Reactions of Tetramethylbenzenedicarbonitriles and Tetramethylbenzonitriles with Fuming Nitric Acid. A New Route to Some Substituted Phthalides and 1,3-Dihydroisobenzofuran-1-imines[1]

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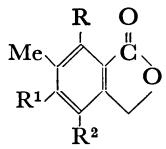
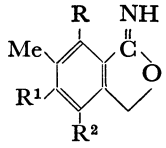
The reaction of tetramethylbenzenedicarbonitriles and tetramethylbenzonitriles with fuming nitric acid ($d=1.5$) has been investigated at room temperature in the dark. 2,4,5,6-Tetramethylbenzene-1,3-dicarbonitrile and 2,3,5,6-tetramethylbenzene-1,4-dicarbonitrile gave, after aqueous work-up, 4-cyano-5,6,7-trimethyl- and 5-cyano-4,6,7-trimethylphthalides, respectively, in high yields, while 3,4,5,6-tetramethylbenzene-1,2-dicarbonitrile produced appreciable amounts of two cyanonitro-3-cyclohexen-1-ones in addition to 7-cyano-4,5,6-trimethylphthalide. Similarly, 2,3,4,6- and 2,3,5,6-tetramethylbenzonitriles afforded 4-nitro-5,6,7-trimethyl- and 5-nitro-4,6,7-trimethylphthalides, respectively, along with the expected nitro compounds. In contrast, 2,3,4,5-tetramethylbenzonitrile underwent normal nitration, giving 6-nitro derivative as the sole product. The phthalide formation was found to proceed through 1,3-dihydroisobenzofuran-1-imines presumably derived from the initially formed *o*-cyanobenzyl nitrates. The reaction appears to provide potential utility in the synthesis of some substituted phthalides and 1,3-dihydroisobenzofuran-1-imines.

Pentamethylbenzonitrile reacts with nitric acid regiospecifically at the *ortho* side-chain to give 6-cyano-2,3,4,5-tetramethylbenzyl nitrate in high yield, which on acid hydrolysis is easily converted into 4,5,6,7-tetramethylphthalide.[2] This reaction appears interesting, since it provides a new route to some substituted phthalides of pharmaceutical interest. We therefore undertook an investigation of the scope of the reaction using as substrate a series of tetramethylbenzenedicarbonitriles (**1a—c**) and tetramethylbenzonitriles (**1d—f**). Simple phthalides are usually prepared by the hydrolysis of *o*-(halomethyl)benzoic acid and its derivatives, reduction of phthalic anhydride and related compounds, or oxidation of appropriate benzene derivatives containing oxidizable adjacent carbon chains.

Tetramethylbenzenedicarbonitriles. Dinitriles **1a—c** were nearly inert toward the action of nitric acid in dichloromethane solution and were recovered almost

Table 1. Physical properties of some polysubstituted phthalides and 1,3-dihydroisobenzofuran-1-imines[a]

Compound		R	R^1	R^2	Mp (°C)	PMR spectra (δ)	IR spectra (cm^{-1})
 7	**7a**	CN	Me	Me	286—287	2.35(Me), 2.37(Me), 2.60(Me), 5.23(CH_2)	2220, 1765, 1115, 1050
	7b	Me	Me	CN	213—214	2.32(Me), 2.61(Me), 2.72(Me), 5.31(CH_2)	2235, 1763, 1121, 1018
	7c	Me	CN	Me	262—264	2.50(Me), 2.59(Me), 2.67(Me), 5.21(CH_2)	2230, 1757, 1126, 1024
	7h	Me	Me	NO_2	191—194	2.37(Me), 2.59(Me), 2.77(Me), 5.38(CH_2)	1765, 1530, 1350, 1120, 1015
	7i	Me	NO_2	Me	203—205	2.23(Me), 2.27(Me), 2.69(Me), 5.21(CH_2)	1775, 1535, 1355, 1290, 1115, 1015
	7j	Me	Me	NH_2	235—245 (dec)	2.20(Me), 2.26(Me), 2.57(Me), 5.03(CH_2)	3500, 3420, 1740, 1650, 1310, 1135, 1010,
 6	**6a**	CN	Me	Me	—[b]	2.30(Me), 2.33(Me), 2.58(Me), 5.21(CH_2)	3250, 2225, 1660, 1290, 1225, 1040, 1005, 945
	6b	Me	Me	CN	197—199[c] (dec)	2.32(Me), 2.59(Me), 2.79(Me), 5.29(CH_2)	3280, 2230, 1680, 1295, 1240, 1030, 960, 900
	6c	Me	CN	Me	200—202[c] (dec)	2.43(Me), 2.56(Me), 2.71(Me), 5.15(CH_2)	3300, 2240, 1670, 1290, 1210, 1020, 950
	6h	Me	Me	NO_2	183—185[c] (dec)	2.38(Me), 2.56(Me), 2.84(Me), 5.38(CH_2)	3300, 1680, 1530, 1350, 1265, 1015, 955
	6i	Me	NO_2	Me	195—200[c] (dec)	2.16(Me), 2.24(Me), 2.73(Me), 5.13(CH_2)	3320, 1670, 1535, 1365, 1290, 1270, 1215, 1025, 955

a) Satisfactory elemental analyses were obtained for all new phthalides and 1,3-dihydroisobenzofuran-1-imines. b) Not determined. c) The melting ranges of the 1,3-dihydroisobenzofuran-1-imines vary depending on the rate of heating.

Table 2. Physical properties of isomeric nitrotetramethylbenzonitriles

Compound	Mp[a] (°C)	PMR spectra (δ)	IR spectra (cm^{-1})
6-Nitro-2,3,4,5-tetramethylbenzonitrile (**1g**)	175—176	2.25(2 Me), 2.34(Me), 2.54(Me)	2225, 1535, 1275, 830
5-Nitro-2,3,4,6-tetramethylbenzonitrile (**1h**)	159—161	2.26(Me), 2.28(Me), 2.46(Me), 2.57(Me)	2225, 1535, 855
4-Nitro-2,3,5,6-tetramethylbenzonitrile (**1i**)	195—198	2.20(2 Me), 2.56(2 Me)	2225, 1535, 830

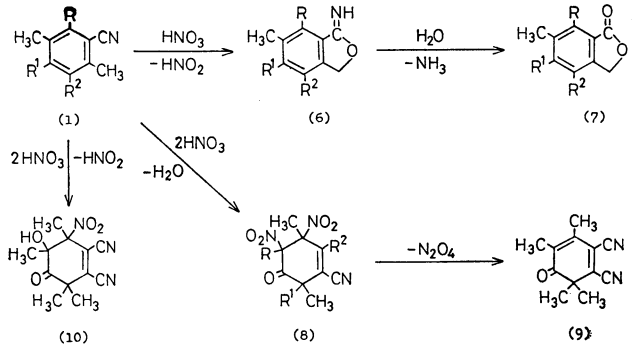
a) These compounds begin to sinter at around 135—150 °C and melt with partial sublimation.

unchanged under the conditions successfully employed for the reaction of pentamethylbenzonitrile. Thus, dinitriles were dissolved in fuming nitric acid (d=1.5) itself and the mixture was allowed to stand at room temperature for several days. When the reaction mixture from **1b** or **1c** was diluted with water, rather surprisingly, little precipitate was obtained. However, when the slightly turbid solution thus obtained was set aside overnight, a white crystalline solid separated out and was readily identified as cyanotrimethylphthalide (**7b**—**c**) on the basis of elemental analysis, molecular weight (m/e 201 (M^+)), and spectral data, as summarized in Table 1.

Of the three isomeric tetramethylbenzenedicarbonitriles, 3,4,5,6-tetramethylbenzene-1,2-dicarbonitrile (**1a**) was the least reactive member and behaved somewhat differently. However, by keeping it in contact with the nitrating agent for a week or longer, an appreciable amount of two cyanonitro-3-cyclohexen-1-ones (**8b** and **10**) was obtained in addition to the expected phthalide (**7a**). The structure proof for these nitro ketones and a possible mode of their formation will be the subject of the accompanying paper.

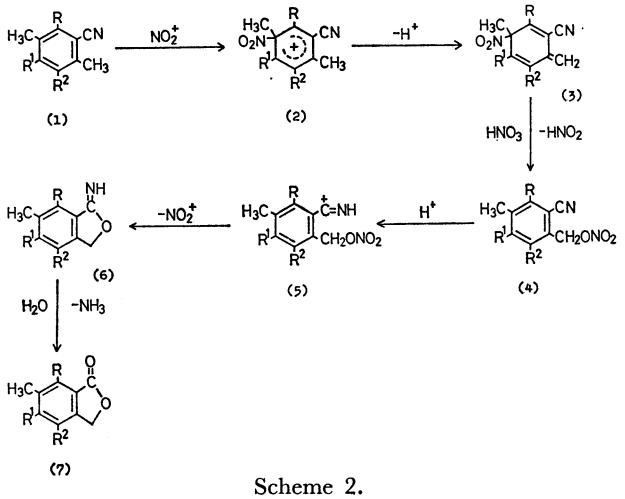
When the reaction mixture was diluted with cold water and the aqueous filtrate was immediately neutralized with sodium hydrogencarbonate, a yellow solid was obtained and crystallized from ethanol to pale yellow fine needles. Its mass spectral data (m/e 200 (M^+)) and elemental analysis were consistent with the formula $C_{12}H_{12}N_2O$. The PMR spectrum showed absorptions due to three methyl groups (δ 2.30—2.84), one methylene group (δ 5.15—5.38), and one imino proton (δ *ca.* 4—5; exchangeable with D_2O). The IR spectrum exhibited absorption bands due to the imino group at 3250—3300 and 1660—1680 cm^{-1}, in addition to the expected absorptions characteristic for a cyano group (2220—2235 cm^{-1}) and unsaturated cyclic ether (1015—1040 and 1210—1290 cm^{-1}). On acid hydrolysis it was converted into phthalide (**7a**—**c**). On the basis of the spectral evidence and the chemical transformation, the compound was identified as cyanotrimethyl-1,3-dihydroisobenzofuran-1-imine (**6a**—**c**). Few cyclic imidates of this type have been described previously, and most of these were obtained in unspecified yields by heating *o*-(halomethyl)benzamides at high temperatures.[3]

The isolation of imidate **6** provides a reasonable mechanism for the conversion of polymethylbenzonitriles into phthalides (Scheme 2). Nitronium ion makes an *ipso* attack at the site *meta* to the cyano group in **1** to form the arenium ion (**2**), which releases a proton from the activated methyl group *para* to the site of attack to give the triene (**3**), which is then transformed into the benzyl nitrate (**4**). In moderately strong protogenic acidic media, the nitrate **4** undergoes intramolecular ring closure through nucleophilic attack of the ester oxygen on the neighboring electron-deficient carbon of the nitrilium ion (**5**), giving **6** as a water-soluble salt.



	R	R^1	R^2
a	CN	Me	Me
b	Me	Me	CN
c	Me	CN	Me
d	H	Me	Me
e	Me	Me	H
f	Me	H	Me
g	NO_2	Me	Me
h	Me	Me	NO_2
i	Me	NO_2	Me
j	Me	Me	NH_2

Scheme 1.



Scheme 2.

Formation of 1,3-dihydroisobenzofuran-1-imines is thus limited to those nitriles having at least one pair of methyl groups *para* to each other; others are simply nitrated on the ring or recovered unchanged. In contrast to the nitration of polymethylbenzenes in acetonitrile, in which *N*-(polymethylbenzyl)acetamides are obtained,[4] no Ritter-type reaction leading to 2,3-dihydro-1-isoindolones[5] was observed. To our knowledge, the formation reaction seems to be the first example in which the electrophilic carbon of the nitrilium ion displaces the acyl component on the ester oxygen, giving imidates as stable products.

Tetramethylbenzonitriles. The reaction of nitriles **1e—f** with fuming nitric acid proceeded with more ease, giving after the usual work-up a mixture of the corresponding nitrotrimethylphthalide (**7h—i**) and nitrotetramethylbenzonitrile (**1h—i**). In addition, a nitro ketone (**8d**) was obtained as a minor product from **1f**. When the reaction mixture was quenched with water and the aqueous filtrate was immediately neutralized with sodium hydrogencarbonate, nitrotrimethyl-1,3-dihydroisobenzofuran-1-imine (**6h—i**) was obtained. In sharp contrast, 2,3,4,5-tetramethylbenzonitrile (**1d**) was simply nitrated on the ring, giving 6-nitro-2,3,4,5-tetramethylbenzonitrile (**1g**) under the same conditions.

As a further extension of the present work, three isomeric trimethylbenzenetricarbonitriles were prepared and similarly treated with fuming nitric acid. However, the combined deactivating effect of three cyano groups surpassed the activating effect of three methyl groups and no reaction could be observed.

Although a limited number of cases have been investigated, it seems likely that many nitriles of the type **1** will yield phthalides and 1,3-dihydroisobenzofuran-1-imines in acceptable yields when appropriately treated with fuming nitric acid. Thus, the present reaction provides a simple direct route to some substituted phthalides and 1,3-dihydroisobenzofuran-1-imines for which no convenient preparative procedures have been available.

Experimental

All melting points were obtained on a hot-stage apparatus and are uncorrected. IR spectra were run as Nujol mulls on a Hitachi 215 spectrophotometer and only prominent peaks are recorded. PMR spectra were measured in deuteriochloroform with a Varian T-60 spectrometer using TMS as an internal standard. Mass spectra (MS) were obtained on a Hitachi RMS-4 mass spectrometer with 70 eV ionizing current.

Materials. Tetramethylbenzenedicarbonitriles and tetramethylbenzonitriles were prepared by allowing the corresponding iodoarenes to react with copper(I) cyanide in phosphoric tris(dimethylamide). The following typical example illustrates the general procedure used in the synthesis of the nitriles.

*2,3,5,6-Tetramethylbenzonitrile (**1f**).* A mixture of iododurene (11.7 g; 45 mmol),[6] copper(I) cyanide (5.2 g; 58 mmol), and phosphoric tris(dimethylamide) (15 ml) was heated with stirring at 90—100 °C for 2 h, and then poured into aqueous iron(III) chloride solution to decompose the complex. The light tan solid was collected by filtration and washed successively with water, aqueous sodium hydrogensulfite, and water. It was sucked as dry as possible and then placed in a filter thimble and extracted with light petroleum using a Soxhlet extractor. The extract was evaporated and the residue was crystallized from ethanol to give **1f** as fine needles: yield, 5.1 g (73%); mp 76—77 °C. PMR: δ 2.20 (s, 6H), 2.37 (s, 6H), and 6.97 (s, 1H); IR: 2205, 1010, and 890 cm^{-1}.

The above procedure applied to other iodo- and diiodotetramethylbenzenes gave the corresponding benzonitriles and benzenedicarbonitriles in 48—75% yields.

*2,3,4,5-Tetramethylbenzonitrile (**1d**)*: Mp 76—77 °C. PMR: δ 2.23 (s, 3H), 2.27 (s, 6H), 2.42 (s, 3H), and 7.17 (s, 1H).

*2,3,4,6-Tetramethylbenzonitrile (**1e**)*: Mp 66—67 °C. PMR: δ 2.17 (s, 3H), 2.28 (s, 3H), 2.44 (s, 6H), and 6.87 (s, 1H).

*3,4,5,6-Tetramethylbenzene-1,2-dicarbonitrile (**1a**)*: Mp 230—231 °C. PMR: δ 2.54 (s, 6H) and 2.35 (s, 6H).

*2,4,5,6-Tetramethylbenzene-1,3-dicarbonitrile (**1b**)*: Mp 178—180 °C. PMR: δ 2.26 (s, 3H), 2.56 (s, 6H), and 2.71 (s, 3H).

*2,3,5,6-Tetramethylbenzene-1,4-dicarbonitrile (**1c**)*: Mp 208—210 °C. PMR: δ 2.52 (s, 12H).

Reaction of Tetramethylbenzenedicarbonitriles with Fuming Nitric Acid. The procedure used in each of the reactions described in the text was identical; therefore, only a typical example of these reactions will be reported in detail.

*2,4,5,6-Tetramethylbenzene-1,3-dicarbonitrile (**1b**).* To stirred fuming nitric acid (d=1.5; 10 g) cooled at −10 — −5 °C, **1b** (0.60 g; 3.26 mmol) was added in portions, and the mixture was allowed to stand at room temperature (25—30 °C) for several days, during the course of which the initial dark brown color faded to light yellow. The mixture was diluted with water (≈100 ml) and the resulting somewhat turbid solution was filtered and set aside overnight. The crystalline deposit was collected by filtration and crystallized from aqueous methanol to furnish *4-cyano-5,6,7-trimethylphthalide (**7b**)* as fine prisms, mp 213—214 °C. Yield, 0.63 g (96%). MS: *m/e* 201 (M^+), 172 (base peak), 144, and 115. Found: C, 71.4; H, 5.4; N, 7.0%. Calcd for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0%.

When the above aqueous solution was immediately neutralized with sodium hydrogencarbonate, *4-cyano-5,6,7-trimethyl-1,3-dihydroisobenzofuran-1-imine (**6b**)* was obtained as a pale yellow precipitate, mp 197—199 °C (dec). MS: *m/e* 200 (M^+), 172, 145, 130, and 115. Found: C, 71.9; H, 6.1; N, 13.9%. Calcd for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0%.

By a similar treatment, dinitriles **1a** and **1c** were converted into the corresponding phthalides **7a** and **7c**, or 1,3-dihydroisobenzofuran-1-imines **6a** and **6c**, respectively, in 18—76% yield. The former dinitrile produced appreciable amounts of 3-cyclohexen-1-one derivatives **8b** and **10** in addition.

Reaction of Tetramethylbenzonitriles with Fuming Nitric Acid. The general procedure is illustrated below with the reaction of *2,3,4,6-tetramethylbenzonitrile (**1e**)*.

A solution of **1e** (1.59 g; 10 mmol) in fuming nitric acid (20 g) was allowed to stand at room temperature for several days, after which the mixture was poured onto crushed ice to give *5-nitro-2,3,4,6-tetramethylbenzonitrile (**1h**)* as a yellow solid (0.62 g). The aqueous part was filtered and set aside overnight to give a further deposit, which was collected by filtration and recrystallized from aqueous methanol, giving *4-nitro-5,6,7-trimethylphthalide (**7h**)* as fine needles, mp 191—194 °C. Yield, 0.70 g (53%). MS: *m/e* 221 (M^+), 205, and 177. Found: C, 60.0; H, 5.2; N, 6.3%. Calcd for $C_{11}H_{11}NO_4$: C, 59.7; H, 5.0; N, 6.3%.

On being neutralized with sodium hydrogencarbonate, the acid solution gave *4-nitro-5,6,7-trimethyl-1,3-dihydroisobenzofuran-1-imine (**6h**)*, mp 183—185 °C. Yield, 0.50 g (23%). MS: *m/e* 220 (M^+), 203, 175, 160, and 147. Found: C, 59.8; H, 5.5; N, 12.4%. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7%.

When **6h** in methanol was treated with hydrogen in the presence of Pd/C catalyst at room temperature, *4-amino-5,6,7-trimethylphthalide (**7j**)* was obtained, which on heating sintered and decomposed at around 235—245 °C. MS: *m/e* 191 (M^+), 176, 162, 146, and 134. Found: C, 69.4; H, 6.8; N, 7.5%. Calcd for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.9; N, 7.3%.

The same procedure applied to nitrile **1f** gave *4-nitro-2,3,-5,6-tetramethylbenzonitrile* (**1i**; 8—40%), *5-nitro-4,6,7-trimethylphthalide* (**7i**; 10—23%), and a nitro ketone (**8d**; 4—9%), or *5-nitro-4,6,7-trimethyl-1,3-dihydroisobenzofuran-1-imine (**6i**)* as a precursor of **7i**.

*2,3,4,5-Tetramethylbenzonitrile (**1d**).* A solution of **1d** in fuming nitric acid was left to stand at room temperature for several days. The usual work-up of the reaction mixture, followed by crystallization of a solid product from ethanol, gave *6-nitro-2,3,4,5-tetramethylbenzonitrile (**1g**)* as the sole product; pale yellow needles, mp 175—176 °C. Found: C, 64.8; H, 6.0; N, 13.7%. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9; N, 13.7%.

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References

1) The reaction of polysubstituted aromatics. Part XLVII; Part XLVI: H. Suzuki and M. Shinoda, *Synthesis*, **1977**, 640. A preliminary account has been published: H. Suzuki, M. Koge, and T. Hanafusa, *J. Chem. Soc. Chem. Commun.*, **1977**, 341.

2) H. Suzuki and T. Hanafusa, *Bull. Chem. Soc. Jpn.*, **46**, 3607 (1973). For a general review of non-conventional processes which occur as a consequence of *ipso* attack, see S. R. Hartshorn, *Chem. Soc. Rev.*, **3**, 167 (1974); B. Moodie and K. Schofield, *Acc. Chem. Res.*, **9**, 287 (1976); H. Suzuki, *Synthesis*, **1977**, 217.

3) S. Gabriel, *Ber.*, **20**, 2235 (1887); S. Gabriel and W. Landsberger, *ibid.*, **31**, 2732 (1898); G. Berti, *Gazz. Chim. Ital.*, **87**, 707 (1957); L. M. Yagupol'ski and R. V. Belinskaya, *Zhur. Obshch. Khim.*, **36**, 1414 (1966). The alternative route involves the reaction of *o*-lithiobenzonitrile with ketone; W. E. Parham and L. D. Jones, *J. Org. Chem.*, **41**, 1187 (1976).

4) E. Hunziker, J. R. Penton, and H. Zollinger, *Helv. Chim. Acta*, **54**, 2043 (1971); H. Suzuki and T. Hanafusa, *Bull. Chem. Soc. Jpn.*, **46**, 3607 (1973).

5) L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969).

6) H. Suzuki, *Org. Synth.*, **51**, 94 (1971).