Iron(III)-catalysed nitration of non-activated and moderately activated arenes with nitrogen dioxide–molecular oxygen under neutral conditions

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In the presence of molecular oxygen and a catalytic amount of tris(pentane-2,4-dionato)iron(III), non-activated and moderately activated arenes, which include alkylbenzenes, halogenobenzenes, phenolic ethers, naphthalene and derivatives, can be nitrated with nitrogen dioxide at ice-bath temperature or below to give the corresponding nitro derivatives in fair to good yields. An electron-transfer mechanism has been proposed, where an activated NO_2-Fe^{III} complex plays a key role in the cyclic process for converting arenes into nitroarenes.

Introduction

Non-activated arenes are inactive toward nitrogen dioxide under ambient conditions.† Under forced conditions, *i.e.*, at elevated temperatures or under irradiation, they usually lead to a complicated mixture of products arising from addition, substitution and oxidative degradation.[4] In the presence of ozone, however, nitrogen dioxide becomes reactive enough to convert a variety of arenes into the corresponding nitro derivatives in high yield (the *kyodai*-nitration).[5] During the course of our efforts to find an alternative means to activate nitrogen dioxide, we have found that some iron(III) complexes can act as good catalysts for nitrating non-activated and moderately activated arenes with nitrogen dioxide at ice-bath temperature or below (Scheme 1).
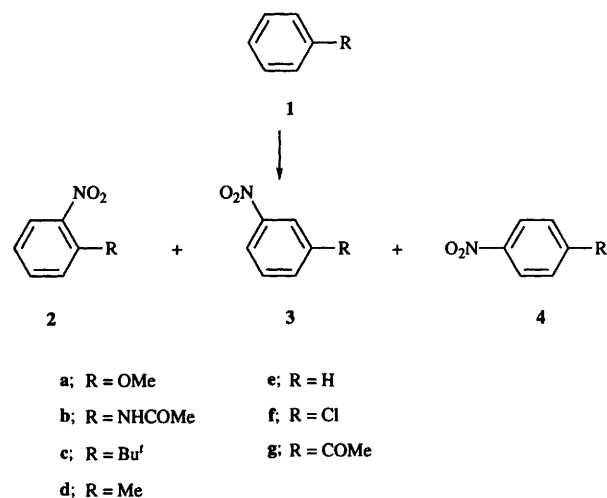
Scheme 1 *Reagents and conditions:* NO_2, O_2, Fe(acac)$_3$, $(CH_2Cl)_2$, 0 °C

Results and discussion

A mixture of chlorobenzene **1f**, liquid nitrogen dioxide and 1,2-dichloroethane as solvent was stirred at 0 °C under oxygen, but

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† Nitrogen dioxide has long been known to nitrate arenes in strong acid medium[1] or in the presence of a strong Lewis acid.[2] Photochemical activation of charge-transfer complexes formed from arenes and nitrogen dioxide leading to nitroarenes has recently been investigated in detail.[3]

Table 1 Nitration of monosubstituted benzenes **1a–g** with NO_2–O_2–Fe(acac)$_3$[a]

Substrate	t/h	Conversion (%)	Yield (%)[b]	2:3:4[c]
1a	1	100	55	40:<1:60
1b[d]	6	98	33	73:<1:27
1c	12	>99	85	12:5:83
1d	12	>99	80	55:2:43
1e	24	>99	83	
1f	36	100	93	32:<1:68
1g	72	43	29	51:49:<1

[a] All reactions were performed at 0 °C using a mixture of substrate (10 mmol), Fe(acac)$_3$ (10 mol%), nitrogen dioxide (10 cm³) and 1,2-dichloroethane (30 cm³) under oxygen, unless otherwise noted. [b] Refers to isolated yield. [c] Determined by GLC. [d] Amount of nitrogen dioxide was reduced to one-half.

there occurred little change even after many hours. However, when a small amount of tris(pentane-2,4-dionato)iron(III) was added to this system, the colour of the reaction mixture immediately turned yellow and the reaction began to proceed. After 36 h the reaction mixture was diluted with water and worked up as usual to give a mixture of isomeric chloronitrobenzenes **2f–4f** in 93% isolated yield. Under similar conditions, benzene **1e**, toluene **1d** and *tert*-butylbenzene **1c** were all smoothly nitrated within 12 to 24 h, giving the respective nitration products in 80–85% isolated yields (Table 1). The isomer composition of the products was similar to those observed for conventional nitration based on nitric acid or nitric acid/sulfuric acid; the *ortho/para* isomers were always predominant over the *meta* isomer, showing the electrophilic nature of the reaction. Nitrophenols were a universal minor product (*ca.* %), as has previously been observed for the *kyodai*-nitration of benzene,[6] which suggests a common mechanism for the formation of nitro compounds in both nitration processes. The reaction performed in the absence of solvent gave similar results, but its progress became somewhat slower. Acetophenone **1g** was relatively slow to react and the proportion of the *ortho* isomer in the product mixture was as high as 50%, which contrasts with ordinary nitration where the *meta* isomer is predominant. Nitrobenzene failed to be nitrated under the conditions employed. Interestingly, strong Lewis acids such as aluminum(III) chloride or antimony(V) chloride were less efficient as catalysts for the present nitration.

o- And *m*-xylene **5a,b** underwent nuclear nitration with ease, giving the nitro derivatives of ordinary isomer proportions in

Table 2 Nitration of disubstituted benzenes **5a–f** with NO_2–O_2–$Fe(acac)_3$ [a]

| Substrate	t/h	NO_2 (cm^3)	$Fe(acac)_3$ $(mol\%)$	Product $(\%)$ [b]
5a	12	10	10	**6a** (27), **7a** (16)
5b	10	10	10	**6b** (68), **7b** (9)
5c	1.5	1	10	Complex mixture [c]
5d	0.33	1	1	**6d** (94)
5d	24	3	10	**6g** (93)
5e	0.5	1	1	**6e** (94)
5f	12	10	10	**6f** (39), **6h** (54)

[a] A mixture of substrate (10 mmol), $Fe(acac)_3$, liquid nitrogen dioxide, and 1,2-dichloroethane (30 cm^3) was stirred for the indicated time under oxygen. [b] Refers to isolated yield. [c] Side-chain-substitution products and their descendants.

Table 3 Nitration of naphthalene **8a** and methylnaphthalenes **8b,c** with NO_2–O_2–$Fe(acac)_3$ [a]

Substrate	Total yield of mononitro compound $(\%)$ [b]	Major isomer	Major isomer/other isomers ratio [c]
8a	>99	**9a**	39
8b	67 [d]	**9b**	2.7
8c	>99	**9c**	2.3

[a] A mixture of substrate (10 mmol), $Fe(acac)_3$ (1 mol %), and nitrogen dioxide (1 cm^3) was kept under oxygen for 30 min. [b] GLC yield determined by using cyclododecane as internal standard. [c] Determined by GLC. [d] Accompanied by side-chain-substitution products and their descendants.

good yields, while *p*-xylene **5c** suffered extensive side-chain attack to afford a complicated mixture of products, in which 2-nitro-*p*-xylene **6c** was a minor component (Table 2; Scheme 2).
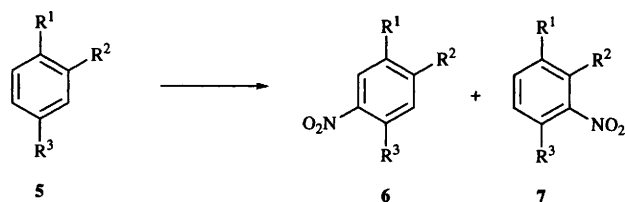

a; $R^1 = R^2 = Me, R^3 = H$

b; $R^1 = H, R^2 = R^3 = Me$

c; $R^1 = R^3 = Me, R^2 = H$

d; $R^1 = R^2 = OMe, R^3 = H$

e; $R^1 = R^3 = OMe, R^2 = H$

f; $R^1 = Me, R^2 = H, R^3 = Cl$

g; $R^1 = R^2 = OMe, R^3 = NO_2$

h; $R^1 = Cl, R^2 = H, R^3 = Me$

Scheme 2 *Reagents and conditions:* NO_2, O_2, $Fe(acac)_3$, $(CH_2Cl)_2$, 0 °C

4-Chlorotoluene **5g** was nitrated cleanly to give the expected nitro products **6g,h** in a good combined yield.

The iron(III)-catalysed nitration of naphthalene **8a** and 2-methylnaphthalene **8c** with nitrogen dioxide proved to be quite satisfactory, giving the nitration products in nearly quantitative yields (Table 3; Scheme 3). The regioselectivity was higher compared with those observed for classical nitration,‡[7,8] the 1-nitro/2-nitro isomer quotient being as high as 39 for naphthalene **8a** while the quotient of the 1-nitro isomer **9c** to the sum of all other nitro isomers was 2.3 for substrate **8c**. 1-Methylnaphthalene **8b** was relatively reactive under the same conditions, and considerable amounts of side-chain substitution products and their descendants were obtained in addition to the expected nitro compound **9b**.

‡ Recently, a remarkably high regioselectivity has been observed in the nitration of arenes with zeolite beta-supported acetyl nitrate.[9]

a; $R^1 = R^2 = H$

b; $R^1 = Me, R^2 = H$

c; $R^1 = H, R^2 = Me$
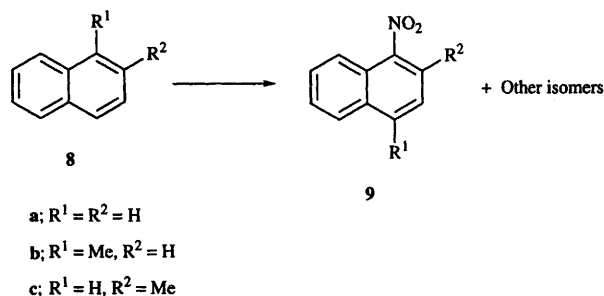
Scheme 3 *Reagents and conditions:* NO_2, O_2, $Fe(acac)_3$, $(CH_2Cl)_2$, 0 °C

Table 4 Nitration of resorcinol dialkyl ethers **10a–f** with NO_2–O_2–$Fe(acac)_3$ [a]

Substrate	t/h	NO_2 (cm^3)	$Fe(acac)_3$ $(mol\%)$	Product $(\%)$ [b]
10a	0.5	1	1	**11a** (52)
10a	24	10	20	**12a** (46)
10b [c]	24	5	30	Complex mixture
10c [c]	24	5	30	**12c** (45)
10d [d]	24	1	30	Complex mixture
10e [c]	24	5	30	Complex mixture
10f [e]	24	5	30	Complex mixture

[a] A mixture of substrate (10 mmol), $Fe(acac)_3$, liquid nitrogen dioxide and 1,2-dichloroethane (30 cm^3) was stirred for the indicated time under oxygen unless otherwise noted. [b] Refers to isolated yields. [c] Scale was reduced to one-half. [d] Scale was reduced to one-fifth. [e] Scale was reduced to three-tenths.

Phenolic ethers are known to be easily nitrated with nitrogen dioxide to give nitro derivatives.[10] Side-products are nitrophenols, quinones and, in some cases, oxidoammonium compounds represented by the formula **15** (Scheme 4).[11] In connection with an ongoing program on the economical manufacture of poly-*p*-phenylenebenzobis(oxazole) **16**, we have attempted to apply the present nitration procedure to the synthesis of 4,6-dinitroresorcinol dialkyl ethers **12**. Direct dinitration of resorcinol derivatives using nitric acid, nitric acid/sulfuric acid (mixed acid), or acetyl nitrate as the nitrating reagent is *inherently dangerous* and usually leads to a mixture of 2,4- and 4,6-dinitroresorcinol derivatives **12** and **13**, accompanied by varying amounts of 2,4,6-trinitro derivative **14**, *which is potentially explosive*. The iron(III)-catalysed nitration of resorcinol dimethyl ether **10a** with nitrogen dioxide gave 4,6-dinitro derivative **12a** in up to 46% isolated yield (Table 4; Scheme 4). Although little or no 2,4-dinitro or 2,4,6-trinitro compound was formed under these conditions, a considerable amount of unidentified degradation products accompanied the main reaction product. Encouraged by the absence of undesirable 2,4-dinitro isomer **13a** as well as troublesome trinitro compound **14a** in the product mixture, we have carried out the nitration of several other resorcinol dialkyl ethers, which included bis(methoxymethyl) **10b**, diisopropyl **10c**, di-*tert*-butyl **10d**, dibenzyl **10e** and bis(4-nitrobenzyl) ethers **10f**. Dimethyl and diisopropyl ethers **10a,c** gave satisfactory results; the product was 4,6-dinitro derivative **12a,c**, almost free from the 2,4-dinitro and trinitro derivatives **13c** and **14c**. In spite of all our efforts, however, the yield of the target compound did not exceed 50%, about half of the starting material being lost into the aqueous phase as an unidentified water-soluble substance during aqueous work-up. The other four dialkyl ethers examined (**10b,d–f**) led to the formation of an intractable mixture of unidentified compounds, the yield of the desired products being low.

In order to shed light on the reaction mechanism, the relative reactivity was determined for four substituted benzenes **1c,d,f** and **5b** and the values obtained were plotted against the anodic

a; R = Me   d; R = Bu^t

b; R = MeOCH$_2$ e; R = PhCH$_2$

c; R = Pr^i f; R = 4-NO$_2$C$_6$H$_4$CH$_2$
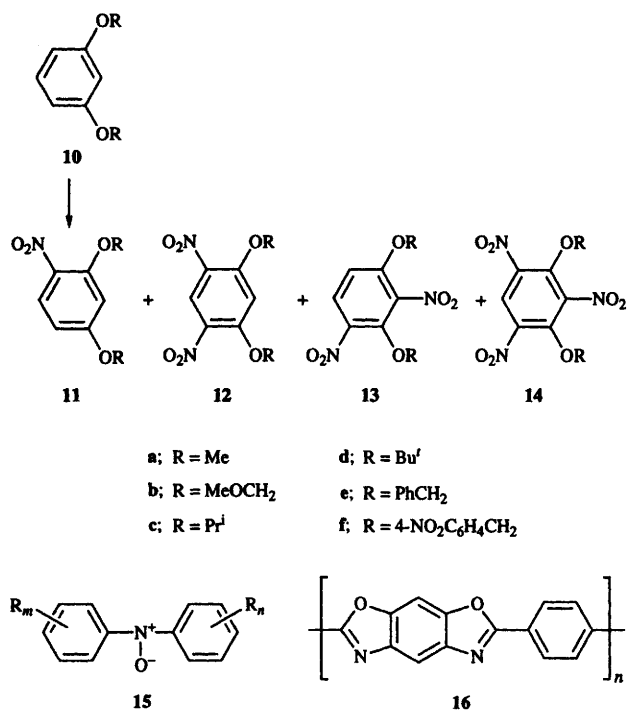
Scheme 4 *Reagents and conditions:* NO$_2$, O$_2$, Fe(acac)$_3$, (CH$_2$Cl)$_2$, 0 °C
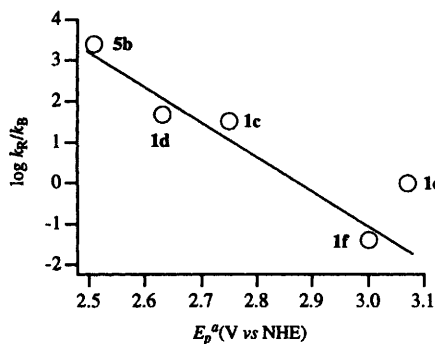

Fig. 1 Correlation betwen the relative rate and oxidation potential

Table 5 Relative reaction rates k_R/k_B and anodic peak potentials $E_p{}^a$ of arenes 1c–f and 5b

Substrate	$k_R/k_B{}^a$	$E_p{}^a$ (V)^b
5b	2600	2.27
1d	50	2.39
1c	32	2.51
1e	1	2.83
1f	0.039	2.76

^{a} At about 15% conversion. ^{b} vs. standard calomel electrode in acetonitrile.[12]

peak potentials of the respective substrates (Fig. 1; Table 5). As is apparent from Fig. 1, a linear relationship holds for the reaction, suggesting a possible involvement of an electron-transfer process. The correlation diagram of the conversion rate and reaction time showed the appearance of a typical first-order reaction. For the nitration of toluene, a logarithmic plot of the concentration ratio log [S]/[S]$_0$, where [S]$_0$ denotes initial concentration, against the reaction time exhibited a good linear relationship, from which the rate constant was calculated to be 5.9 × 10^{-5} dm^3 mol^{-1} s^{-1}. In the absence of oxygen, *i.e.*, under argon, the reaction did not proceed even in the presence of the added iron(III) complex. Among several iron(III) complexes examined, tetrakis(pentafluorophenyl)porphine iron(III) chloride, phthalocyanine iron(III) and ferrocene all failed to show
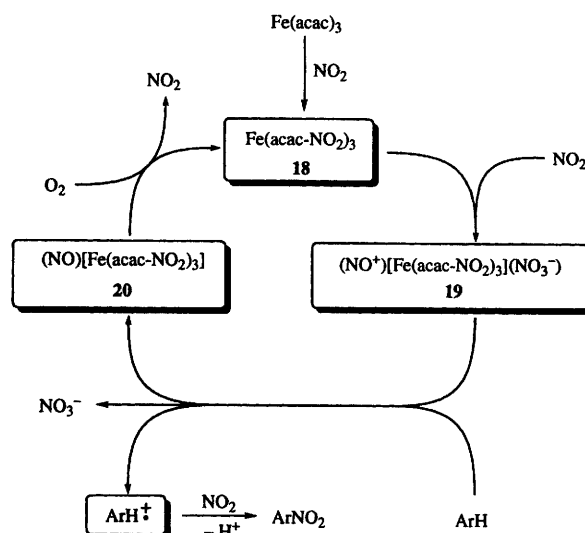

Fig. 2 A possible catalytic cycle for Fe^{III}-catalysed nitration of arenes

any catalytic activity under the conditions employed, while the catalytic action of inorganic iron salts such as iron(III)/iron(II) chlorides and iron(II) acetate was unsatisfactorily low.

2,3-Dimethyl-2,3-diphenylbutane (bicumene) **17** is well recognized as an excellent probe for the electron-transfer process, since it readily forms a cation radical which easily undergoes mesolytic cleavage to give one cumyl cation and one cumyl radical species.[3,13] In order to probe the nature of the present reaction, we have carried out the nitration of hydrocarbon **17** on a 1 mmol scale using 1 cm^3 of nitrogen dioxide and dichloromethane (20 cm^3) under oxygen. The products obtained from the 1 h reaction were 2-phenylpropene (24%), acetophenone (18%), 2-phenylpropan-2-ol (7%) and nitrobicumenes (15%; $o:m:p$ = 11:18:71), thus substantiating the proposed extensive involvement of an electron-transfer process in the present nitration (Scheme 5). Furthermore, the
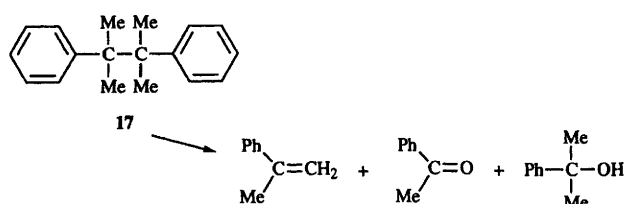
Scheme 5 *Reagents and conditions:* NO$_2$, O$_2$, Fe(acac)$_3$, CH$_2$Cl$_2$, 0 °C

present nitration of chlorobenzene was found to be considerably slowed down by added pyridine and the isomer composition of the nitration products obtained was 9:88:3, strongly suggesting the involvement of an electron-transfer process, followed by addition–elimination sequences.[14]

On the basis of the experimental results obtained, a possible reaction pathway is depicted in Fig. 2, in which nitrogen dioxide first reacts with tris(pentane-2,4-dionato)iron(III) to produce a new complex **18** bearing the nitrated ligands. The new iron(III) complex **18** combines with molecules of nitrogen dioxide to form an activated adduct **19** in which the electrophilic nature of the nitrogen oxide function is highly enhanced. This active species **19** oxidizes an aromatic substrate to produce a cation radical, which follows the ordinary course of the *kyodai*-nitration to give the corresponding nitro derivatives. The complex **19** is deactivated by rapid release of a nitrate anion to form a complex **20**, which loses nitrogen oxide to regenerate the original complex **18**. The assumed active species **19** is most likely to bear a resemblance to the known complex Fe(NO$_3$)$_3$·N$_2$O$_4$, derivable from iron(III) chloride and nitrogen dioxide.[15] This complex was shown by X-ray analysis to

possess an ionic structure $[NO^+][Fe(NO_3)_4^-]$, where the iron(III) centre is symmetrically eight-coordinated with four bidentate nitrate groups.[16]

With an intention to gain support for the above mechanistic interpretation, an attempt was made to synthesize the presumed iron(III) complex 18. Action of nitrogen dioxide on tris(pentane-2,4-dionato)iron(III) in an ice-cooled 1,2-dichloroethane solution readily gave a reddish brown solid of composition $C_{15}H_{18}FeN_3O_{12}$. When the nitrated complex thus obtained was employed as a catalyst for the nitration of toluene, a catalytic activity similar to that of the original iron(III) complex was observed. This complex was recovered without change from the reaction mixture of the Fe^{III}-catalysed nitration of benzene. Contrary to our expectation, however, tris-(1,1,1-trifluoropentane-2,4-dionato)- and tris-(1,1,1,5,5,5-hexa-fluoropentane-2,4-dionato)-iron(III) failed to show any enhancement in catalytic activity [below 50% as compared with tris(pentane-2,4-dionato)iron(III)], although these complexes also bear a strong electron-withdrawing substituent, a trifluoromethyl group. Owing to our failure to obtain the complex 18 in a crystalline form suitable for X-ray analysis, its molecular structure could not be elucidated.

In summary, non-activated arenes such as halogenobenzenes and chlorotoluene, as well as moderately activated arenes such as alkylbenzenes and naphthalenes, can be nitrated successfully with nitrogen dioxide in the presence of an iron(III) complex under oxygen, giving the corresponding nitro derivatives in fair to good yields. A mechanistic pathway involving electron transfer between an activated NO_2-Fe^{III} complex and an arene to produce a cation radical species as the key step has been proposed for the reaction.

Experimental

Materials

All reagents were reagent-grade commercial samples. Solvents were distilled from CaH_2 prior to use. Tris(pentane-2,4-dionato)iron(III), its trifluoro and hexafluoro derivatives, and phthalocyanine iron(III) were commercially available. Tetrakis(pentafluorophenyl)porphine iron(III) was prepared according to the reported procedure.[17] Nitrogen dioxide was used as obtained in a cylinder from Sumitomo Seika Co. Ltd. Oxygen gas was obtained from Kyoto Teisan Co. Ltd., and used after passage over a NaOH–Drierite® tube. All nitration products are known and identified by direct comparison with authentic specimens.

Iron(III)-catalysed nitration of arenes with nitrogen dioxide. Typical procedure

(a) Chlorobenzene 1f. In a 50 cm³ two-necked flask was placed a mixture of chlorobenzene 1f (1.125 g, 9.99 mmol), tris(pentane-2,4-dionato)iron(III) (0.356 g, 1.01 mmol) and freshly distilled 1,2-dichloroethane (30 cm³) in the dark, and the mixture was cooled to 0 °C externally with a cooling bath (EYELA COOL ECS-1 with two thermocontrollers, THS-40 and THD-50). After the flask was flushed with oxygen, one neck was connected to a balloon filled with oxygen gas while liquid nitrogen dioxide (10 cm³; ~280 mmol) was introduced all at once from the other neck. The reaction mixture was stirred for 36 h at the same temperature and was then treated with ice–water. The organic phase was extracted with 1,2-dichloroethane and the extract was washed successively with water and brine, and dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel to give an isomeric mixture of chloronitrobenzenes (1.472 g, 93%). The isomer distribution determined by GLC (Shimadzu gas chromatograph GC-14A instrument equipped with J & W Scientific capillary column, DB-5-30N-STD, and flame ionization detector) was $o:m:p = 32: <1:68$. A trace amount of 4-chloro-2,6-dinitrophenol was also isolated.

(b) Resorcinol diisopropyl ether 10c. Resorcinol diisopropyl ether 10c (0.976 g, 5.02 mmol) and tris(pentane-2,4-dionato)-iron(III) (0.531 g, 1.50 mmol) were dissolved in 1,2-dichloroethane (15 cm³), and the resulting mixture was treated with nitrogen dioxide (5 cm³; ca. 140 mmol) under oxygen. The colour of the solution immediately turned dark green, suggesting the concurrent formation of oxidoammonium compound as by-product. After 12 h with the exclusion of sunlight, the reaction mixture was worked up as usual. Chromatography of the product mixture on silica gel gave 4,6-dinitro derivative 12c (0.633 g, 45%) as light yellow crystals.

Synthesis of tris(3-nitropentane-2,4-dionato)iron(III) complex 18

A mixture of tris(pentane-2,4-dionato)iron(III) (3.53 g, 10 mmol), nitrogen dioxide (5 cm³), and 1,2-dichloroethane (35 cm³) was vigorously stirred at 0 °C for 30 min and then the solvent, together with unchanged nitrogen dioxide, was removed under reduced pressure. The solid residue was recrystallized from hexane–dichloromethane to yield complex 18 as a red-dish brown powder (1.93 g, 40%). The iron(III) complex thus obtained exhibited an IR pattern closely resembling those of the known tris(3-nitropentane-2,4-dionato)-copper(II), -nickel(III) and -platinum(III) complexes;[18] ν_{max}(KBr)/cm^{-1} 1576, 1522, 1466, 1416, 1347, 1113, 1044, 1022, 1001, 928, 824, 749, 687, 669, 588, 446 and 419 (Found: C, 36.5; H, 3.7; N, 9.4. $C_{15}H_{18}FeN_3O_{12}$ requires C, 36.91; H, 3.72; N, 8.61%).

Acknowledgements

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