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Nitration of Polyalkylbenzenes in Acetonitrile. Another View on Side-chain Acetamidation[1]

Hitomi SUZUKI and Terukiyo HANAFUSA

Department of Chemistry, Faculty of Science, Hiroshima University, Higashi-sendamachi, Hiroshima 730

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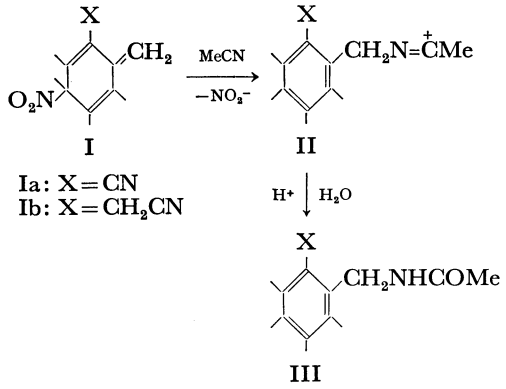
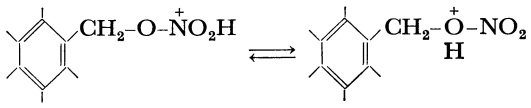
Nitration of polyalkylbenzenes in acetonitrile is known to give *N*-benzylacetamides in a good yield. The reaction was explained to proceed through the nucleophilic attack by the solvent on the nitro-methylenecyclohexadiene intermediate (I) followed by the release of a nitrite ion to give the carbonium ion (II), which was hydrolyzed to give *N*-benzylacetamide (III).[2]



In inert solvents such as dichloromethane and chloroform, the major process was the side-chain nitrooxylation, for which we have proposed a mechanism involving the rearrangement of nitro-methylenecyclohexadiene to benzyl nitrite.[3] In view of the high potency of polyalkylbenzylic compounds,[4] especially benzyl nitrite, to act as a benzylating agent in the presence of an acid catalyst, the possibility that the *N*-benzylacetamides are derived from the reaction of the initially formed benzyl nitrite with acetonitrile cannot be ruled out.

Hexamethylbenzene was nitrated with excess fuming nitric acid (d=1.5) in acetonitrile at 0—10 °C to give *N*-(pentamethylbenzyl)acetamide (IV) as the major product. Yields based on the unrecovered hydrocarbon often exceeded 50%. When pentamethylbenzyl nitrite was similarly treated in the same solvent, the product was a mixture of IV, pentamethylbenzyl nitrate, pentamethylphenylnitromethane, and 1,2-bis(nitrooxymethyl)-3,4,5,6-tetramethylbenzene in the approximate ratio 3:3:1:2. Formation of IV can be rationalized by assuming that the nucleophilic attack of the solvent upon the benzylic carbon atom of the conjugate acid (V) produces an imino-carbonium ion type intermediate (II; X=Me).



V

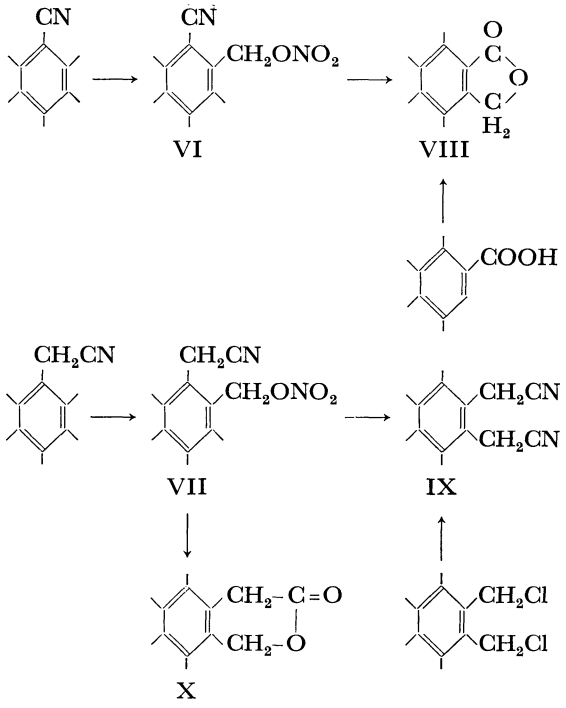
On treatment with excess fuming nitric acid in dichloromethane at room temperature, pentamethylbenzonitrile gave 1-cyano-2-nitrooxymethyl-3,4,5,6-tetramethylbenzene (VI) in 85% yield. Similarly, pentamethylbenzyl cyanide readily gave 1-cyanomethyl-2-nitrooxymethyl-3,4,5,6-tetramethylbenzene (VII) in 62% yield. The structures of VI and VII were determined by their conversion into 4,5,6,7-tetramethylphthalide (VIII) and 1,2-bis(cyanomethyl)-3,4,5,6-tetramethylbenzene (IX), respectively. Acid-catalyzed hydrolysis of VII yielded 5,6,7,8-tetramethyl-1,4-dihydro-3*H*-2-benzopyran-3-one (X), and the structure was deduced from the elemental analysis and spectral data.

1) The reaction of polysubstituted aromatics. Part XXXIII; Part XXXII: H. Suzuki and T. Hanafusa, *Synthesis*, **1973**, in press.

2) E. Hunziker, J. R. Penton, and H. Zollinger, *Helv. Chim. Acta*, **54**, 2043 (1971).

3) H. Suzuki and K. Nakamura, This Bulletin, **43**, 473 (1970); K. Nakamura, *ibid.*, **44**, 133 (1971); H. Suzuki and K. Nakamura, *ibid.*, **44**, 227 (1971); H. Suzuki, K. Nakamura, and M. Takeshima, *ibid.*, **44**, 2248 (1971).

4) H. Suzuki and K. Nakamura, *ibid.*, **41**, 2197 (1968).



The initial attack by nitronium ion on these compounds should occur at an aromatic carbon atom at 3-position, since the benzenium ion intermediates can be most effectively stabilized by three methyl groups. The nitro-methylenecyclohexadienes Ia and Ib should then be formed, and should be subject to some intramolecular interaction between the neighboring cyano and methylene groups, according to the reaction squence proposed.[2] The present results were contrary to this; the cyano group remained intact.

Benzyl nitrites are readily hydrolyzed to the corresponding benzyl alcohols. In organic mediums containing nitrite or acetate ions, they can be partly converted into phenylnitromethanes and benzyl acetates, respectively. Nitration of hexamethylbenzene with fuming nitric acid in acetic anhydride gives a mixture of varying amounts, depending on the conditions employed, of pentamethylbenzyl nitrate, pentamethylphenylnitromethane, and pentamethylbenzyl acetate. The latter two compounds can arise either from the anion-exchange of the benzylic intermediate-nitrite ion pair, or from the nucleophilic displacement on the benzylic carbon atom of the conjugate acid (V). These findings seem to favor our view that the side-chain acetamidation products arise from the reaction of the initially formed benzyl nitrite with the solvent rather than that proposed by previous workers.[2]

Experimental

All melting points are uncorrected. ^1H NMR spectra were determined in deuteriochloroform on a Varian T-60 spectrometer using TMS as an internal standard. IR spectra were recorded in Nujol on a Perkin-Elmer Model 137 spectrophotometer, only prominent peaks being given. Pentamethylbenzonitrile was prepared by heating iodopentamethylbenzene with cuprous cyanide in hexamethylphosphoric triamide. Pentamethylbenzyl cyanide and pentamethylbenzyl nitrite were prepared by treating the corresponding chloride with sodium cyanide and silver nitrite, respectively, in acetonitrile.

N-(Pentamethylbenzyl)acetamide (IV). A mixture of hexamethylbenzene (4.1 g) and acetonitrile (30 ml) was cooled in an ice-bath, fuming nitric acid ($d=1.5$; 8.4 g) being added with vigorous stirring over a period of 30 min. After the mixture was left to stand for several hours at room temperature, it was poured into water, and the precipitated solid was filtered off, washed with cold carbon tetrachloride, and crystallized from ethanol to give amide as fine white needles, mp 229—231 °C. Yields based on unrecovered hydrocarbon ranged from 28 to 60%. *m/e* 219 (M^+); NMR: 8.03 (s, 3H), 7.77 (s, 6H), 7.74 (s, 9H), 5.52 (d, 2H), and *ca.* 4.7 τ (broad, 1H); IR: 593, 1059, 1272, 1349, 1535, 1642, and 3300 cm^{-1}. Found: C, 76.52; H, 9.63%. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65%.

1-Cyano-2-nitrooxymethyl-3,4,5,6-tetramethylbenzene (VI). Fuming nitric acid ($d=1.5$; 6.3 g) was added dropwise to a magnetically stirred solution of pentamethylbenzonitrile (1.73 g) in dichloromethane (15 ml) at 0—5 °C over a period of 30 min. The solution rapidly turned yellow, the color being intensified to dark brown. After the addition, the mixture was left to stand at room temperature for 5 hr, and then diluted with water. The organic layer was taken up, thoroughly washed with water and dilute aqueous sodium hydrogen carbonate, and evaporated to give a light brown pasty cake (*ca.* 2.3 g) which, on crystallization from a mixture of dichloromethane and light petroleum, yielded nitrate as colorless fine needles (1.98 g; 85%), mp 85—86 °C. NMR: 7.70 (s, 6H), 7.69 (s, 3H), 7.49 (s, 3H), and 4.29 τ (s, 2H); IR: 705, 858, 870, 970, 1281, 1638, and 2218 cm^{-1}.

Found: C, 61.57; H, 6.08; N, 11.66%. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96%.

VI was heated under gentle reflux with hydrochloric acid in ethanol to give *4,5,6,7-tetramethylphthalide (VIII)*, identical with the authentic sample obtained from the zinc chloride-catalyzed condensation of chloromethyl methyl ether with 2,3,4,5-tetramethylbenzoic acid. Mp 233—235 °C. NMR: 7.78 (s, 3H), 7.72 (s, 3H), 7.70 (s, 3H), 7.37 (s, 3H), and 4.91 τ (s, 2H); IR: 780, 966, 1016, 1126, 1264, 1297, 1350, and 1741 cm^{-1}. Found: C, 75.66; H, 7.38%. Calcd for $C_{12}H_{14}O$: C, 75.76; H, 7.42%.

1-Cyanomethyl-2-nitrooxymethyl-3,4,5,6-tetramethylbenzene (VII). Pentamethylbenzyl cyanide was similarly treated with the nitrating agent to give VII as fine needles, mp 116—118 °C. NMR: 7.75 (s, 6H), 7.67 (s, 6H), 6.26 (s, 2H), and 4.37 τ (s, 2H); IR: 702, 870, 957, 1283, 1296, 1629, and 2248 cm^{-1}.

Found: C, 62.54; H, 6.70; N, 11.44%. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28%.

VII was agitated with saturated aqueous sodium cyanide in acetonitrile to give *1,2-bis(cyanomethyl)-3,4,5,6-tetramethylbenzene (IX)*, mp 178—179 °C, identical with the compound obtained by the action of sodium cyanide on 1,2-bis(chloromethyl)-3,4,5,6-tetramethylbenzene. NMR: 7.75 (s, 6H), 7.69 (s, 6H), and 6.28 τ (s, 4H); IR: 801, 1068, 1286, 1302, and 2245 cm^{-1}. Found: C, 79.43; H, 7.50; N, 12.87%. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.19%.

VII was heated with a mixture of hydrochloric acid and ethanol to give white needles of formula $C_{13}H_{16}O_2$, which exhibited ^1H NMR peaks at 7.78 (s, 6H), 7.75 (s, 6H), 6.32 (s, 2H), and 4.63 τ (s, 2H); IR bands at 1026, 1226, 1261, and 1743 cm^{-1}. On heating with dilute sodium hydroxide it went into solution and was again precipitated on acidification. From the mode of reaction and spectral data, it was formulated as *5,6,7,8-tetramethyl-1,4-dihydro-3H-2-benzopyran-3-one (X)*. Found: C, 76.14; H, 7.83%. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%.