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OXIDATIVE REACTIONS OF NITRILES—I

AUTOXIDATION*

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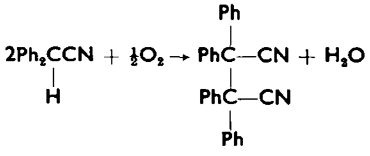
Abstract—It has been shown that, in the absence of any base, diphenylacetonitrile, *cyclo*hexylphenylacetonitrile and phenylacetonitrile do not react with oxygen. In the presence of a strong base, oxygen is slowly absorbed, and ketones or acids are formed in fair to excellent yields, depending upon the nitrile used. In the presence of a base and a trace of a copper salt a different reaction occurs. Excellent yields of tetraphenylsuccinonitrile are obtained from diphenylacetonitrile; methylphenylacetonitrile gives a poor yield of dimethyldiphenylsuccinonitrile; under comparable conditions *cyclo*hexylphenylacetonitrile, phenylacetonitrile and dimethylacetonitrile do not give dimers.

IN connection with the investigation of the mechanism of autoxidation, the reactions of a series of substituted acetonitriles with oxygen were thoroughly investigated. Solutions of diphenylacetonitrile (I) in pyridine, di*iso*propylamine, or di*cyclo*hexylamine do not absorb oxygen; the nitrile may be recovered. On the other hand, a solution of diphenylacetonitrile in freshly distilled piperidine slowly absorbs oxygen to give benzophenone (II) (yield 65 per cent) and a small amount of tetraphenylsuccinonitrile (III). Addition of small amounts of sodium methoxide to a piperidine solution of (I) causes a more rapid oxygen absorption and leads to the formation of the same products. Higher, but inconsistent, yields (18–44 per cent) of tetraphenylsuccinonitrile and correspondingly lower yields (60–40 per cent) of benzophenone are obtained when piperidine solutions of (I) are oxygenated in the presence of small amounts of benzyltrimethylammonium hydroxide (Triton B).

On the other hand, oxygen is readily absorbed when a small amount of cuprous or cupric bromide (1–2 mole per cent on the basis of nitrile used) is added to a solution of diphenylacetonitrile (I) in piperidine. Under these conditions, the oxygen absorption is complete within 3–10 min, instead of the 9–25 hr required when no copper salt is present. Since the yield of tetraphenylsuccinonitrile (III) is nearly quantitative, this reaction provides an excellent method for the preparation of (III). The stoicheiometry of the reaction is as follows:



$$2\mathrm{Ph_2}\underset{\mathrm{H}}{\underset{|}{\mathrm{C}}}\mathrm{CN} + \tfrac{1}{2}\mathrm{O_2} \rightarrow \begin{array}{c}\mathrm{Ph}\\ | \\ \mathrm{PhC{-}CN}\\ | \\ \mathrm{PhC{-}CN}\\ | \\ \mathrm{Ph}\end{array} + \mathrm{H_2O}$$

(I) (III)

In the presence of traces of copper salts, solutions of diphenylacetonitrile (I) in bases weaker than piperidine (di*iso*propylamine, diethylamine, or morpholine) absorb oxygen more slowly than do solutions of the nitrile in piperidine; relatively low yields

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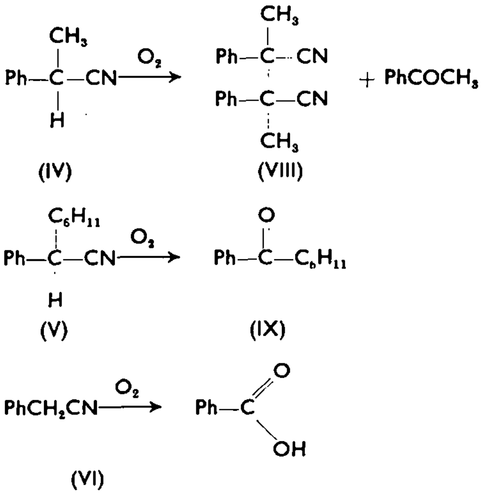
† Deceased.

(26–38 per cent) of tetraphenylsuccinonitrile (III) are obtained, along with benzophenone and unchanged starting material. However, in ethylenediamine solution the absorption of oxygen is rapid, and the yield of (III) is nearly quantitative. In the presence of inorganic bases (potassium hydroxide, sodium hydroxide or ammonium hydroxide) and copper salts, solutions of diphenylacetonitrile (I) in methanol rapidly absorb the calculated amount of oxygen; the yields of (III) are again nearly quantitative. It is, however, necessary to use an excess of the base; the optimum amount is 3–5 moles of base per mole of (I). In neutral media, oxidants such as potassium ferricyanide do not react with diphenylacetonitrile (I); but in basic media, the oxidation of (I) is rapid and excellent yields of (III) are obtained. In acetone, diphenylacetonitrile (I) reacts only slowly with potassium permanganate to give (III), but the reaction can be accelerated by addition of a base. In aqueous acetone, the reaction of potassium permanganate with (I) leads to the formation of benzophenone. The results of these experiments are shown in Table 1.

An ammoniacal solution of silver oxide in methanol is less effective than a similar solution of a copper salt as a catalyst for the autoxidation of diphenylacetonitrile; ferrous, nickelous, cobaltous and manganous salts are totally ineffective.

The autoxidations of methylphenylacetonitrile (IV), *cyclo*hexylphenylacetonitrile (V), phenylacetonitrile (VI) and dimethylacetonitrile (VII) in the presence of a base and of catalytic amounts of copper salts were also investigated. From methyl phenylacetonitrile (IV), a low yield (17 per cent) of dimethyldiphenylsuccinonitrile (VIII) was obtained, along with a large amount of acetophenone.* Under similar conditions, *cyclo*hexylphenylacetonitrile (V) gave only *cyclo*hexyl phenyl ketone (IX); phenylacetonitrile gave benzoic acid; and dimethylacetonitrile gave only traces of acetone, along with unchanged starting material.



$$Ph-\overset{CH_3}{\underset{H}{C}}-CN \xrightarrow{O_2} \begin{matrix} CH_3 \\ Ph-C-CN \\ Ph-C-CN \\ CH_3 \end{matrix} + PhCOCH_3$$

(IV) (VIII)

$$Ph-\overset{C_6H_{11}}{\underset{H}{C}}-CN \xrightarrow{O_2} Ph-\overset{O}{C}-C_6H_{11}$$

(V) (IX)

$$PhCH_2CN \xrightarrow{O_2} Ph-C(=O)OH$$

(VI)

DISCUSSION

In view of the fact that, in the absence of bases, nitriles do not react with oxygen,

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* This reaction compares favorably with the method of preparation of (VIII) by the reaction of (IV) with iodine in a basic medium.[1]

[1] B. Knoevenagel, *Ber. Dtsch. Chem. Ges.* **25**, 289 (1892).

TABLE 1.—OXIDATION OF DIPHENYLACETONITRILE AT ROOM TEMPERATURE

Ph_2CHCN	Solvent	Volume of solvent (ml)	Base*	Catalyst	Oxidant (moles/mole of nitrile)	Rate of oxygen absorption (ml/min)	Reaction products	
							TPSN† (per cent)	Ph_2CO (per cent)
0·02	methanol or pyridine	20	0·025 $NaOCH_3$ or Triton B	—	O_2(0·75–1·1)	340–490/540–720	0	90–100
0·02	piperidine	10	0·0002 $NaOCH_3$ or Triton B	—	O_2(0·70–0·95)	310–430/1500	20	50
0·01	piperidine	10	—	CuBr	O_2(ca. 0·25)	60/3	80	0
0·01	piperidine	10	—	$CuBr_2$	O_2(ca. 0·25)	70/10	95	0
0·01	di*iso*propylamine	20	—	CuBr	O_2(ca. 0·25)	60/30	40	‡
0·01	diethylamine	10	—	CuBr	O_2(ca. 0·25)	65/45	25	‡
0·01	diethylamine	10	—	CuBr	O_2(ca. 0·75)	155/120	10	70
0·01	morpholine	10	—	CuBr	O_2(ca. 0·25)	60/50	30	‡
0·005	ethylenediamine	5	—	CuBr	O_2(ca. 0·25)	25/25	80–95	0
0.005	methanol	10	0·0045 KOH	$CuBr_2$	O_2(ca. 0·25)	30/20	10	‡
0·005	methanol	10	0·027 $NaOCH_3$	$CuBr_2$	O_2(ca. 0·25)	30/15	95	0
0·005	methanol	40	0·4 NH_4OH	—	$CuBr_2(N_2)$(1·00)	—	45§	0
0·005	acetone	40	0·17 NH_4OH	—	$KMnO_4$(1·00)	(rapid)	90	0
0·005	acetone	40	—	—	$KMnO_4$(1·00)	(slow)	70	‡
0·005	acetone + water	40 + 5	—	—	$KMnO_4$(1·00)	(slow)	0	85§
0·005	methanol	40	—	—	$K_3Fe(CN)_6$(1·00)	—	0	0
0·005	methanol	40	0·25 NH_4OH	—	$K_3Fe(CN)_6$(1.00)	(rapid)	100	0

* Moles of base other than solvent.

† Tetraphenylsuccinonitrile.

‡ Product not isolated in this instance.

§ The yields were calculated on the reacted starting material in this case.

the results obtained with diphenylacetonitrile may be explained as follows:

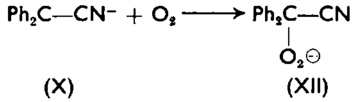
$$\mathrm{Ph_2CHCN} \xrightarrow{\mathrm{B^-}} \underset{(\mathrm{X})}{\mathrm{Ph_2C{-}CN^{\ominus}}} + \mathrm{HB} \qquad (1)$$

$$(\mathrm{X}) + \mathrm{Cu^{++}} \longrightarrow \underset{(\mathrm{XI})}{\mathrm{Ph_2\underset{\bullet}{C}{-}CN}} + \mathrm{Cu^{+}} \qquad (2)$$

$$2(\mathrm{XI}) \longrightarrow (\mathrm{III}) \qquad (3)$$

In this formulation, cupric ion removes one electron from anion (X), and the function of oxygen is to regenerate the cupric ion. In fact, even in the absence of oxygen tetraphenylsuccinonitrile (III) is readily obtained from diphenylacetonitrile, if the stoicheiometric amount of a cupric salt is used. A similar explanation applies when the oxidant is a ferricyanide. It is interesting that, in this instance, even potassium permanganate serves as a one-electron oxidizing agent, since it, too, gives high yields of tetraphenylsuccinonitrile in alkaline solutions.

In the absence of copper salts, but in the presence of strong bases, diphenylacetonitrile (I) slowly absorbs oxygen to give benzophenone (II):



$$\underset{(\mathrm{X})}{\mathrm{Ph_2C{-}CN^-}} + \mathrm{O_2} \longrightarrow \underset{(\mathrm{XII})}{\mathrm{Ph_2}\underset{\mathrm{O_2^{\ominus}}}{\underset{|}{\mathrm{C}}}\mathrm{{-}CN}} \qquad (4)$$

$$(\mathrm{XII}) \xrightarrow{\mathrm{NaOH}} \underset{(\mathrm{II})}{\mathrm{Ph_2C{=}O}} + \mathrm{HCN} + [\mathrm{H_2O_2}] \qquad (5)$$

Reactions (4) and (5), therefore, compete with reactions (2) and (3). Since the concentration of dissolved oxygen is rather low, reaction (2) may proceed more rapidly than reaction (4), because cuprous ions in basic solution are good oxygen "scavengers." With the other nitriles here mentioned reaction (2) is slow, because these compounds contain only one activating phenyl group; consequently, reaction (4) predominates. With methylphenylacetonitrile (IV), both reactions (2) and (4) take place, although at different rates, and symmetrical dimethyldiphenylsuccinonitrile (VIII) as well as acetophenone are formed. In other words, in the reactions of substituted acetonitriles with oxygen in the presence of catalysts the nature of the products formed depends on the nature of the substituents. These substituents determine (i) the ease of formation of the anion from the nitrile and (ii) the tendency of the anion thus formed to donate an electron to the catalyst.

EXPERIMENTAL

Autoxidation of diphenylacetonitrile (I)

(a) *In the presence of Triton B.* A solution of diphenylacetonitrile (3·86 g, 0·02 mole) and trimethylbenzylammonium hydroxide (Triton B, 0·0002 mole) in piperidine (20 ml) was stirred under an atmosphere of oxygen gas at room temperature. After 375 ml (0·015 mole) of oxygen had been absorbed (in about 25 hr), the reaction mixture was treated with ice–water, acidified with hydrochloric acid and extracted with ether. The ether was removed at reduced pressure, and light petroleum was added to the remaining oil. Crystals (0·58 g) slowly separated out; these were identified as unreacted diphenylacetonitrile. The oil was taken up in a small amount of benzene and chromatographed on a silica gel column, a mixture consisting of 80 per cent of benzene and 20 per cent of light petroleum being used as eluent. Tetraphenylsuccinonitrile (0·77 g, 20 per cent) was eluted first. This was followed by unreacted diphenylacetonitrile, which was combined with the material previously recovered (0·85 g, 21 per cent). Finally, benzophenone (1·75 g, 49 per cent) was obtained. Alternatively, the reaction mixture could be separated by steam-distillation. The diphenylacetonitrile and benzophenone that distilled were separated by fractional crystallization from light petroleum. Tetraphenylsuccinonitrile was extracted from the residue with benzene and crystallized from glacial acetic acid. The tetraphenylsuccinonitrile thus obtained melted at 222–224° (dec.). *Anal.* Calcd. for $C_{28}H_{20}N_2$: C, 87·47; H, 5·24. Found: C, 87·30; H, 5·10 per cent.

(b) *In the presence of sodium methoxide.* Diphenylacetonitrile (3·86 g, 0·02 mole) was dissolved in a solution of sodium methoxide (0·027 mole) in methanol (55 ml). The solution was stirred under oxygen at room temperature and slightly above atmospheric pressure. After 12 hr, 335 ml (0·014 mole) of oxygen was absorbed. At this time, the rate of absorption decreased appreciably. On further addition of sodium methoxide (0·027 mole in 5 ml of methanol) no change in the rate of oxygen uptake was observed. The reaction mixture was poured into ice water, acidified and extracted with ether. After the ether had been removed by distillation, the residual oil (3·3 g 92 per cent) solidified. The solid was crystallized from light petroleum, m.p. 47°; the m.p. of a mixture with an authentic sample of benzophenone showed no depression.

(c) *In the presence of cuprous bromide.* To a solution of diphenylacetonitrile (0·97 g, 0·005 mole) in methanol (20 ml) was added a solution of cuprous bromide (0·02 g, 0·07 millimole) in concentrated ammonia solution (5 ml). The mixture was stirred under an atmosphere of oxygen, and the precipitation of tetraphenylsuccinonitrile commenced immediately. A total of 0·0025 moles of oxygen was absorbed. After the reaction mixture had been acidified, the product (0·90 g, 94 per cent) was collected on a filter and washed with small portions of methanol and ether. The tetraphenylsuccinonitrile thus obtained melted with decomposition at 220°.

Preparation of tetraphenylsuccinonitrile (III)

(a) *Oxidation of* (I) *with hydrogen peroxide and cuprous bromide.* To a well stirred mixture of diphenylacetonitrile (1·93 g, 0·01 mole) and cuprous bromide (0·02 g, 0·07 millimole) in piperidine (10 ml) under an atmosphere of nitrogen, hydrogen peroxide (10 ml of a 3% solution) was added. A precipitate formed immediately. The reaction mixture was stirred for a few minutes after the addition of hydrogen peroxide. The whole mixture was then poured into dilute hydrochloric acid, and the solid product was collected on a filter. The solid was washed first with water and then with methanol. Crude tetraphenylsuccinonitrile (1·4 g, 74 per cent) was thus obtained. After a single crystallization from acetic acid, the material melted with decomposition at 220°.

(b) *Oxidation of* (I) *with potassium ferricyanide.* To a solution of diphenylacetonitrile (0·97 g, 0·005 mole) in methanol (40 ml) was added a solution of potassium ferricyanide (1·7 g, 0·005 mole) in concentrated ammonia solution (15 ml). Tetraphenylsuccinonitrile (0·96 g), m.p. 220° (dec.), was recovered in the manner described above.

(c) *Oxidation of* (I) *with potassium permanganate.* Concentrated ammonia solution (10 ml) was added to a solution of diphenylacetonitrile (0·97 g, 0·005 mole) and potassium permanganate (0·89 g, 0·005 mole) in acetone (40 ml). The reaction began at once, and manganese dioxide was deposited. After 30 min, the reaction mixture was acidified, and sodium hydrosulfite was added to reduce the manganese dioxide. Tetraphenylsuccinonitrile (0·86 g, 90 per cent), melting at 220° (dec.), was isolated from the reaction mixture.

(d) *Oxidation of* (I) *with* tert-*butyl hydroperoxide.* To a well stirred mixture of diphenylacetonitrile (1·93 g, 0·01 mole), cuprous bromide (0·1 g, 0·4 millimole) and piperidine (5 ml) under an atmosphere of nitrogen, *tert*-butyl hydroperoxide (0·02 mole) was slowly added. The resulting exothermic reaction was moderated by external cooling. The reaction mixture was then acidified. The solid (1·90 g, 98 per cent) which separated was collected on a filter, m.p. 220° (dec.); it was in all respects identical with an authentic sample of (III).

Methylphenylacetonitrile (IV)

The synthesis of (IV) was based on the procedure of Hancock and Cope[2] for the preparation of *cyclo*hexylphenylacetonitrile. This method gave a material purer than the products prepared by previously reported methods.[3,4,5] A few crystals of ferric nitrate were added to 200 ml of liquid ammonia contained in a Dewar flask. To the stirred solution sodium (8·1 g, 0·35 mole) was slowly added. When the reaction was complete, phenylacetonitrile (41 g, 0·31 mole) was added over a period of 15 min; stirring was continued for another 15 min. After the addition of dry benzene (200 ml), and ether (25 ml) the mixture was allowed to warm slowly to 0–5°. The mixture was then transferred by suction into a flask fitted with a condenser protected by a soda-lime drying tube. The Dewar flask was rinsed several times with ether, and the washings were transferred to the new reaction vessel. Ammonia and most of the ether were removed by gentle warming, with the aid of a stream of nitrogen. The reaction mixture was then cooled, and methyl iodide (70 g, 0·5 mole) was slowly added. External cooling was necessary to control the exothermic reaction. After the addition of methyl iodide, the mixture was heated under reflux for 3 hr. When the mixture had cooled, it was poured into ice–water. The layers were separated, and the aqueous layer was washed with benzene. The benzene solutions were combined and dried; the solvent was removed by evaporation. Distillation of the residue yielded an oil (35 g, 77 per cent), b.p. 76–77°/3 mm, n_D^{20} 1·5288. The infrared spectrum of this compound showed the methyl band at 1380 cm^{-1}. *Anal.* Calcd. for C_9H_9N: C, 82·40; H, 6·92; N, 10·68. Found: C, 82·79; H, 7·19; N, 10·80 per cent.

Autoxidation of methylphenylacetonitrile (IV)

To a solution of methylphenylacetonitrile (2·6 g, 0·02 mole) in piperidine (10 ml), cuprous bromide (0·2 g, 0·07 millimole) was added, and the mixture was stirred under nitrogen at room temperature and atmospheric pressure. In 5 hr about 500 ml of oxygen was absorbed, and a white precipitate had formed. The reaction mixture was diluted with water and acidified. The solid was collected on a filter (0·45 g, 17 per cent) After crystallization from glacial acetic acid, the dimethyldiphenylsuccinonitrile

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[2] E. M. Hancock and A. C. Cope, *Organic Synthesis* (Vol. 25) p. 25. Wiley, New York (1945)

[3] V. Meyer, *Ann. Liebigs* **250**, 118 (1889).

[4] R. Hastings and J. B. Cloke, *J. Amer. Chem. Soc.* **56**, 2136 (1934).

[5] J. V. Murray and J. B. Cloke, *J. Amer. Chem. Soc.* **68**, 126 (1946).

(VIII) obtained melted at 227°; the m.p. of a mixture with an authentic sample showed no depression. *Anal.* Calcd. for $C_{18}H_{16}N_2$: C, 83·04; H, 6·20; N, 10·76; mol. wt., 260. Found: C, 83·20; H, 6·48; N, 10·76 per cent; mol. wt., 261 (Rast method).

The filtrate was extracted with ether. After evaporation of the solvent, there remained an oil (2 g), b.p. 83°/4 mm. The infrared spectrum of this oil indicated the presence of both ketone and nitrile groups. A portion of the oil (0·1 g) was treated with 2,4-dinitrophenylhydrazine to give acetophenone 2,4-dinitrophenylhydrazone (0·14 g), m.p. 239–241°; the m.p. of a mixture with an authentic sample showed no depression. The yield of acetophenone (based on the hydrazone formed) was 56 per cent.

Oxidation of methylphenylacetonitrile by cupric acetate

Over a period of 3 hr a solution of cupric acetate monohydrate (2·0 g, 0·01 mole) in piperidine (40 ml) was added with stirring to methylphenylacetonitrile (1·31 g, 0·01 mole) dissolved in piperidine (10 ml) under an atmosphere of nitrogen. When the mixture was acidified, (VIII) (0·25 g, 11 per cent) was precipitated, and it was collected on a filter, m.p. 225–227°. Unreacted nitrile (IV) (1·0 g) was recovered from the filtrate.

Preparation of diphenyldimethylsuccinonitrile (VIII)

A solution of iodine (2·56 g, 0·01 mole) in ether (20 ml) was added slowly to a mixture of phenylmethylacetonitrile (2·62 g, 0·02 mole), sodium methoxide (from 1·0 g of sodium), and methanol (20 ml). The reaction mixture was set aside for 1 hr and was then diluted with water. The resulting precipitate (0·35 g, 14 per cent) was collected and crystallized from glacial acetic acid, m.p. 227–228°.

Autoxidation of cyclo*hexylphenylacetonitrile* (V)

*cyclo*Hexylphenylacetonitrile[2] (9·0 g, 0·045 mole) was dissolved in piperidine (30 ml) containing cuprous bromide (0·5 g, 0·18 millimole). The mixture was stirred under an atmosphere of oxygen. The resulting exothermic reaction was moderated by external cooling. In 1 hr about 1 mole of oxygen per mole of nitrile was absorbed. When the reaction mixture was treated as described above for the preceeding autoxidation experiment, an oil (8–9 g) was obtained. A portion of this oil (7·0 g) was separated into two main fractions by distillation at 4 mm through a spinning-band column:

(1) *cyclo*hexyl phenyl ketone (1·5 g, 20 per cent), b.p. 130–132°/4 mm, m.p. 53–54°. *Anal.* Calcd. for $C_{13}H_{16}O$: C, 82·95; H, 8·52; mol. wt., 188.

Found: C, 82·75; H, 8·94 per cent; mol. wt., 179 (cryoscopic method in benzene).

(2) recovered (V) (4·6 g), b.p. 148–151°, n_D^{20} 1·5301.

The yield of *cyclo*hexyl phenyl ketone varied in different experiments from 25 to 32 per cent; it was determined as the 2,4-dinitrophenylhydrazone, m.p. 196–198°. *Anal.* Calcd. for $C_{19}H_{20}N_4O_4$: C, 61·94; H, 5·47.

Found: C, 62·14; H, 5·60 per cent.

Autoxidation of phenylacetonitrile

Phenylacetonitrile (7·0 g, 0·05 mole) and a solution of sodium methoxide (0·135 mole) in methanol (25 ml) were placed in a pressure vessel, and the mixture was shaken under oxygen at a pressure of 30 lb/sq. in. Immediately an exothermic reaction set in, and the mixture became brown. The reaction vessel was immersed in cold water in order to maintain the mixture at room temperature. The calculated amount of oxygen (0·05 mole) was consumed in 3½ hr. The reaction mixture was then taken up in ether and extracted with aqueous sodium hydroxide. The alkaline extract, when acidified, gave benzoic acid (5·5 g, 75 per cent), m.p., 120–121°; the m.p. of a mixture with an authentic sample showed no depression.

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