Studies on Anodic Substitution Reactions. XVI. Anodic Side-chain Substitution of 1,2,5-Trimethylpyrrole is Preceded by 2,5-Addition of Cyano Groups
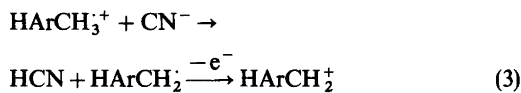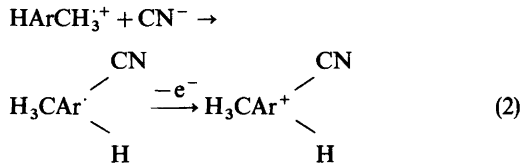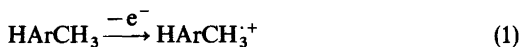
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The anodic and potassium hexacyanoferrate(III) oxidation of 1,2,5-trimethylpyrrole in the presence of cyanide gives the 2,5-dicyano adduct, 2,5-dicyano-1,2,5-trimethyl-3-pyrroline as the primary product. The adduct is chemically and thermally unstable. Base treatment in methanol induces elimination of HCN, followed by a carbocation rearrangement to give a mixture of the side-chain cyanation product, 1,5-dimethylpyrrole-2-acetonitrile and the corresponding methoxy derivative. The same reaction takes place in methanol/NaCN, the rate constant being 3.0×10^{-4} min^{-1} at 30 °C. Thermal decomposition of the adduct gives predominantly the side-chain cyanation product and in addition some nuclear cyanation product, 1,2,5-trimethylpyrrole-3-carbonitrile.
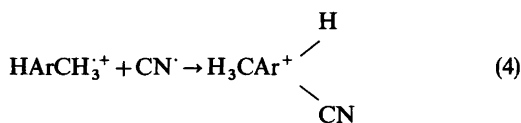
Thus, the formation of side-chain cyanation product in the anodic cyanation of TMP is the result of secondary reactions of the 2,5-dicyano adduct. It still remains to find an authentic case of direct α cyanation of an alkylaromatic substance.

The anodic cyanation of aromatic compounds with benzylic hydrogens available for substitution takes place exclusively in the ring.[1] Such anomalous behaviour is not easily explained in terms of the commonly accepted radical cation mechanism for anodic substitution (eqns. 1–3). Why should not cyanide ion, a relatively strong

$$HArCH_3 \xrightarrow{-e^-} HArCH_3^{\cdot+} \qquad (1)$$

$$HArCH_3^{\cdot+} + CN^- \rightarrow$$

$$H_3CAr^{\cdot} \overset{CN}{\underset{H}{<}} \xrightarrow{-e^-} H_3CAr^+ \overset{CN}{\underset{H}{<}} \qquad (2)$$

$$HArCH_3^{\cdot+} + CN^- \rightarrow$$

$$HCN + HArCH_2^{\cdot} \xrightarrow{-e^-} HArCH_2^+ \qquad (3)$$

base, abstract a proton from the benzylic position of a radical cation, when, e.g., acetate ion, a considerably weaker base, does?

We have recently[1] tried to explain the anomalies of anodic aromatic cyanation by postulating that the product-forming elementary step is *not* an attack by cyanide ion upon the radical cation (eqn. 3) but instead by cyano radical (eqn. 4) formed either directly by concurrent anodic discharge of cyanide ion or by electron transfer (ET) oxidation

$$HArCH_3^{\cdot+} + CN^{\cdot} \rightarrow H_3CAr^+ \overset{H}{\underset{CN}{<}} \qquad (4)$$

$$HArCH_3^{\cdot+} + CN^- \rightarrow HArCH_3^{\cdot} + CN^{\cdot} \qquad (5)$$

of cyanide ion by a radical cation[2] (eqn. 5). In other words, this hypothesis requires that no bond formation but only ET should take place when a radical cation of sufficiently high oxidation potential interacts with cyanide ion. A second ne-

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cessary requirement would be that CN⁻ for some reason favors an attack on the ring of HArCH₃⁺ and does not abstract an α hydrogen atom in competition.

As a corollary of this idea, it was predicted that a radical cation of sufficiently low (say, <1.0 V) reduction potential would not act as an ET oxidant toward cyanide ion. In such a case the base properties of cyanide ion would have a possibility to express themselves in the normal way, *i.e.* in terms of α proton abstraction (eqn. 3) and concomitant side-chain substitution. We were, therefore, intrigued by a recent study[3,4] of the anodic cyanation of a series of methylpyrroles, where almost exclusive α substitution was shown to occur in 2,5-dialkyl-substituted compounds. As an example, 1,2,5-trimethylpyrrole (lowest $E_P = 0.81$ V *vs.* the saturated calomel electrode [SCE] gave a 29 % yield of 1,5-dimethylpyrrole-2-acetonitrile besides minor amounts of nuclear substitution products, 1,5-dimethylpyrrole-2-carbonitrile (1 %) and 1,2,5-tri-methylpyrrole-3-carbonitrile (1 %). Since the methylpyrroles, especially the higher alkylated ones, have very low oxidation potentials (lowest E_P between 0.5 and 0.9 V *vs.* SCE), it seemed indeed as if the above-mentioned prediction had been experimentally verified.

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We have now studied the 1,2,5-trimethylpyrrole (TMP) system in detail, and demonstrated that the anodic side-chain cyanation of this compound is a result of secondary reactions of an initially formed 2,5-dicyano adduct (*1*, see eqn. 6). These are chemical in nature and take place either in the electrolyte solution or during work-up (Yoshida[4] employed distillation and/or GLC for the isolation of products). Thus the adduct is very sensitive toward base and slowly eliminates HCN in the electrolyte employed, methanol/0.4 M NaCN, with formation of *2* which eventually rearranges to the

side-chain substitution product (*3*). The same reaction (eqn. 7) takes place by simply heating the adduct to temperatures above its melting point (>105 °C).

RESULTS

The first indication that the seemingly straightforward anodic cyanation chemistry of methylpyrroles, reported by Yoshida,[4] might be wrong, originated from attempts to find a metal ion oxidant which would (1) act as an ET oxidant and (2) be compatible with cyanide ion. Such a reagent would obviously be of value in mechanistic studies of oxidative cyanation. Potassium hexacyanoferrate(III) was then a reasonable choice,[5] provided one could find suitable easily oxidizable substrates. As mentioned above, highly methylated pyrroles possess this property, and 1,2,5-trimethylpyrrole (TMP) was, therefore, selected for a study.

When TMP was stirred with an aqueous solution of potassium hexacyanoferrate(III) and sodium cyanide (molar ratio 1:2:4) the organic phase solidified after $1-2$ h. The solid was isolated and recrystallized from ethyl acetate/light petroleum, m.p. $95-105$ °C with decomposition. A brisk gas evolution took place in the melt. According to analytical and spectral data the solid was the 2,5-dicyano adduct (*1*); from the appearance of double peaks in its ¹H NMR spectrum, taken in CD₃OD, it was concluded that the crude product was an 80:20 mixture of the two possible diastereomers.

The adduct *1* turned out to be chemically as well as thermally unstable. Thus heating it above its melting point — and consequently GLC analysis conditions — led to the formation of almost exclusively *3* (see below). Also column chromatography on neutral alumina induced elimination and rearrangement (eqn. 7). Treatment of *1* with a small amount of NaOCD₃ in CD₃OD rapidly converted *1* into a 1:2 mixture of *3* and 1,5-dimethyl-2-methoxymethylpyrrole (*4*), and under similar conditions as those prevailing during the anodic cyanation of TMP[4] (0.4 M NaCN in methanol, 25 °C), *1* underwent base-induced elimination with an

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2   *3*

approximate rate constant of 3×10^{-4} min^{-1} at 30 °C.

The GLC analysis of *1* was studied in some detail in order to be able to distinguish between primary and secondary anodic products (see below). It was found that the yield of *3* was 71 % and that minor by-products were 1,2,5-trimethylpyrrole-3-carbonitrile (4 %) and a compound of dimeric nature (0.6 %, M.W. 202). Apparently some of the material had become attached to the GLC column.

With these results in mind, one would immediately suspect that the anodic cyanation of TMP might actually give *1* as the primary product, followed by some base-induced elimination and rearrangement of *1* in the electrolyte. There are precedents for 1,4-addition being the preferred reaction made in the anodic cyanation of other simple heteroaromatics; thus both 2,5-dimethylfuran[6] and 2,5-dimethylthiophene[7] give thermally and chemically stable 2,5-methoxycyano adducts upon anodic oxidation in methanol/sodium cyanide, whereas 1,2,3,5-tetraphenylpyrrole could be anodically oxidized in acetonitrile/tetraethylammonium cyanide to give the 2,5-dicyano adduct.[8] Such addition reactions are also well documented for carboaromatic systems.[9-11]

We therefore conducted a number of TMP electrolyses under the conditions employed by Yoshida.[4] In a divided cell, the crude product mixture after work-up consisted of a 16:84 mixture of *3* and *1*, respectively, (apart from unchanged TMP, 40 % of the total product mixture) in a yield of *ca.* 60 %. GLC analysis showed the expected thermal decomposition products from *1* (*3*, 73 %; 1,2,5-trimethylpyrrole-3-carbonitrile, 6 %; "202-dimer", 5 %) and in addition 5 % of 1,5-dimethyl-2-carbonitrile and 8 % of a dehydrodimer of molecular weight of 216.

In a non-divided cell the acid-base balance is quite different. At the anode reaction 6 takes place whereas the cathode reaction produces base *via* reaction 8. Accordingly, the crude product mixture

$$2CH_3OH \xrightarrow{+2e^-} 2CH_3O^- + H_2 \qquad (8)$$
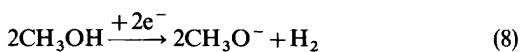
contained little of *1* and mostly the elimination-rearrangement products. Thus a typical experiment yielded *1* (9 %), *3* (66 %), *4* (21 %) and 1,5-dimethyl-2-carbonitrile (4 %) according to NMR spectral analysis. In addition, GLC analysis of the same mixture revealed the presence of the two dimers previously mentioned (*ca.* 1 % of each).

In order to avoid the possibility of base-induced transformation of *1*, the anodic cyanation of TMP was also conducted in the two-phase system earlier developed in this laboratory,[11] dichloromethane/aqueous sodium cyanide (1 M)/tetrabutylammonium sulfate. With this technique the only basic species in the organic phase is cyanide ion (note that 0.4 M NaCN in methanol is about 0.02 M in methoxide ion due to protonation of cyanide ion[10]). Under these conditions, NMR spectral analysis of the crude product showed the adduct to be the only primary product.

We conducted a few experiments with another compound, 1,2,3,5-tetramethylpyrrole. Both with hexacyanoferrate(III) and the anode as oxidants did the primary product consist of mainly the 2,5-dicyano adduct; on GLC analysis it was converted to a mixture of 1,4,5- and 1,3,5-trimethylpyrrole-2-acetonitrile in a ratio of 62:38 (Yoshida[4] gave 60:40).

DISCUSSION

Many cases of oxidative addition of two cyano groups or one cyano and one methoxy group across an aromatic or heteroaromatic ring have been reported.[6-11] With the advantage of hindsight this is not so surprising: All mechanisms so far proposed involve the intermediacy of a cyano-cyclohexadienyl cation and one would expect that a strong nucleophile like cyanide or, to some extent, methoxide, should have a chance to capture such a cation. The case presented here is no exception, and thus one should actually expect addition to take place upon anodic cyanation of 1,2,5-trimethyl-pyrroles — and presumably most of the methyl-pyrroles studied by Yoshida.[4] It is only the chemical and, above all, thermal instability of the adduct that led to the erroneous conclusion of direct side-chain cyanation being feasible.

To deal with the base sensitivity first, it is obvious that in a divided cell only little secondary reaction of *1* takes place. The half-life of *1* in CD$_3$OD/0.4 M NaCN is close to 40 h at 30 °C and in the course of an electrochemical experiment (up to 5 h in our study and 10 h in Yoshida's) most of the adduct survives intact. It is highly probable that it is actually methoxide ion (from CN$^-$ + MeOH $\rightleftharpoons$ MeO$^-$ + HCN) that is the basic catalyst in the electrolyte, since no secondary reactions took place in the two-phase system, which has cyanide ion as the only base present in the organic phase. On the

other hand, when the electrolysis was run in a non-divided cell, methoxide ion generated at the cathode almost completely eliminated the adduct from the crude product mixture.

The thermal instability of *1* is perhaps unexpected in view of the stability of similar derivatives of 2,5-dimethylfuran[6] and 2,5-dimethylthiophene.[7] The loss of HCN is rapid above the m.p. and of course instantaneous in the injection port of the GLC instrument. Distillation of *1 in vacuo* gave a 47 % yield of *3*, the remaining material being an intractable tar.

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The formation of 1,5-dimethyl-2-methoxymethyl-pyrrole (*4*) in the base-induced elimination and rearrangement of *1* indicates that the rearrangement step is a carbocationic one (eqn. 9). The carbocation *5* can react either at ring position 3 to give *6* or at the side-chain to give *2*. Rearomatization of *6* would give the nuclear cyanation product, 1,2,5-trimethyl-pyrrole-3-carbonitrile.

Finally, we wish to draw attention to the use of potassium hexacyanoferrate(III) as an effective ET oxidant for additive cyanation of easily oxidized compounds. Its use for substitutive cyanation of certain unsaturated hydrocarbons[12a] and hetero-aromatic *N*-oxides[12b] has been reported earlier.

EXPERIMENTAL

Oxidation of TMP by potassium hexacyano-ferrate(III) with formation of 2,5-dicyano-1,2,5-trimethyl-3-pyrroline (1). TMP[13] (4.4 g, 0.04 mol) was vigorously stirred with a solution of potassium hexacyanoferrate(III) (27.6 g, 0.08 mol) and sodium cyanide (8.0 g, 0.16 mol) in water (400 ml). After 1.5 h the organic phase had solidified. The solid was

filtered off and washed several times with water and then stirred three times with 20 ml portions of light petroleum. After drying in a desiccator, the solid (3.5 g, 54 %) was recrystallized from ethyl acetate – light petroleum (1:1) to give brownish crystals, m.p. 103 – 106 °C. A brisk gas evolution was observed in the melt. Anal. $C_9H_{11}N_3$: C, H, N. ^{1}H NMR (100 MHz, CD_3OD): δ 1.56 (6 H, s), 2.59 (3 H, s), 6.10 (2 H, s). ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.57 (6 H, s), 2.62 (3 H, s), 5.97 (2 H, s). ^{13}C NMR (25.14 MHz, $CDCl_3$): 24.75 (2–CH_3), 29.8 (N–CH_3), 65.8 (2–C), 116.1 (CN), 132.95 (3–C). MS [IP 70 eV; direct inlet at *ca.* 50 °C; *m/e* (% rel. int.)]: 161 (8), 146 (100), 134 (65), 133 (73), 131 (24), 119 (62), 108 (25).

Anodic oxidation of TMP in the presence of cyanide ion. A. In a divided cell. The cell consisted of a 300 ml water-jacketed vessel, equipped with a glass-lid with five necks. The anode was a 50 cm² Pt foil connected *via* a Pt wire. The cathode was an iron coil, immersed into a clay cylinder (the cell divider) filled with catholyte (methanol/0.4 M NaCN). The anolyte consisted of TMP (0.02 mol) in 220 ml of methanol/0.4 M NaCN. It was stirred by bubbling in a slow stream of nitrogen.

The electrolysis was run at a constant current of 500 mA (current density 10 mA cm^{-2}) until a charge corresponding to 2 F mol^{-1} had been passed (*ca.* 2.5 h). The anolyte temperature was 15 – 20 °C.

The anolyte was worked-up by addition of water (750 ml) and diethyl ether extraction. After drying the ether solution by magnesium sulfate, the ether was evaporated leaving behind 1.85 g of crude semi-solid product, consisting of 20 % unchanged TMP and 80 % of a 16:84 mixture (^{1}H NMR analysis) of *3* and *1*, respectively, (yield *ca.* 60 %).

B. In a non-divided cell. The cell components were the same as under A, except that the cell divider was omitted and the cathode was a 60 cm² stainless steel foil. The electrolyte was the same as the anolyte in A. Magnetic stirring was employed and nitrogen was used as a protecting atmosphere. The electrolysis was run in the same way as in A, and the work-up procedure was the same.

A typical experiment gave *ca.* 2 g of crude product, containing *1* (9 %), *3* (66 %), *4* (21 %) and 1,5-dimethyl-2-carbonitrile (4 %) (^{1}H NMR analysis). There was considerable variation, though, and in some cases the adduct *1* had disappeared almost completely.

C. In a non-divided cell, using a two-phase electrolyte. The same cell components as under B were used. The semicylindrically shaped anode and cathode foils were placed parallel to each other, separated by a piece of polypropylene gauze (mesh size 1 × 1 mm). This arrangement gives an electrode separation of *ca.* 2 mm. A nitrogen atmosphere

was maintained in the cell.

The two-phase electrolyte system was composed of dichloromethane (100 ml), TMP (0.02 mol), aqueous 1 M NaCN (100 ml), tetrabutylammonium hydrogen sulfate (10 mmol, dissolved in 15 ml of water and neutralized by NaOH before addition!). In line with recent developments in the technique of two-phase electrolysis[14] (an anode wetting mechanism seems to operate) stirring was effected at a moderate rate by a magnetic stirrer, and not by the extremely vigorous emulsification stirrer used previously.[11]

Electrolysis was performed as under A and B. Work-up was effected by separating the dichloromethane layer, washing it with a dilute aqueous solution of potassium hydrogen sulfate (caution: HCN is formed) and water. After drying by magnesium sulfate and evaporation, 1.6 g of a solid was left behind. According to ^{1}H NMR spectral analysis it consisted of 1 to more than 90 % (the rest was unchanged TMP), yield ca. 50 %).

Thermal decomposition of 1. A. By distillation. A sample (0.7 g) of 1 was distilled at 10 mmHg over a Bunsen flame. A vigorous gas evolution took place and 0.27 g (47 %) of 3, m.p. 90−91 °C (lit.[4] 90−91 °C) was collected in the receiver. The residue in the distilling flask was a black tar.

B. By GLC. All GLC analyses made on 1 or mixtures containing 1 were made using a 2.5 m × 0.3 mm 5 % neopentylglycol succinate on a Chromosorb W column, operated isothermally at 205 °C. 2,4-Dimethoxybenzonitrile was used as an internal standard.

Base-induced transformation of 1. A. By CD_3ONa. A sample of 1 (100 mg) was dissolved in CD_3OD (1.5 ml) in an NMR tube. The ^{1}H NMR spectrum of the sample was taken (by a separate experiment, it was shown that 1 is unchanged for at least 48 h in CD_3OD) and 0.8 ml of an approximately 0.4 M $NaOCD_3$ solution was added. The disappearance of 1 was so fast that the signal at δ 1.56 ppm could just barely be seen in the next spectrum (after 3 min), and the products formed were 3 and 4 in a 1:2 ratio.

B. By $CD_3OD/0.4$ M NaCN. Adduct (0.145 mg) was dissolved in 2.5 ml of $CD_3OD/0.4$ M NaCN and subjected to ^{1}H NMR spectral analysis at regular intervals (every hour for the first 8 h, then every 6−12 h up to 50 h). Least squares analysis of the data obtained gave a rate constant for disappearance of 1 at 3.0×10^{-4} min^{-1} (correlation coefficient 0.984). The sample was kept at the probe temperature (30 °C).

Preparation of 1,5-dimethyl-2-methoxymethyl-pyrrole (4). TMP (2.2 g, 0.02 mol) was oxidized anodically in an electrolyte consisting of sodium methoxide (4.5 g) in methanol (250 ml).[15] The anode was a 50 cm^2 Pt foil and the electrolysis was run at a potential of 1.0 V *vs.* SCE. The electrolysis was stopped when the current was below 10 mA (only *ca.* 40 % of the theoretically needed charge for 2 F/mol conversion). After pouring the electrolyte into water (700 ml) the organic material was taken up in dichloromethane. Evaporation left behind *ca.* 0.7 g of a liquid from which 4 was isolated by GLC (1.5 m × 8 mm 20 % SE-30 on Chromosorb W column). ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.14 (3 H, s, C−CH_3), 3.24 (3 H, s, N−CH_3), 3.43 (3 H, s, O−CH_3), 4.30 (2 H, s), 5.75 (1 H, d) and 5.99 (1 H, d).

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