J. Chem. Soc. (C), 1967

The Displacement of All Six Fluorine Atoms from Hexafluorobenzene by Sodium Cyanide in Methanol

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A by-product from the reaction of pentafluorobenzonitrile or hexafluorobenzene with sodium cyanide in methanol has been identified as 1,4-dicyano-2,3,5,6-tetramethoxybenzene. Its formation from hexafluorobenzene involves the displacement of all six fluorine atoms.

We have reported[1] that in the reaction of pentafluorobenzonitrile with sodium cyanide in methanol, the principal product, 3,5-difluoro-2,4,6-trimethoxybenzonitrile (I) was accompanied by a small amount of a high-melting by-product. A careful investigation of the products from the reaction of hexafluorobenzene with sodium cyanide in methanol revealed a small amount of the same by-product, in addition to pentafluoroanisole and the difluorotrimethoxybenzonitrile (I) previously reported.[1] The proportion of sodium cyanide and the time of reaction were varied, but although some of the by-product was always formed, the amount was always small. The by-product was purified by fractional crystallisation from light petroleum (in which it was sparingly soluble); when pure, it had m. p. 201·5—202°. Its infrared (i.r.) spectrum showed absorption due to the C≡N ($\nu_{max.}$ 2230 cm.$^{-1}$) and aliphatic C–H ($\nu_{max.}$ 2965 cm.$^{-1}$) groupings. Its mass spectrum indicated that the molecular formula was $C_{12}H_{12}N_2O_4$, and that the molecule contained no fluorine. The formula

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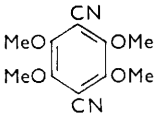
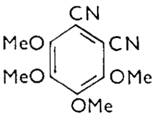
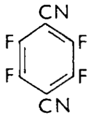
[1] E. Felstead, H. C. Fielding, and B. J. Wakefield, *J. Chem. Soc.* (*C*), 1966, 708.

$C_{12}H_{12}N_2O_4$ suggested that the compound was a dicyanotetramethoxybenzene. The two most likely isomers were considered to be 1,4-dicyano-2,3,5,6-tetramethoxybenzene (II) and 1,2-dicyano-3,4,5,6-tetramethoxybenzene (III), whose formation could be rationalised as follows. Hexafluorobenzene, in a solution of sodium cyanide in methanol, may be attacked either by methoxide ion leading to pentafluoroanisole, or by cyanide ion leading to pentafluorobenzonitrile. In the latter case, the ring is strongly activated to further attack, by methoxide, leading to the difluorotrimethoxybenzonitrile, or by cyanide, leading to a dicyanotetrafluorobenzene, which is rapidly attacked further, to give a dicyanotetramethoxybenzene, or products containing more cyano-groups. The relative proportions of the various products would depend on the concentrations and reactivities of the nucleophiles.


(I)


(II)


(III)


(IV)

Under our conditions, the cyanide ion apparently reacts much more slowly than the methoxide ion, and hence little of the dicyano-compound is obtained even with a large excess of cyanide.

Our previous work [1] indicated that the cyano-group is *para* directing to further substitution in pentafluorobenzonitrile. It was therefore considered that a second cyano-group would probably enter *para* to the first and that the by-product would therefore be 1,4-dicyano-2,3,5,6-tetramethoxybenzonitrile (II). This structure was confirmed by synthesis by a route which provided some evidence in support of the suggested mode of formation. On treatment with potassium carbonate in methanol, 1,4-dicyano-2,3,5,6-tetrafluorobenzene (IV) was readily converted into 1,4-dicyano-2,3,5,6-tetramethoxybenzene (II), which was identical with the by-product from the reaction of hexafluorobenzene or hexafluorobenzonitrile with sodium cyanide in methanol.

Besides revealing a unique example of the complete displacement of fluorine from hexafluorobenzene under mild conditions, these experiments provide further evidence for the extremely strong activating effect of the cyano-group on nucleophilic aromatic substitution reactions (cf. refs. 2 and 3).

EXPERIMENTAL

The mass spectrum was recorded using an A.E.I. MS9 double-focusing spectrometer. Melting points were determined on a Köfler hot-stage apparatus, and are uncorrected. The i.r. spectra were recorded for KBr discs, using a Perkin-Elmer spectrometer.

Reaction of Pentafluorobenzonitrile with Sodium Cyanide in Methanol.—The reaction was carried out as previously described.[1] Variation of the time of reaction between 1 and 24 hr., or the use of a very large excess of sodium cyanide, failed to yield more than 50 mg. of the crude, high-melting by-product (m. p. >180°) from pentafluorobenzonitrile (1·0 g.).

Reaction of Hexafluorobenzene with Sodium Cyanide in Methanol.—Several reactions were carried out, with reaction times from 1 to 24 hr. and with either 3·5 or 7 molar proportions of sodium cyanide. The amount of the high-melting by-product formed was not appreciably more than that indicated below in any case. A typical run is described.

Hexafluorobenzene (5·0 g.) was added to a stirred solution of sodium cyanide (10·0 g.) in methanol (150 ml.), and the mixture was stirred and heated under reflux for 18½ hr. The resulting black suspension was left to cool and poured into water (500 ml.). The suspension was filtered, and the black solid was dried, and repeatedly extracted with boiling light petroleum, b. p. 40—60°. On cooling, the extracts deposited white crystals (60 mg.), m. p. 202—204° (subl.). The mother-liquors, on concentration, yielded crude 3,5-difluoro-2,4,6-trimethoxybenzonitrile (0·29 g.), m. p. 80—83° (lit.,[1] m. p. 79·5—80°). The high-melting material from several runs was combined and fractionally crystallised from light petroleum, b. p. 60—80°, to yield 1,4-*dicyano*-2,3,5,6-*tetramethoxybenzene*, m. p. 201·5—202° (subl.); *M* (mass spectrum), 248·0800 ± 1·5 p.p.m. (Calc. for $C_{12}H_{12}N_2O_4$, *M*, 248·0797) (for elemental analysis, see below); $\nu_{max.}$ 2965 cm.$^{-1}$ (C–H), 2230 cm.$^{-1}$ ($C\equiv N$); and further small quantities of 3,5-difluoro-2,4,6-trimethoxybenzonitrile.

1,4-*Dicyano*-2,3,5,6-*tetramethoxybenzene*.— 1,4-Dicyano-2,3,5,6-tetrafluorobenzene (0·200 g.), anhydrous potassium carbonate (2·0 g.), and methanol (25 ml.) were stirred and heated under reflux for 21 hr. The mixture was left to cool, and poured into water (100 ml.). The resulting suspension was filtered, and the precipitate was washed with water and dried. The product was 1,4-dicyano-2,3,5,6-tetramethoxybenzene (0·160 g.; 65%), m. p. 200—201° (subl.). On recrystallisation from light petroleum, b. p. 80—100°, the compound was almost colourless, and had m. p. 202—202·5° (subl.) (Found: C, 58·0; H, 5·0; N, 11·4. $C_{12}H_{12}N_2O_4$ requires C, 58·1; H, 4·9; N, 11·3%). The i.r. spectrum was identical with that of the material prepared from hexafluorobenzene, and a mixed m. p. showed no depression.

I thank E. Clayton (Imperial Chemical Industries Ltd., Mond Division, Heath Laboratories, Runcorn) for determining the mass spectra, and Imperial Smelting Corporation, Avonmouth, for a gift of 1,4-dicyano-2,3,5,6-tetrafluorobenzene.

[6/946 *Received, July 25th*, 1966]

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[2] O. W. Webster, M. Brown, and R. E. Benson, *J. Org. Chem.*, 1965, **30**, 3250.

[3] K. C. Ho and J. Miller, *Austral. J. Chem.*, 1966, **19**, 423.