Direct Cyanation of Aromatic Compounds

I. Diazotation of Cyanamide in the Presence of Aromatic Compounds

LENNART EBERSON, SVEN NILSSON and BERND RIETZ

*Division of Organic Chemistry 1, Chemical Center, University of Lund,
P.O. Box 740, S-220 07 Lund, Sweden*

Diazotation of cyanamide in the presence of aromatic compounds produces small amounts of substituted benzonitriles. The isomer distribution has been determined for some representative aromatic substrates, and a mechanism involving cyano radicals is suggested to account for the low selectivity observed.

In connection with our work on the direct introduction of cyano groups in aromatic compounds by anodic oxidation[1] a number of methods for generating cyano radicals in homogeneous solution were needed for purpose of comparison. Previous work on cyano radicals all use photolytic methods of generation such as photolysis of cyanogen,[2] halogen cyanides,[2–5] cyanoformate,[6] mercuric cyanide,[7,8] or organomercury cyanides.[9] The intermediacy of CN· in these reactions has been inferred by trapping experiments, using cyclohexene or other olefines as trapping agents.

There is, however, no good thermal method of generation described in the literature. Compounds like $NC-N=N-CN$,[10] Ph_3C-CN,[11] and CF_3-CN [12] are all very stable thermally and give no indication of cyano radical formation upon heating. Thus it appears necessary to start with less stable precursors in order to compensate for the high heat of formation of the cyano radical.[13]

Diazotation of cyanamide is a logical method for generating this type of precursor. The Gomberg reaction [14] (reaction of diazonium ions with aromatic compounds to give biaryls) is known to proceed *via* formation of aryl radicals. It was therefore reasonable to hope for a similar course in the case of cyanamide. Several reports deal with the treatment of this compound with nitrous acid [15–17] but to our knowledge the presence of cyano radicals has never been established nor have any experiments been conducted in which trapping of possible intermediates has been attempted. In the following report we demonstrate that direct cyanation of the aromatic nucleus by diazotation of cyanamide is feasible, although yields of cyano products are low.

RESULTS AND DISCUSSION

Diazotation of cyanamide under carefully controlled conditions (see below) in the presence of aromatic substrates gave aromatic nitriles with the isomer distributions shown in Table 1. The total yields of aromatic nitriles are re-

Table 1. Isomer distribution of aromatic nitriles formed by diazotation of cyanamide in the presence of aromatic compounds.

Compound	Isomer distribution of nitriles, %		
	ortho or α-	*meta* or β-	*para*
Anisole	44	13	43
Biphenyl	54	29	17
Chlorobenzene	41	9	50
Toluene	50	27	23
Ethylbenzene	14	10	76
Isopropylbenzene	29	0	71
Naphthalene	60	40	

grettably low, 5 − 12 %, even under the most favorable reaction conditions. The best yields were obtained using isoamyl nitrite as the source of nitrous acid at high temperature and with somewhat less than one equivalent of acetic acid present, the aromatic compound being present in excess and with no solvent added. Numerous attempts were made in order to improve the yield of the reaction. In most cases toluene was used as the model compound to be cyanated and the combined yield of tolunitriles was compared with the result (12 %) when the reaction was run according to the conditions described above. Since acids, bases, and water catalyze the dimerization and polymerization of cyanamide [16,18,19] we tried to run the reaction at different hydrogen ion concentrations and used other acids like sulfuric acid, hydrochloric acid and *p*-toluenesulfonic acid. The addition of solvents like dimethylformamide, chloroform, carbon disulfide, formic acid, dioxane, or sulfolane gave no or only traces of tolunitriles.

Rüchardt and coworkers [20] have studied the Gomberg reaction in considerable detail and have proposed a cyclic mechanism in which phenyl radicals are formed by homolytic decomposition of a diazoanhydride (eqn. 1, $R = C_6H_5$).

$$\longrightarrow R-N_2^+ \longrightarrow R-N=N-OH$$

(1)
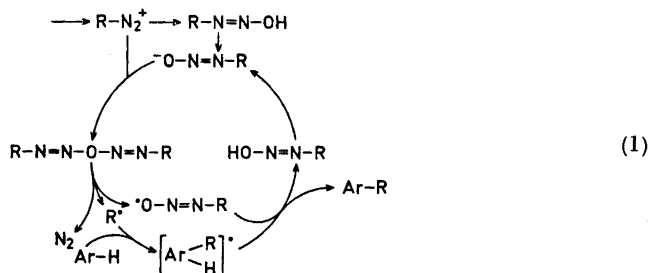
The pH dependence of the reaction and the isomer distribution of the biaryls formed were taken as evidence for the pathway proposed. The cyanation reaction described above certainly exhibits an isomer distribution pattern resembling that of a radical process and we therefore tentatively propose that an analogous mechanism operates also here (eqn. 1, R = CN).

If the diazonium ion eliminates nitrogen (in analogy with certain reactions of aryldiazonium ions) a cyano cation would be formed. We deem this possibility less probable because of the high energy of the cyano cation [13] and the isomer distribution observed; it is to be expected that a cyano cation would give isomer distributions more resembling those from other electrophilic substitution processes.

A major by-product in the diazotation of cyanamide by isoamyl nitrite was isoamyl carbamate which may have been formed from isoamyl alcohol and cyanamide,[21] its isomer carbodiimide, or its hydrolysis product urea.[22] Isomerization, polymerization, and hydrolysis of cyanamide may partly be responsible for the low yields observed.

EXPERIMENTAL

General. The purity of solvents and chemicals was carefully checked by gas chromatography (retention times for the nitriles prepared are given in Table 2) before use.

Table 2. Retention times of some aromatic nitriles, Ar − CN. 1.5 m × 3 mm column with 5 % neopentylglycol succinate on Chromosorb P.

Parent compound ArH	Retention times, min			Oven temp. °C
	ortho or α-	*meta* or β-	*para*	
Toluene	2.0	2.5	2.8	80
Ethylbenzene	4.0	5.8	6.4	100
Isopropylbenzene	4.4	6.0	8.8	130
Anisole	8.2	4.9	7.4	130
Chlorobenzene	6.4	4.9	5.5	130
Biphenyl	17.4	21.6	27.8	170
Naphthalene	8.4	10.6		170

Products were identified by gas chromatographic/mass spectral (LKB-9000 mass spectrometer system; column material 5 % neopentylglycol succinate on Chromosorb P), NMR (Varian A-60) and/or IR (Perkin-Elmer 237) comparison with authentic specimen.

2-, 3-, and 4-Methoxybenzonitrile. A mixture of 2-methoxybenzamide (5 g) and phosphorus pentoxide (6 g) was heated in *vacuo*, giving 2-methoxybenzonitrile (2.15 g, 50 %), b.p. 140 − 145/23 mm. Similarly, the 3- and 4-derivatives were prepared.

2-, 3-, and 4-Cyanobiphenyl. The 2- and 4-cyanobiphenyls were obtained from the corresponding amino compounds *via* a Sandmeyer reaction.[23] 3-Cyanobiphenyl was prepared from benzonitrile *via* nitration to 3-nitrobenzonitrile, reduction by tin and hydrochloric acid, diazotation of the amino compound and a Gomberg reaction with benzene.

2-, 3-, and 4-Chlorobenzonitrile. These compounds were commercially available (Fluka AG, Switzerland).

2-, 3-, and 4-Methylbenzonitrile. The 2- and 4-derivatives were prepared from the corresponding toluidines in a Sandmeyer reaction. 3-Methylbenzonitrile was prepared from 3-methylbenzamide as described above.

2-, 3-, and 4-Ethylbenzonitrile. The 2- and 4-derivatives were prepared from the corresponding amino compounds in a Sandmeyer reaction. The 3-isomer was prepared from benzonitrile by treatment with aluminium chloride in ether.[24]

2- and 3-Isopropylbenzonitrile. A mixture of concentrated nitric acid (72 g) and concentrated sulfuric acid (84 ml) was added dropwise to isopropylbenzene (120 g) at a temperature $< 20°C$. After 24 h the mixture was poured on ice, extracted with ether, the extracts dried, and distilled. Two product fractions were collected: b.p. $120 - 130°/12$ mm (35.0 g) and $130 - 136°$ (5.0 g, mostly the 4-isomer). The first fraction was redistilled on a spinning band column and gave a lower-boiling fraction which was better than 95 % enriched in the 2-isomer. This fraction was converted into 2-isopropylbenzonitrile *via* catalytic reduction (H_2, PtO_2, 50 p.s.i.) and a Sandmeyer reaction. A second fraction consisted of all three isopropylnitrobenzenes and was converted into the cyano derivatives *via* catalytic hydrogenation and the Sandmeyer reaction. The cyano derivative not identical to either of the 2- or 4-isomer (see below) was assigned the structure of the 3-isomer.

4-Isopropylbenzonitrile. A solution of 4-isopropylbenzaldehyde (0.50 mol) in ethanol (200 ml) was treated with hydroxylammonium chloride (0.50 mol) in water (50 ml). The mixture was made with alkaline sodium hydroxide (30 g) dissolved in water (40 ml). After 2.5 h the mixture was poured onto ice and neutralized with lumps of solid carbon dioxide. The crystalline oxime was filtered off, washed with water and dried. The oxime was then dehydratized by warming it with acetic anhydride (100 ml). After the sudden start of the reaction the mixture was refluxed for 30 min, cooled, and poured in cold water. The nitrile was extracted by ether, and the ether extracts were washed with sodium bicarbonate solution and water. Distillation gave 4-isopropylbenzonitrile (47.7 g, 66 %) boiling at $117 - 119°/12$ mm.

1- and 2-Cyanonaphthalene. These compounds were commercially available (Fluka AG, Switzerland).

Diazotation procedure. In a three-necked flask equipped with a reflux condenser, stirrer, and dropping funnel were mixed the aromatic substrate (0.50 mol) and isoamyl nitrite (0.10 mol). A solution of cyanamide (0.10 mol) in acetic acid (0.060 mol) was added dropwise at room temperature, whereafter the reaction mixture was refluxed for 1.5 h. After cooling and neutralization with sodium bicarbonate the organic material was taken up in ether and the ether solution dried. The solution was analyzed by gas chromatography and the product distribution determined using a suitable internal standard. In some cases the nitrile mixture was isolated by distillation.

Isoamyl carbamate. Urea was mixed with a fourfold amount of isoamyl alcohol and the mixture refluxed for 6 h. The unreacted alcohol was distilled off and the residue re-crystallized from ligroin, m.p. 63° (lit.[22] 63°), yield 25 %.

REFERENCES

1. Eberson, L. and Nilsson, S. *Discussions Faraday Soc.* **45** (1968) 242.
2. Basco, N. *Advan. Chem. Ser.* **36** (1962) 26.
3. Müller, E. and Huber, H. *Chem. Ber.* **96** (1963) 670.
4. Goy, C. A., Shaw, D. H. and Pritchard, H. O. *J. Phys. Chem.* **69** (1965) 1504.
5. Milligan, D. E. and Jacox, M. E. *J. Phys. Chem.* **47** (1967) 278.
6. Tominaga, T., Odaira, Y. and Tsutsumi, S. *Bull. Chem. Soc. Japan* **37** (1964) 596.
7. Yoshida, K. and Tsutsumi, S. *Tetrahedron Letters* **1965** 2417.
8. Yoshida, K. and Tsutsumi, S. *J. Org. Chem.* **31** (1966) 3635.
9. Yoshida, K. and Tsutsumi, S. *Tetrahedron Letters* **1966** 281.
10. Marsh, F. D. and Hermes, M. E. *J. Am. Chem. Soc.* **87** (1965) 1819.
11. Fischer, A. and Fischer, O. *Ann.* **194** (1878) 261.
12. Perettie, D. J. and Janz, G. J. *J. Am. Chem. Soc.* **91** (1969) 6590.
13. Dibeler, V. H. and Liston, S. K. *J. Chem. Phys.* **47** (1967) 4548.
14. Gomberg, M. and Bachmann, W. E. *J. Am. Chem. Soc.* **46** (1924) 2339.

15. Drechsel, E. *J. prakt. Chem.* [2] **8** (1873) 327.
16. Drechsel, E. *J. prakt. Chem.* [2] **11** (1875) 284.
17. Werner, E. A. *J. Chem. Soc.* **107** (1915) 715.
18. Houben-Weyl, *Methoden der organischen Chemie*, Band 8 209.
19. Christ, C. L. *Acta Cryst.* **4** (1951) 77.
20. Rüchardt, C. *Angew. Chem.* **77** (1965) 974.
21. Houben-Weyl, *Methoden der organischen Chemie*, Band 8 170.
22. Krook, D. and Miller, C. E. *Chem. Abstr.* **49** (1955) 8817.
23. Vogel, A. I. *A Textbook of Practical Organic Chemistry*, Longmans, London 1961, p. 607.
24. Baddeley, G. *J. Chem. Soc.* **1949** S 229.