: 252 (1974)
13. Cassar, L., Foa, M., Montanari, F. and Marinelli, G.P. - *J. Org. Chem.* 173: 335 (1979)
14. Japan patent : 68 22,298 (1968)
15. Jackson, C.L. and Carlton, H.A. - *Ber.* 35: 3855 (1902)
16. Yakobson, G.G.; Kobrina, L.S., Rubina, T.O. and Vorozhtsov, N.N. - *Zh. Obshch. Khim.* 33 (4) : 1273 (1963)
17. Doyle, M.P. and Bryker, W.J. - *J. Org. Chem.* 44 (9): 1572 (1979)
18. Barker, I.R.L. and Waters, W.A. - *J. Chem. Soc.* 150 (1952)
19. Chabannes, B., Ville, A., Grouiller, A. and Pacheco, H. - *Bull. Soc. Chim.* 223 (1967)
20. Stoecklin, G. and Vogelbruch, K. - *Radiochim. Acta* 10: 177 (1968)