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Advances in the application of N_2O_4/NO_2 in organic reactions

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This article is dedicated to Professor Shadpour Mallakpour, who has dedicated so much to progress the science of organic chemistry especially N_2O_4 in Iran

Contents

1. Introduction

Nitrogen oxides (NO_x) such as NO, NOCl, NO_2X (X=Py, RO^-, RCO_2^-, Cl^-, BF_4^-, PF_6^-), N_2O_3, N_2O_5 and NO_2/N_2O_4, have found a wide range of applications in organic synthesis, both in industry and in research laboratories.[1–3] Amongst these, NO_2/N_2O_4 exhibits important advantages as a versatile reagent over the others. Such advantages include its application as a multifunctional agent (nitration, nitrosation and oxidation agent), as well as it being a powerful reagent and cost effective. Although it is an ancient reagent of which the chemistry is well known, recent findings have revealed some crucial advances in terms of ease of handling. In this regard, N_2O_4 organic complexes such as 18-crown-6 ether/N_2O_4[4,5] and heterogeneous systems such as activated charcoal/N_2O_4[6] were explored as useful reagents that solve numerous handling problems and also serve to increase the selectivity of N_2O_4/NO_2 in organic reactions. Metal nitrate/N_2O_4 adducts, $M(NO_3)_x \cdot yN_2O_4$, in which N_2O_4 molecules are trapped in the metal nitrate lattice, were synthesised from the reaction of N_2O_4 and the corresponding metal salts.[7] Since liquid N_2O_4 evaporates at 21.15 °C

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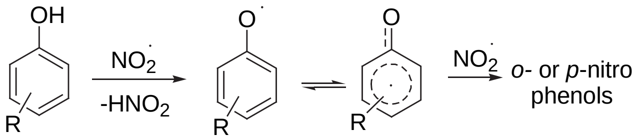
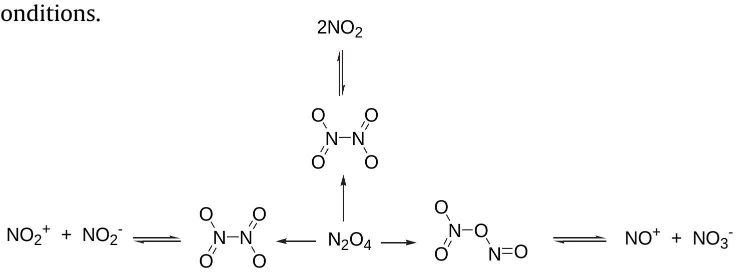
under atmospheric pressure, $M(NO_3)_x \cdot yN_2O_4$ is a very convenient and thermally stable source of N_2O_4. In order to increase the rate and selectivity of NO_2 in the laboratory, some modifications have been introduced for the reaction conditions such as the involvement of O_3, O_2, or zeolites, etc. and also the use of ionic liquids.

Dinitrogen tetroxide has long been regarded as an equilibrium mixture (Eq. 1). Homolytic dissociation to dimeric NO_2 (radical) is always present in the liquid form and heterolytic dissociation as NO^+/NO_3^- appears under polar conditions.



Scheme 2.



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In relation to this topic, three review articles have been reported, namely 'The reaction of dinitrogen tetroxide with organic compounds',[8] in 1945, 'The reactivity and structure of nitrogen dioxide', in 1955,[9] and 'Dinitrogen tetroxide, nitric acid, and their mixtures as media for inorganic reactions', in 1980.[7]

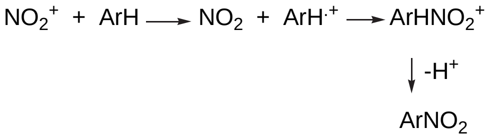
In the present review, only useful organic transformation reactions employing NO_2/N_2O_4 and related complexes as reagents are included. Emphasis is placed on recent advances in the field.

2. Nitration with N_2O_4

2.1. Nitration of aromatic compounds

Nitration of arenes is an interesting process, not only for the application of nitroarenes as explosives, but also due the versatile use of nitroarenes as intermediates in various important functional-group transformations. Although a recent book[10] on such methods has been published, this section will focus on some new applications.

Perrin,[11] Eberson et al.,[12] Achord and Hussey,[13] Olah et al.[14] and Ross et al.[15] have studied the mechanism of nitration of naphthalene with N_2O_4. A similar study by Pryor et al. on other polycyclic aromatic hydrocarbons (PHAs) was performed.[16] These results support an electron-transfer mechanism for the aromatic nitration reaction, as presented in Scheme 1.



Scheme 1.

Studies on the nitration of fluoranthene with NO_2 revealed that the mechanism can be dramatically dependent on the solvent[17,18] and temperature.[18] The reaction mechanism for the nitration of fluoranthene,[17,18] anthracene[19] and naphthalene[20] with NO_2 in CCl_4, at 25 °C is best formulated as a homolytic process.

The reactions of polysubstituted phenols with excess nitrogen dioxide were thoroughly studied by Hartshorn and his group.[21,22] Kinetic studies of this reaction revealed that the mechanism involves initial hydrogen-atom abstraction and subsequent reaction of the phenoxy radical with NO_2 (Scheme 2).[23–25]

Schmitt et al. reported that aromatic radical cations ($ArH^{+\cdot}$) readily react with NO_2 to give the σ-bonded $ArH{-}NO_2^+$ radical in the gas phase and under a pressure of 10 Torr.[26,27] Under the same conditions, the reaction of the nitronium ion (NO_2^+) with neutral ArH yields only $ArH^{+\cdot}$ and $ArH{-}O^+$, products of electron or oxygen transfer.

The mechanism for the nitration of arenes with species such as NO^+, $NO_2^{\cdot}$, $NO_3^{\cdot}$ and N_2O_5 was discussed in a review article published by Ridd.[28]

Recently, Astolfi and his group found that phenols react with nitrogen dioxide in different solvents at room temperature.[29] Although the products of oxidation (**3**), nitrosation (**4**) and dimerisation (**5**) have been observed, in all cases the nitration product (**2**) is the major product (Scheme 3). The interconversion reaction of 2,5-di-*tert*-butylphenol **1** with N_2O_4/NO_2 is presented in Scheme 3.

Monomeric phthaloyl peroxide **6** reacts with nitrogen dioxide in carbon tetrachloride to yield *o*-dinitrobenzene and *o*-nitrobenzoic acid (Scheme 4).[30]

Treatment of thebaine **7** with dinitrogen tetroxide, after hydrolysis gives a mixture of 14-β-nitrocodeinone **8** (23%) and 8-nitrothebaine **9** (7%) (Scheme 5).[31]

Mochalov et al. demonstrated that relatively simple quantum-chemical calculations are able to predict the course of the reaction. They calculated the frontier orbital energy of the reagents, intermediates and products in N_2O_4 reactions with cyclopropylmethyl- and allylbenzenes. The calculations included the effect of solvents on the reaction. It was then experimentally shown that, in solvents with low polarity such as dichloromethane, *para*-cyclopropylmethoxybenzene **10** reacts with N_2O_4 to give a mononitroanisole derivative **11** (8%), a dinitroanisole derivative **12** (21%) and nitrophenol **13** in 35% yield (Scheme 6).[32] The theoretical results agreed well with the experimental results.

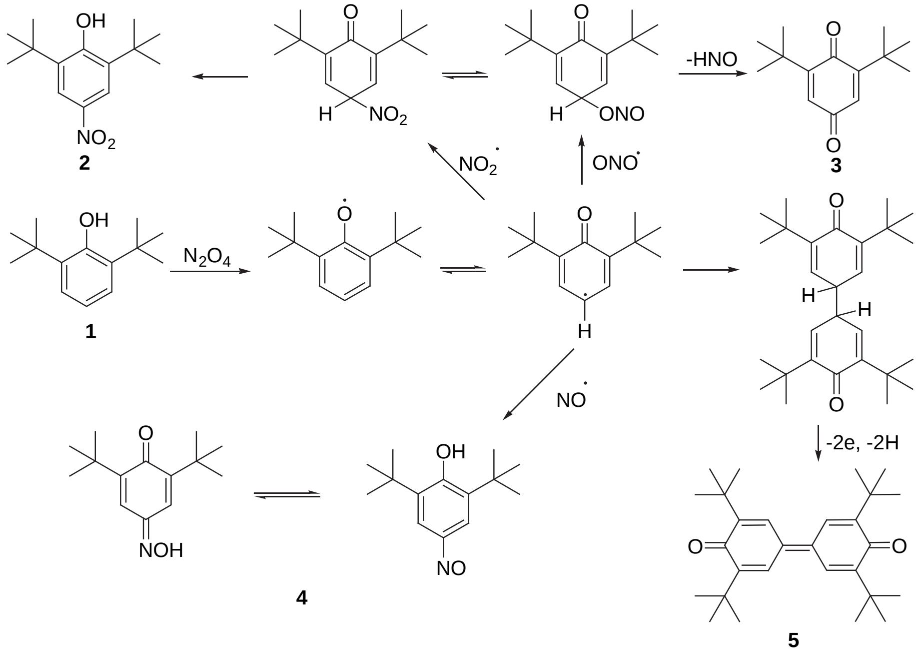
In another interesting study, some other substituted aromatic compounds[33,34] were investigated in the reaction with N_2O_4. Mochalov found that 4-methoxybenzylcyclopropane **14** reacts with N_2O_4 to form the nitroarenes **15**–**18** (Scheme 7).[35]

γ-Tocopherol **19** reacts in hexane with NO_2 to yield two products, identified as 2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-5,6-chromaquinone (tocored) **20** and 2,7,8-trimethyl-2-(4,8,12-trimethyldecyl) 5-nitro-chroman-6-ol (tocoyellow) **21** (Scheme 8).[36]

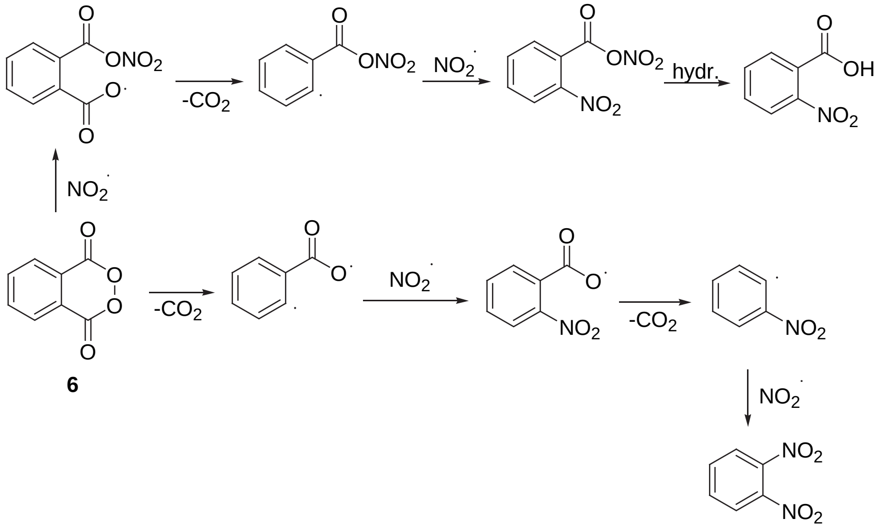
Addition of dinitrogen tetroxide to acenaphthylene **22** in ethyl ether at 0 °C in the absence of oxygen gives 1-nitroacenaphthylene **23**, 1,2-dinitroacenaphthylene **24** and an amorphous polymer in 16, 14 and 9%, respective yields (Scheme 9).[37] Excess acenaphthylene **22** favours the formation of the mononitroacenaphthylene **23**.

Barlas et al. investigated the photochemical reactions of naphthalene,[38] anthracene, pyrene[39] and indane[40] with NO_2 in solution.

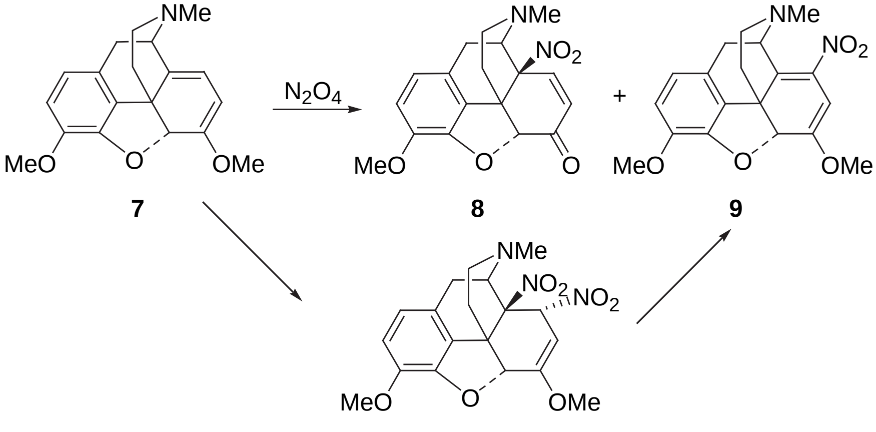
Boughriet et al.[41] studied the reaction of naphthalene with N_2O_4 under electrocatalytic conditions. In this process, small amounts of NO_2^+ are prepared in dry sulfolane by partially controlled potential electrolysis of dinitrogen tetroxide. The latter induces effective nitration of naphthalene through a catalytic process involving the well-known NO^+ species.



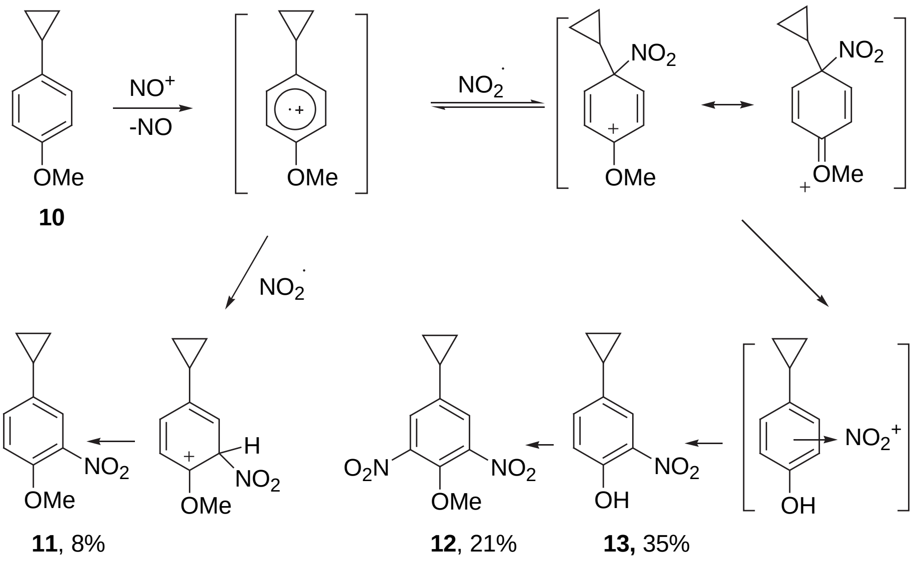
Scheme 3.



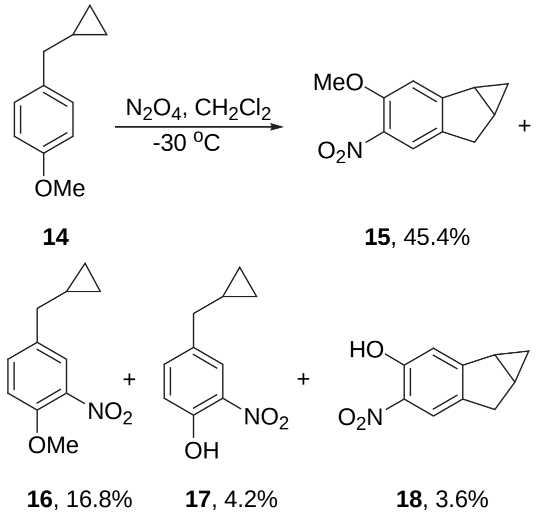
Scheme 4.



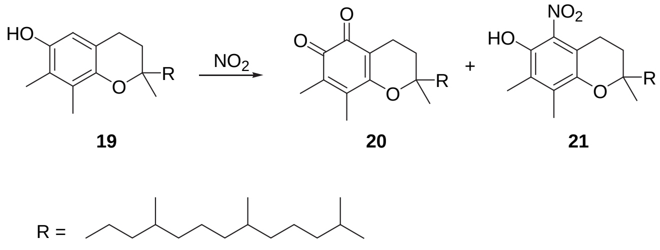
Scheme 5.



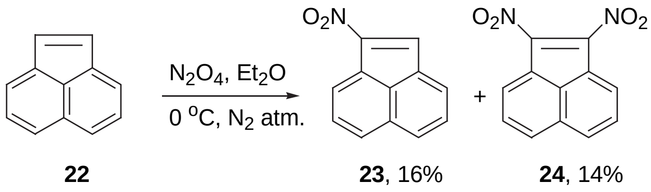
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

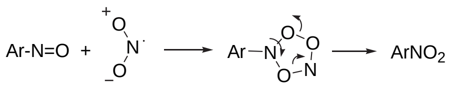
Radner reported a selective method for the synthesis of mononitro polycyclic aromatic hydrocarbons (PAHs) such as 3-nitroperylene **25**, 1-nitropyrene **26**, 3-nitrofluoranthene **27**, 9-nitroanthracene **28** and chrysene **29** from the reaction of the corresponding PHAs and N_2O_4 in CH_2Cl_2 at room temperature (Fig. 1).[42]

In an alternative process, the synthesis of some nitro PAHs such as **32** from the nitration of **30** with N_2O_4 followed by induced aromatisation of **31** with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) was reported by Fu et al. (Scheme 10).[43]

Nitration of a variety of PAHs that were adsorbed on solid beds such as silica with gaseous NO_2 under different conditions has been widely investigated.[44–52]

The reaction of 2-phenylindole and 1-methyl-2-phenylindole (**33** and **34**) with nitrogen dioxide or with nitrous acid ($NaNO_2$–MeCOOH) in benzene leads mainly to the formation of the 3-nitroso- and isonitroso-indole derivatives (**35** and **36**), respectively (Table 1). When reacted with nitrous acid, 1-methyl-2-phenylindole (**34**) also gives the corresponding azo-bis-indoles in good yields. With excess NO_2, these indoles (**33** and **34**) give the corresponding 3-nitro compounds (**38** and **39**).[53]

Bonner et al.[54–56] and Gowenlock et al.[57] used N_2O_4 for the conversion of nitroso compounds into the corresponding nitro compounds. They suggested the possibility of a 1,3-cycloaddition mechanism with nitrogen dioxide (Eq. 2). Oxidation of nitrosobenzene to nitrobenzene has also been reported.[58]



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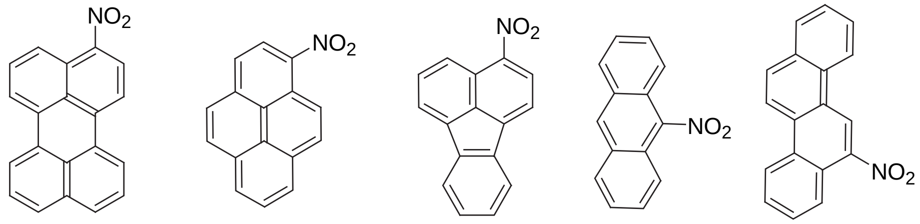
N_2O_4 is also efficiently used for the synthesis of *p*-nitrocalixarenes,[59,60] nitroporphyrins[61–63] and nitroporphyrazines.[64]

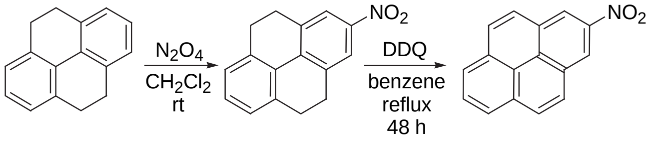
Reaction conditions leading to the effective nitration of C_{60} molecules for the production of substantially pure hexanitro-[60] fullerenes using gaseous nitrogen dioxide as the nitration agent were developed.[65,66] The chemisorption of NO_2 on carbon nanotubes was modelled by Yim et al.[67]

1,3-Diarylurea **40** is a special model of an aryl compound that contains active functional groups. This urea is converted in to a mononitro urea **41** (60%) in a solution of N_2O_4 in DMF and, with excess N_2O_4, the dinitro urea **42** is obtained in 42% yield (Scheme 11).[68]



25, 99.2% **26**, 100% **27**, 63% **28**, 100% **29**, 97%

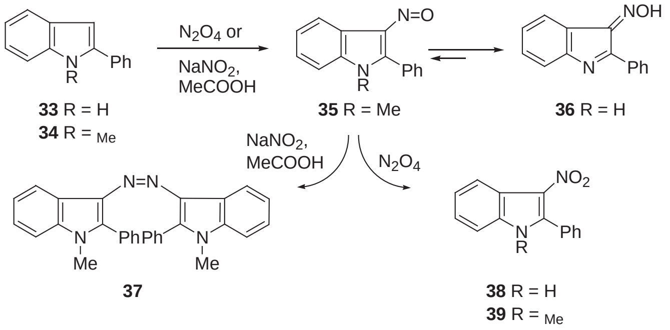
Fig. 1. Mononitro PAHs **25**–**29**.



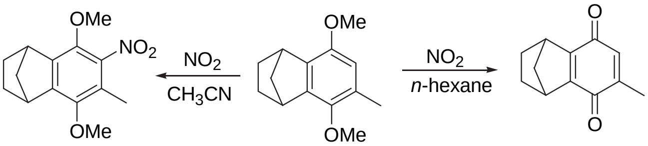
30 **31**, 98% **32**, 98%

Scheme 10.

Table 1
Products obtained for reactions of indoles **33** and **34** with nitrogen dioxide and nitrous acid

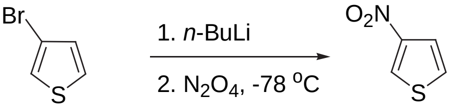


Indole	Products obtained (% yields in brackets)		NaNO$_2$/MeCOOH
	Gaseous NO$_2$ 1:1	Gaseous NO$_2$ 1:2	
33	**33** (15) **36** (85) 2 h	**36** (15) **38** (85) 10 min	**36** (90) 4 h
34	**34** (20) **35** (80) 2 h	**35** (15) **39** (85) 10 min	**34** (33) **35** (32) **37** (35) 4 h



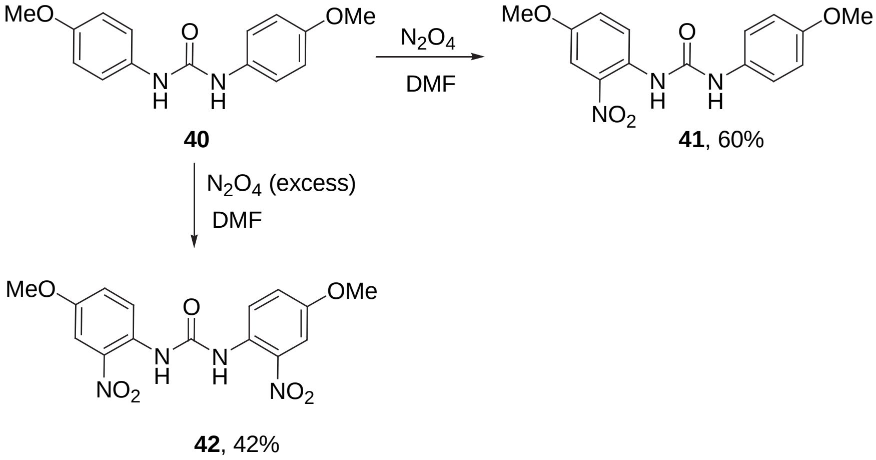
Scheme 12.

Nitrations of organothallium,[70] organotin,[71,72] organolithium and Grignard reagents with N_2O_4 were developed for the preparation of various kinds of nitro compounds.[73] The success of this process depends on the reaction conditions (low temperature) and the structure of the substrates. As an example, 3-nitrothiophene can be obtained in 70% overall yield from 3-bromothiophene, this process being far superior to previous methods (Scheme 13).[73]



Scheme 13.

Another example in this area is the C-2 lithiation of *N*-Boc- and *N*-(phenylsulfonyl)-indoles, followed by reaction with dinitrogen tetroxide at low temperature to afford the corresponding 2-nitroindoles in 60–80% yields (Table 2).[74] Deprotection of the *N*-Boc-2-nitroindoles with trifluoroacetic acid gives 2-nitroindole and 3-methyl-2-nitroindole in essentially quantitative yields.

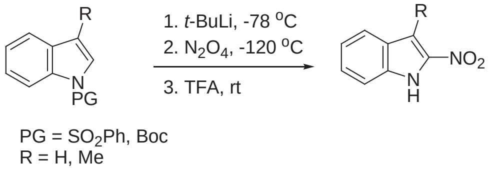


Scheme 11.

Rathore et al. have discovered the electrochemical selective nitration reaction versus oxidative dealkylation of hydroquinone ethers with nitrogen dioxide in different solvents (Scheme 12).[69]

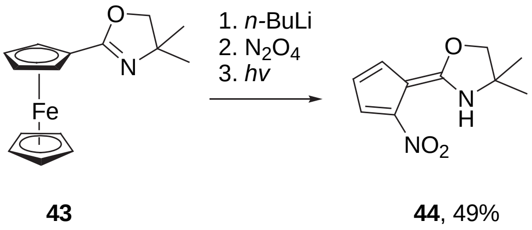
After lithiation of the ferrocenyl derivative **43**, followed by the addition of N_2O_4, the corresponding 2-nitroferrocenyloxazoline is obtained, which undergoes facile photodecomplexation to give the nitrofulvalene **44** (Scheme 14).[75]

Table 2
Synthesis of 2-nitroindoles



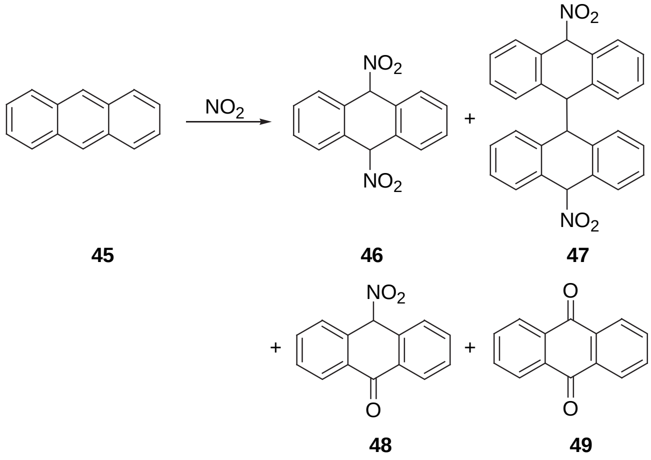
Indole	PG	R	Yield (%)
1	Boc	H	78
2	Boc	Me	74
3	$PhSO_2$	H	67
4	$PhSO_2$	Me	63
5	Me	H	0
6	CO_2Li[a]	H	0

[a] Generated by bubbling CO_2 into the solution of 1-lithioindole (Katritzky's method).



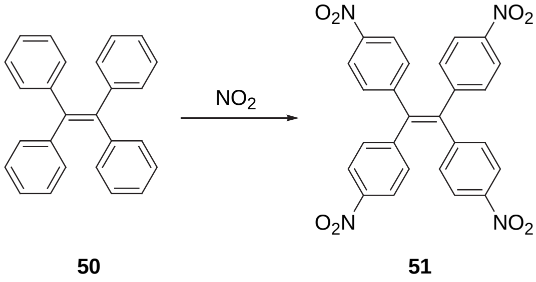
Scheme 14.

In the solid state, arenes react with gaseous NO_2; the selectivities are different from those of the corresponding nitration reaction in solution.[76] As an example, the solution-state nitration of anthracene **45** with nitric acid or N_2O_4 provides numerous products including **46**, **48** and **49**,[19] but not the dimeric product **47** (Scheme 15). The variability is believed to be derived from both *N* and *O* attack of NO_2 on the 9/10 positions of anthracene and from secondary reactions of the intermediates. At 25 °C and after 28% conversion, the proportions of *trans*-**46**/*cis*-**46**/**47**/**48**/**49** products are 1:1.2:1.5:3.2:0.2. After complete conversion of anthracene at room temperature, 75% of **48**, 20% of **49**, 4% of *cis*-**46** and a trace amount of the dimeric product **47** were obtained.[76]



Scheme 15.

A synthesis of tetrakis(*p*-nitrophenyl)ethylene **51**[77] from tetrakis (phenyl)ethylene **50** and N_2O_4 has been described via a gas/solid synthetic method. If the water of reaction is removed with a drying agent such as $MgSO_4$, **51** is obtained in 95% yield (Scheme 16).[76] In the absence of a drying agent, the reaction is severely hindered by liquid water condensing on the crystals, and a mixture of the mono-, tri- and tetra-*p*-nitro products is observed.



Scheme 16.

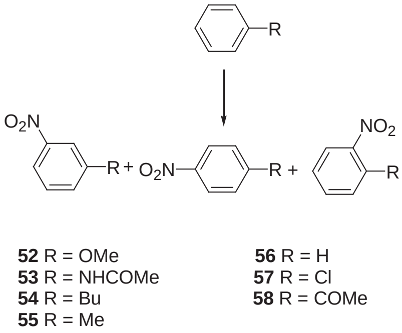
Nitration of less active aromatic compounds does not usually occur with N_2O_4 as the sole reagent. The addition of activators such as catalysts and oxidants can solve this problem. Although the nitration of arenes with N_2O_4 in a strongly acidic medium[78] can be used, mild catalysts such as $AlCl_3$,[79] BF_3,[80,81] CF_3COOH,[82–84] $PhSO_3H$,[85,86] Hg(II),[87] Pd[88] and Pd(II) have also been reported.[89]

Vapour-phase nitration of benzene in the presence of SiO_2/$PhSO_3H$,[90] and polyorganosiloxanes bearing sulfonic groups[91] has been achieved. Zeolites serve as mild activators for the same reaction and were reported by several researchers.[92–95]

Malhotra and Ross have found that benzene and toluene could not be nitrated by liquid N_2O_4 at 0 °C, but simultaneous passage of NO and O_2 through a solution of benzene in liquid N_2O_4 leads to nitration of benzene giving mono-, di-, and even trinitrobenzenes.[96]

Iron(III) complexes are utilised as catalysts for the nitration of non-activated and moderately activated arenes with nitrogen dioxide and oxygen at ice-bath temperature or below.[97] As demonstrated in Table 3, the conversion of arenes into nitroarenes is nearly quantitative, except for acetophenone that undergoes nitration in only 29% yield after elongated reaction times.[97]

Table 3
Nitration of monosubstituted benzenes **52**–**58** with $NO_2/O_2/Fe(acac)_3$[a]



Substrate	Time (h)	Conversion (%)	Yield[b] (%)	*ortho*/*meta*/*para*[c]
52	1	100	55	40:<1:60
53[d]	6	98	33	73:<1:27
54	12	>99	85	12:5:83
55	12	>99	80	55:2:43
56	24	>99	83	
57	36	100	93	32:<1:68
58	72	43	29	51:49:<1

[a] All reactions performed at 0 °C using mixture of substrate (10 mmol), $Fe(acac)_3$ (10 mol %), nitrogen dioxide (10 cm^3) and 1,2-dichloroethane (30 cm^3) under oxygen atmosphere, unless otherwise noted.
[b] Isolated yields.
[c] Determined by GLC.
[d] Amount of nitrogen dioxide reduced by 50%.

The postulated mechanism for this nitration reaction demonstrates the effect of Fe(III) via the formation of the active complex **59** (Fig. 2). Arenes react with the complex **59** and are converted into an aryl radical. This radical reacts with NO_2 to form nitroarenes (Fig. 2).[97]

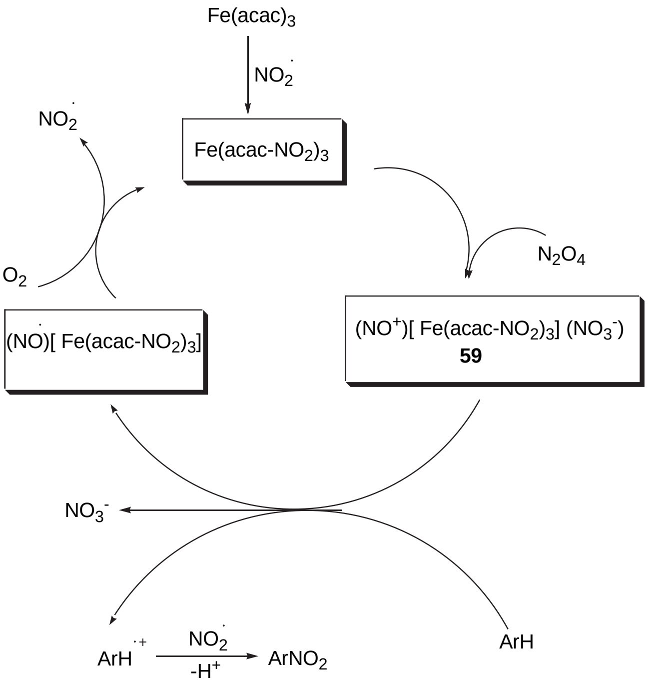


Fig. 2. Possible catalytic cycle for Fe(III)-catalysed nitration of arenes.

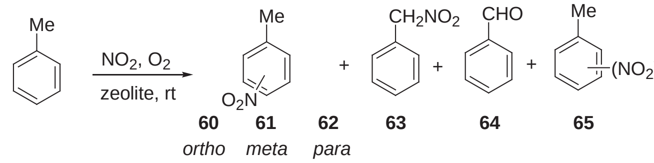
Very recently nitration of benzene with the NO_2/O_2 system in the presence of a mixture of solid oxides and $Ln(OTf)_3$[98] has been studied. This system is also successful on large scale with $FeCl_3 \cdot 6H_2O$ as the catalyst.[99]

Smith et al. reported that a mixture of arenes, N_2O_4, air and zeolite in a sealed system leads to nitration products in high yields with high selectivity for the *para*-products in a relatively clean process.[100–102] It was found that the type of zeolite has a strong influence on the reaction rate and selectivity.[102] In a related study, Suzuki and his group have found a superior selectivity for the production of *para*-nitroisomers using HZSM-5 (zeolite) in neat conditions with a NO_2/O_2 system (Table 4).[103]

1-Nitronaphthalene and naphthonitriles are smoothly nitrated at room temperature by the combined action of nitrogen dioxide and molecular oxygen in the presence of zeolites.[104] The regioselectivity is considerably improved as compared with the conventional nitration methodology based on nitric and sulfuric acids.

Nitration of toluene, anisole and chlorobenzene in the presence of an acidic ionic liquid as both green catalyst and solvent with NO_2/air has showed higher *para*-selectivity and moderate yield. The acidic ionic liquid could be recovered and reused with a loss of about 9.4% for five cycles.[105,106]

Table 4
Regioselective nitration of toluene[a]



Catalyst	Yield[b] (mmol)	Product distribution (%)						*ortho*/*para*[c]	*R*/*S*[d]
		60	**61**	**62**	**63**	**64**	**65**		
—[e]	0.47 (1)	7	7	5	34	35	12	1.48	0.45
—	1.15 (5)	34	7	23	6	12	18	1.47	4.6
HZSM-5[f]	2.12 (11)	17	4	57	10	7	5	0.3	4.9
HZSM-5[f,g]	4.62 (24)	6	2	74	10	7	1	0.08	4.9
HZSM-5/$MeSO_3H$	7.30 (46)	51	3	44	Trace	Trace	2	1.15	>99

[a] All reactions carried out by stirring mixture of toluene (5.0 ml), liquid NO_2 (0.5 ml), catalyst (2.0 g), 3 Å molecular sieves (0.5 g) and cyclododecane (internal standard) at room temperature for 22 h under oxygen. Toluene dried over 4 Å molecular sieves.

[b] Sum of products **60**–**65**, estimated by GC. Number in parenthesis refers to total yield of nitrotoluenes based on NO_2.

[c] Calculated from GC data.

[d] Ratio of ring and side-chain reaction products.

[e] Under exclusion of oxygen.

[f] HZSM-5 is commercial product (Acros) of Si/Al ratio 1000. All catalysts except HZSM-5/$MeSO_3H$ calcined in air at 500 °C for 8 h prior to use.

[g] Double amount of catalyst.

Nitrogen dioxide in the presence of O_3 is a powerful nitrating system and this is referred to in the literature as the *Kyodai* nitration reaction.[107–110] The *Kyodai* nitration mechanism has been studied by Suzuki et al.[111,112] They proposed that NO_2 reacts with O_3 to form NO_3, which oxidises the aromatic substrate to form a radical cation, which serves as an intermediate in the ring substitution reaction (Eq. 3). In the absence of an appropriate oxidisable substrate, the nitrogen trioxide reacts with another NO_2 to form N_2O_5; the latter is a powerful nitrating agent in the presence of an acid (Eq. 3). Acid sensitive compounds are nitrated without decomposition under neutral conditions (Eq. 3).[113]

$$\begin{aligned} NO_2 + O_3 &\longrightarrow NO_3^{\cdot} + O_2 \\ ArH + NO_3^{\cdot} &\longrightarrow ArH^{\cdot+} + NO_3^- \\ ArH^{\cdot+} + NO_2 &\longrightarrow ArNO_2 + H^+ \\ NO_3^{\cdot} + NO_2 &\longrightarrow N_2O_5 \end{aligned} \qquad (3)$$

By using the *Kyodai* nitration method at low temperature, chloro- and bromo-benzenes were smoothly nitrated to the corresponding nitro derivatives in nearly quantitative yield. The nitration products are generally *ortho*-rich as compared with those obtained by the conventional procedures based on the use of nitric acid or mixed acids. Interestingly, the *ortho*/*para* isomer ratios of the products can be reversed from *ortho*-rich (o/p=1.14 and 1.09) to *para* predominant (o/p=0.45 and 0.68) simply by altering the initial concentration of the substrates.[114] A similar preference for *ortho* substitution to the halogen substituent has been observed with 4-chloro- and 4-bromotoluene, which concurrently suffer extensive *ipso* attack by the present reagent system, leading to the formation of 4-methyl-2-nitrophenol as a common side product. The mechanism of these conversions is outlined in Fig. 3.

The reaction of benzanthrone **66** with NO_2 alone or in a mixture with O_3 gives a variety of nitrated products, including 3-nitrobenzanthrone,[115] as a new class of powerful mutagens of atmospheric origin.[116,117] A remarkable change of product distribution has been observed, depending on the solvent employed; 3-nitrobenzanthrone was the main product from the reaction in CH_2Cl_2, while 2-nitrobenzanthrone was obtained as the major product in CCl_4 (Table 5).[115] Addition of a protic acid or an inorganic solid support was found to promote the reaction, favouring the formation of the former nitro compound at the expense of the latter (Table 5).

The regioselectivity of the aromatic nitration via the *Kyodai* system is highly dependent on the conditions of the nitration reaction (Table 6).

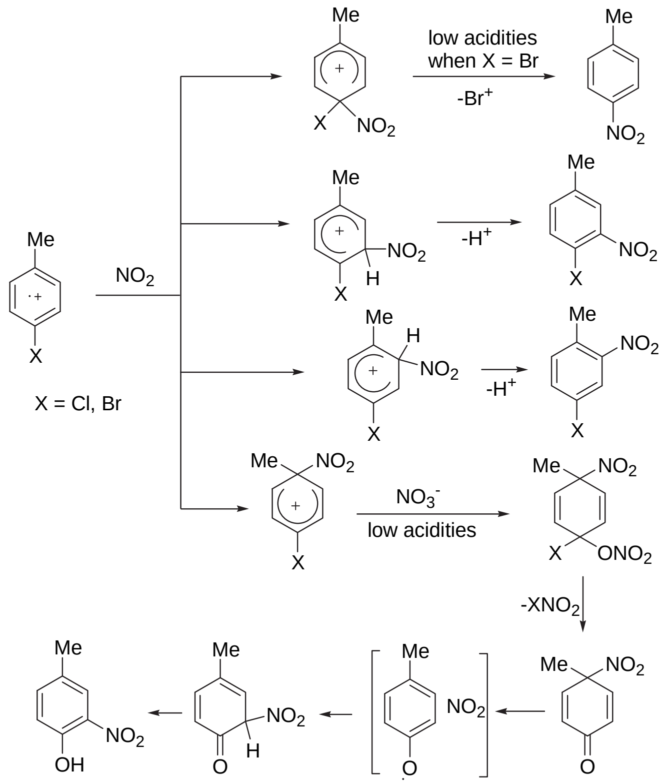
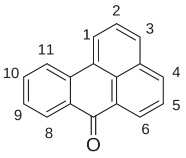


Fig. 3. Proposed mechanism for reaction of 4-chloro- or 4-bromotoluene under *Kyodai* conditions.

Table 5
Nitration of benzanthrone **66** and resulting product distribution



66

Run	Nitrating agent	Solvent	Temp (°C)	Conversion (%)	Isomer distribution (%)						3-Nitro/1-nitro
					1-Nitro	2-Nitro	3-Nitro	9-Nitro	11-Nitro	1,3-Nitro	
1	NO_2	CH_2Cl_2	25	82	2.8	13.3	53.2	2.1	0	7.1	19.0
2	NO_2[a]	CH_2Cl_2	25	84	0.6	46.8	9.0	2.3	0	7.4	15.5
3	NO_2/O_3[b]	CH_2Cl_2	−70	98	7.7	0.6	58.8	Trace	Trace	0	7.6
4	NO_2/O_3	CH_2Cl_2	0	100	6.6	2.1	80.0	1.6	0.4	0	12.1
5	NO_2/O_3	CH_2Cl_2	20	100	4.9	1.5	79.8	1.9	0.4	0	16.3
6	NO_2/O_3	—[c]	20	98	3.3	1.17	82.4	2.2	0	Trace	25.0
7	NO_2	CCl_4[d]	20	100	0	5.2	1.5	0.3	0	0	—
8	NO_2/O_3	CCl_4	20	100	0	67.3	0	1.6	0	6.3	—
9	NO_2/O_3[e]	CCl_4	20	90	3.8	7.8	57.1	3.2	0	0	15.0

[a] 2,6-Di-*tert*-butylpyridine (1 mmol) added.

[b] Procedure for *Kyodai* nitration employed.

[c] SiO_2 used as supported material for benzanthrone.

[d] 2,3-Dinitro-3-hydro-2-hydroxybenzanthrone has been obtained in 80% yield.

[e] HNO_3 (50 μl) added.

Kyodai conditions were also used for the nitration of aryl sulfides that are directly converted into nitroaryl sulfones in good yield (Scheme 17).[131]

This nitration system also works well for aryldicarboxylic acid diesters to give the corresponding mononitro derivatives in good yield. In one example, naphthalene-1,8-dicarboxylic acid diester **67** is nitrated in the absence of a catalyst to give the expected nitro compounds **68**–**72** (Scheme 18).[132]

When bibenzyl is treated with nitrogen dioxide and ozone at low temperature, mono-nitro derivatives are observed as the main products, but bis-nitration products are formed with prolonged reaction times. Benzaldehyde is the only non-nitro by-product observed. The mechanism of the reaction is presented in Scheme 19.[133]

It was found that, when benzimidazole was subjected to the NO_2/O_3 system, a mixture of nitro products such as 1-nitrobenzimidazole derivatives were obtained.[134] 1-Nitrobenzotriazole derivatives were also unexpectedly identified (Scheme 20). It was proposed that benzotriazoles are formed via 1-nitrobenzimidazoles and subsequent nitration of these benzotriazoles result in the formation of 1-nitrobenzotriazoles (Scheme 20).

Suzuki and Nonoyama reported the selective N-nitration of pyrazole and uracil with nitrogen dioxide in the presence of ozone in CH_2Cl_2 at 0 °C to give the corresponding 1-nitro derivatives.[135] Imidazole is *C*-nitrated in the presence of methanesulfonic acid as catalyst to afford a 4-nitro derivative (Scheme 21).

N_2O_4 and O_3 in the presence of an appropriate catalyst[136] (or without catalyst[137]) has been successfully used for the polynitration of aromatic compounds.

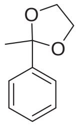
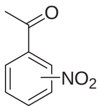
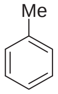
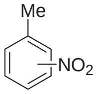
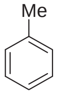
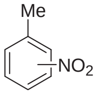
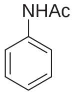
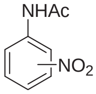
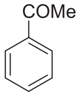
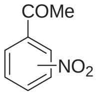
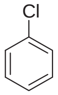
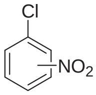
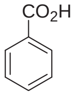
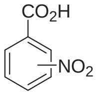
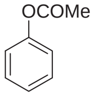
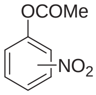
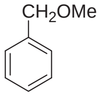
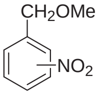
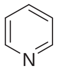
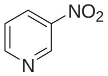
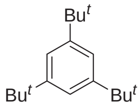
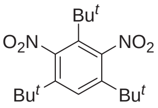
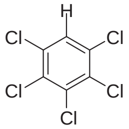
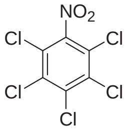
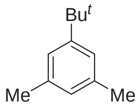
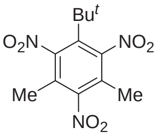
Thermally stable and neat N_2O_4 is produced when incorporated onto a solid support. This is achieved by mixing it with organic materials such as metal nitrates. N_2O_4 supported on polyethylene glycol was reported to be a suitable reagent for the selective nitration of phenols.[138] In addition, the metal nitrate N_2O_4 adducts, such as $Cr(NO_3)_2 \cdot 2N_2O_4$,[139] $Cu(NO_3)_2 \cdot N_2O_4$[140] and $2Fe(NO_3)_3 \cdot 3N_2O_4$,[140,141] are satisfactory agents for this purpose. $Zn(NO_3)_2 \cdot 2N_2O_4$ was used in the mono-, di- and tri-nitration of phenols and the mono- and di-nitration of substituted phenols.[142] It was demonstrated that the selectivity of this reaction is improved by providing a charcoal support for $Zn(NO_3)_2 \cdot 2N_2O_4$ (Table 7).

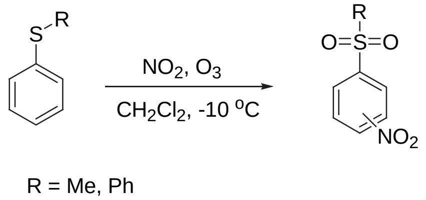
Table 8 provides the results for different forms of N_2O_4 in the mononitration of phenol. In this table *ortho*-nitrophenol was obtained with 98% selectivity, using N_2O_4 in pyridine and this is an outstanding result.[143]

2.2. Nitroalkyl synthesis

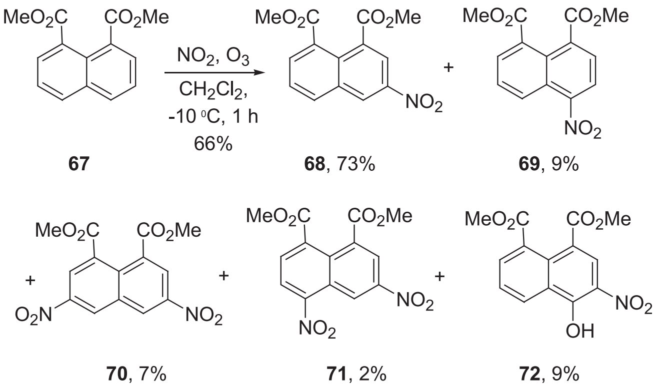
Nitroalkyl compounds can be synthesised from the reaction of NO_2 and alkanes, alkenes or alkynes by different pathways. Usually, nitration of alkanes is more difficult than alkenes or alkynes.

Table 6
Nitration of aromatic compounds with NO_2/O_3 system under various conditions

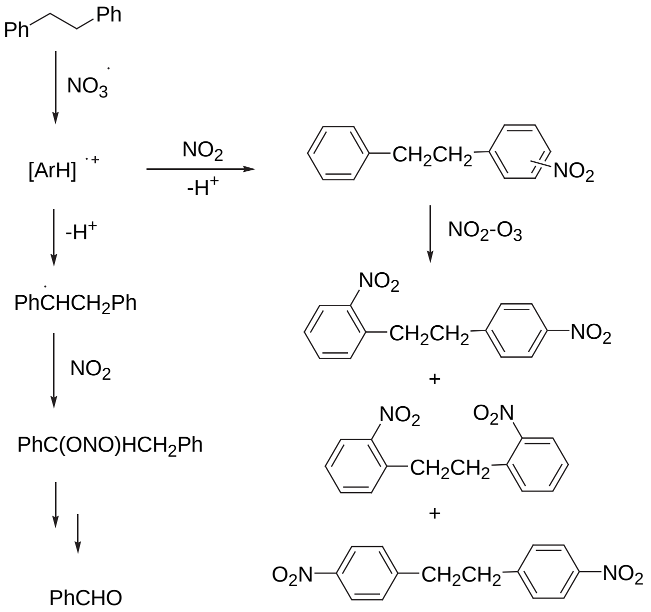
Substrate	Conditions and Ref.	Product	Yield (%)	Total yield (%)
	CH_2Cl_2/0 °C[118]		*o*-22 *m*-19 *p*-59	58
	CH_2Cl_2/0 °C[119]		*o*-51 *m*-6 *p*-43	99
	CH_2Cl_2/0 °C pyridine (3 equiv)[119]		*o*-22 *m*-66 *p*-13	21
	CH_2Cl_2/0 °C[120]		*o*-81 *p*-19	98
	CH_2Cl_2/−10 °C[113]		*o*-52 *m*-48	99
	CH_2Cl_2/0 °C[111]		*o*-43 *m*-1 *p*-56	97
	$ClCH_2CH_2Cl$/0 °C[121–123]		*o*-29 *m*-69 *p*-2	98
	CH_2Cl_2/0 °C[124]		*o*-60 *p*-40	100
	CH_2Cl_2/0 °C[125]		*o*-69 *m*-4 *p*-27	99
	(1) CH_2Cl_2/−78 °C (2) aq $NaHSO_3$[126,127]		63.8	63.8
	CH_2Cl_2/−10 °C[128]		83	83
	CH_2Cl_2/5 °C/$MeSO_3H$[129]		97	100
	*n*-Hexane/−10 °C[130]		97	97



Scheme 17.



Scheme 18.

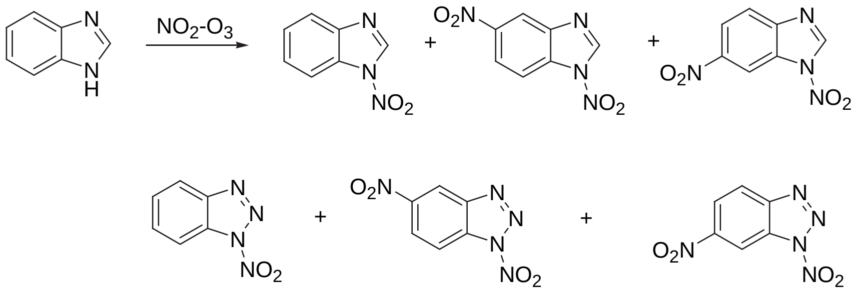


Scheme 19.

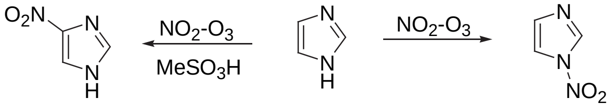
Currently, nitration of light alkanes by nitrogen dioxide or nitric acid is achieved at higher reaction temperatures (200–350 °C) to generate thermal alkyl radicals through the C–H bond scission of alkanes.[148] It has been reported that the nitration of propane with NO_2 at 300 °C produces 1- and 2-nitropropanes along with cleaved nitro compounds such as nitroethane and nitromethane.[148] Studies to improve the yield and selectivity of alkane nitration have made use of additives such as oxygen, ozone, or halogen. These additives not only promote the generation of alkyl radicals but also the production of oxygenated or halogenated by-products.[149–152]

In another attempt, H_2O_2 was used for the activation of NO_2 in the reaction with alkanes to form nitroalkanes.[153]

Sodium salts of 1,3,5,7-tetranitrocubane **73** and 1,2,3,5,7-pentanitrocubane were successfully nitrated with N_2O_4 in THF at low temperature (Scheme 22).[154] Octanitrocubane was synthesised from a solution of the lithium salt of heptanitrocubane under essentially the same conditions.[155] Such highly nitrated cubanes were



Scheme 20.



Scheme 21.

Table 7
Nitration of phenol with $Zn(NO_3)_2\cdot2N_2O_4$ and $Zn(NO_3)_2\cdot2N_2O_4$/charcoal in EtOAc at room temperature

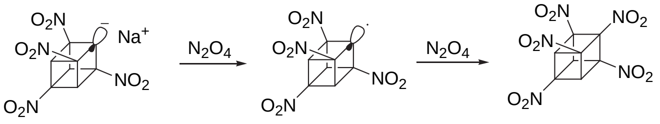
Time[a]	Reagent/subs.	Yield (%)	Distribution of products (isolated yield %)[a,b]			
			2-Nitro	4-Nitro	2,4-Dinitro	2,4,6-Trinitro
1 h (5 min)	1	90 (95)	34 (38)	56 (49)	—	—
4 h (15 min)	2	85 (79)	—	—	85 (79)	—
12 h[c] (15 min)	3	Trace (86)	—	—	—	Trace (86)

[a] Data in parentheses refer to use of $Zn(NO_3)_2\cdot2N_2O_4$; data without parentheses refer to reaction with $Zn(NO_3)_2\cdot2N_2O_4$/charcoal.
[b] In both reactions, 5–8% benzoquinone also isolated.

Table 8
Comparison of data for mononitration of phenol with N_2O_4 complexes

Reagent/conditions	*ortho* (%)	*para* (%)	Ref.
Py/N_2O_4	98	<1	143
$Cr(NO_3)_2\cdot2N_2O_4$	40	59	139
$Fe(NO_3)_3\cdot1.5N_2O_4$	36	62	141
$Cu(NO_3)_2\cdot N_2O_4$	39	58	141
$N_2O_4/CHCl_3$	49.8[a]	1.7	144
$Zn(NO_3)_2\cdot2N_2O_4$	38	49	142
$Zn(NO_3)_2\cdot2N_2O_4$-charcoal	34	56	142
Silica/tetraethylene glycol ether/N_2O_4	40	60	145
$[NO^+18\text{-Crown-6}(HNO_3)_3^-]$	35	58	146
Silica acetate/N_2O_4	33	53	147

[a] 2,4-dinitrophenol 44.2% and 2,4,6-trinitrophenol 4.4% were produced.



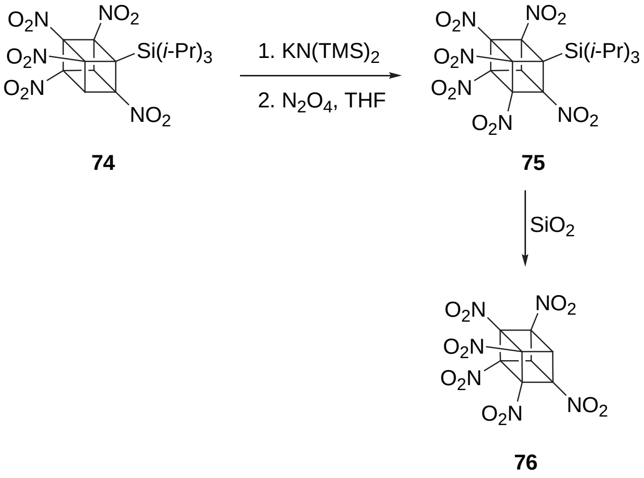
73

Scheme 22.

predicted to be shock insensitive, very dense, high-energy compounds with great potential as explosives and propellants.[156] Unfortunately, the X-ray structure of octanitrocubane demonstrated that the density of the crystal was not high enough for a revolutionary new explosive.[156]

A similar metallation/nitration on the TIPS-substituted pentanitrocubane **74** provides a new method for the preparation of hexanitrocubane **76**. An anion generated from **74** and potassium bis(trimethylsilyl)amide followed by nitration with N_2O_4 gives a mixture of **74** and **75**, in a 40:60 ratio, by ^1H NMR analysis. Surprisingly, column chromatography of a mixture of **74** and **75** on silica gel selectively removed the TIPS group from **75**. The liberated hexanitrocubane **76** has then been easily separated on the column in 30% isolated yield (Scheme 23).[157]

Nitration of cubane-1,4-dicarboxylic acid dimethyl ester by N_2O_4 at −20 °C has also been reported.[158]

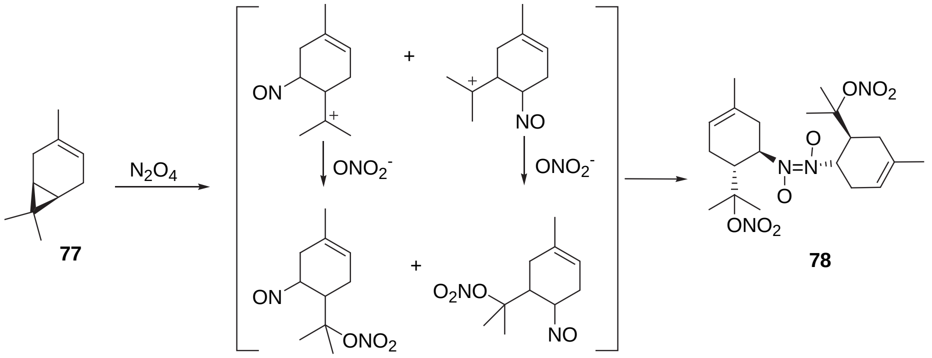


Scheme 23.

Perfluoroalkyl compounds such as CF_3NO_2,[159] and $C_3F_7NO_2$[160] were, respectively, synthesised from the direct photolysis of CF_3I and C_3F_7I when exposed to NO_2.

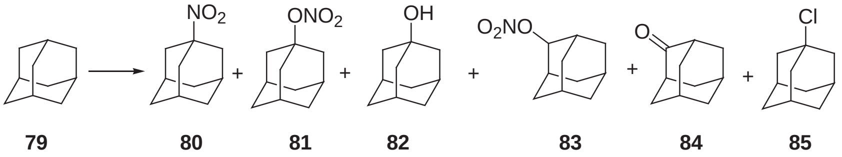
3-Carene **77** during exposure to N_2O_4 and zeolite HY yields *N*-[(1*R*,6*R*)-3-methyl-6-(1-methyl-1-nitroxyethyl)-cyclohex-3-enyl]-*N*′-[1*S*,6*S*]-4-methyl-6-(1-methyl-1-nitroxyethyl)cyclohex-3-enyl]-*E*-diazene-*N*,*N*′-dioxide **78** in 30% yield (Scheme 24).[161,162] Without zeolite HY and with K-10 clay, the yields attained were 27 and 18%, respectively.

Adamantane was nitrated with nitrogen dioxide[163] and also with the NO_2/O_3 system.[164] Recently, it was reported that ozone active nitrogen dioxide is able to nitrate adamantane and its derivatives at the bridgehead position as the major product. During the optimisation of the reaction conditions, it was found that dichloromethane is the best solvent for the reaction with the NO_2/O_3 system (Table 9).



Scheme 24.

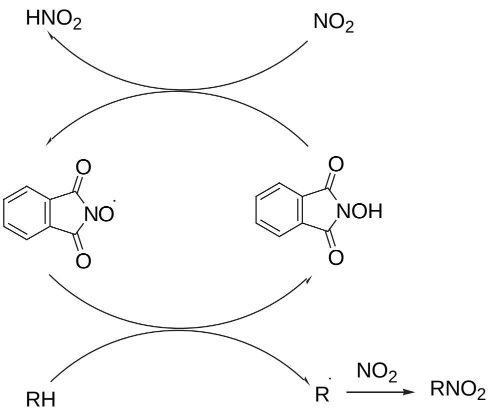
Table 9
Effect of solvents on product distribution in *Kyodai* nitration of adamantane



Solvent	Temp (°C)	Conversion (%)	Yield (%)					
			80	**81**	**82**	**83**	**84**	**85**
CH_2Cl_2	−78	100	82	10	1	1	1	—
C_6H_{14}	−78	85	46	17	19	<1	1	—
CCl_4	−20	64	10	3	<1	2	<1	49
MeCN	−30	31	23	5	1	1	<1	—
$MeNO_2$	−20	28	22	5	<1	1	<1	—

As expected, the ease of the reaction was largely dependent on the temperatures employed, but, quite interestingly, the reaction became faster as the temperature was lowered.[165]

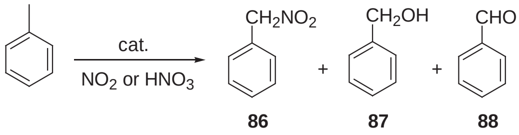
The nitration of adamantane and cyclohexane with NO_2 in the presence of *N*-hydroxyphthalimide (NHPI) has also been investigated by Ishii and his group. In this reaction, NO_2 homolytically abstracts H from NHPI.[166,167] In the next step, the formed NPI radical abstracts a radical H from the alkane feedstock followed by the reaction of alkane radical with NO_2 to produce nitroalkane (Scheme 25). The synthesis of multinitro adamantane as a potential high-energy material was also attempted.[156]



Scheme 25.

Alkylbenzenes such as toluene are selectively nitrated with NO_2 on the alkyl chain without ring nitration being observed. The reaction is catalysed by NHPI (Table 10).[168] The reaction provides an efficient and selective method for the nitration of light aromatic alkanes.

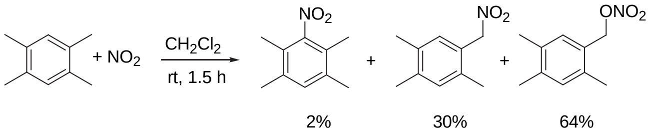
Table 10
Selective alkyl chain nitration versus ring nitration[a]



Run	Catalyst	Method/Temp (°C)/time (h)	Yields (%)		
			86	**87**	**88**
1	NHPI	A/60/5	60	21	19
2	NAPI	A/60/15	11	3	4
3	NHPI	B/60/5	46	14	19
4	NAPI	B/90/15	68	14	13
5	NHPI	B/90/5	43	11	23
6	NAPI	C/90/15	13	Trace	Trace

[a] Method A: toluene (5 ml) reacted with concentrated HNO_3 (1.5 mmol) and NHPI or NAPI (0.2 mmol) under argon. Method B: toluene (5 ml) reacted with NO_2 (3.2 mmol) and NHPI or NAPI (0.6 mmol) under air. Method C: toluene (3 mmol) reacted with NO_2 (3.2 mmol) and NHPI (0.6 mmol) under air in $PhCF_3$ (5 ml).

Thermal and photochemical activation of charge-transfer complexes from polymethylbenzenes (hexamethylbenzene to toluene) and N_2O_4 mainly lead to nitro functionalisation of the alkyl chains. These reactions were investigated in detail by Bosch and Kochi (Scheme 26).[169]



Scheme 26.

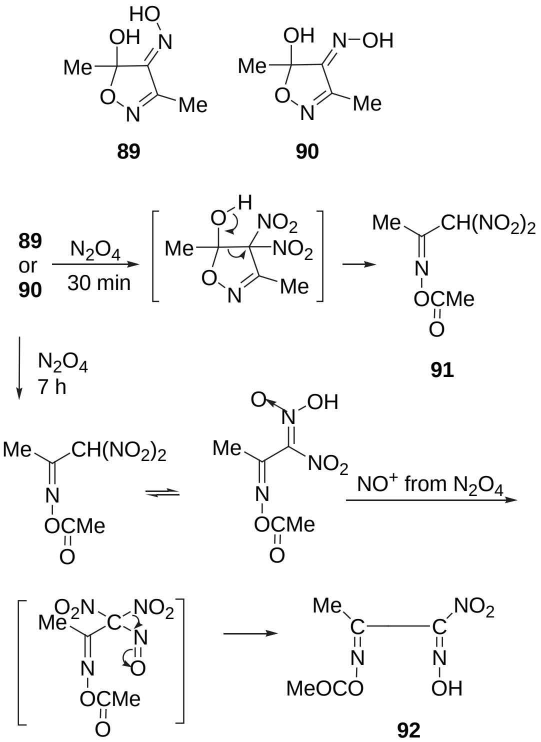
Banus reported the reaction of silver perfluorobutyrate with nitrogen dioxide from which decarboxylation occurs in a sealed tube at 200 °C.[160] This reaction affords a small amount of 1-nitroperfluoropropene. Scribner performed a related study using carboxylic acids instead of their salts (Table 11).[170]

Table 11
Preparation of 1-nitrofluoro alkanes from fluorocarboxylic acid

Acid	NO_2/acid	Temp (°C)	Time (h)	Product	Yield (%)
CF_3CO_2H	6	200	6	CF_3NO_2	30
$ClCFHCF_2CO_2H$	3	180	4	$ClCFHCF_2NO_2$	5
$H(CF_2)_4CO_2H$	5	160	6	$H(CF_2)_4NO_2$	30
$C(CF_2)_5CO_2H$	8	160	6	$C(CF_2)_5NO_2$	15
$F_3C(CF_2)_6CO_2H$	7	150	2	$F_3C(CF_2)_6NO_2$	10–15

An alternative method for the preparation of nitroalkanes is the oxidation of nitrosoalkanes.[171,172] In a similar method, CF_3NO_2 was prepared by means of laser-induced photoreaction of CF_3NO with NO_2.[173]

The group of Gasco found that 5-hydroxy-3,5-dimethyl-4-oximido-2-isoxazoline stereoisomers **89** and **90** in the presence of N_2O_4 give **91** after 30 min. When the reaction of **89** or **90** is carried out for 7 h, white crystals of **92** are obtained (Scheme 27).[174]



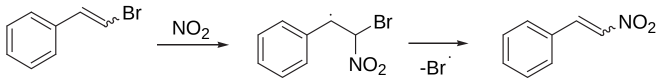
Scheme 27.

The addition of N_2O_4 to olefins has been well investigated and usually yields vicinal dinitroalkanes, nitronitrites (often hydrolysed to nitro alcohols) and nitronitrates (Scheme 28).[175–179]

Pryor et al. demonstrated that the reaction of NO_2 with olefins is first order for the alkenes.[180] At high concentrations of NO_2/N_2O_4, a first order kinetic dependence for N_2O_4 and second order for NO_2 is observed. As the concentration of NO_2/N_2O_4 approaches zero, the kinetic order in NO_2 approaches unity. These workers suggested two distinct reaction pathways, one involving the diamagnetic dimer, N_2O_4, in an addition mechanism and the other(s) involving the paramagnetic monomer, NO_2. The reaction of the monomer proceeds, at least in part, through abstraction of allylic hydrogen atoms.

Since air contains NO_2, polyunsaturated fatty acids (PUFA) in the lungs react with NO_2 delivered by breathing. This is a similar addition process to that which is responsible for the initiation of PUFA autooxidation. The reaction of N_2O_4 with PUFA is therefore an attractive field of study.[181,182]

Fluoroolefins with the general structure, $CF_2CH{=}CF_2$, react with N_2O_4 and form (after hydrolysis) the nitro alcohols, $CF_2CHOHCF_2NO_2$, and α-hydroxy carboxylic acids, $CF_2CHOHCO_2H$.[183] β-Bromostyrene is an alternative vinyl derivative, which reacts with NO_2 to produce β-nitrostyrene as the major product (Scheme 29).[184]



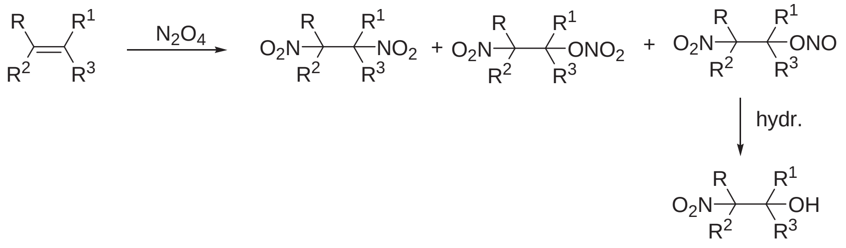
Scheme 29.

Styrene in the reaction with NO_2 yields several products [PhCHO, PhCOCN, $PhCO_2H$, $PhCH{=}CHNO_2$, $PhCOCH_2NO_2$ and $PhCH(OH)CH_2NO_2$] that can be explained by a radical addition mechanism of two NO_2 molecules.[185]

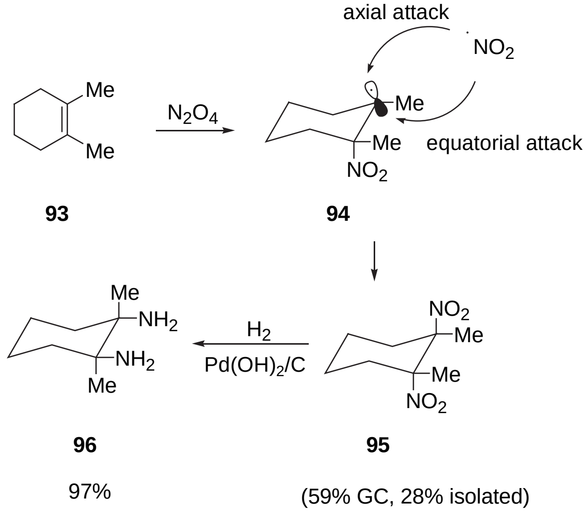
In the case of stereoselective nitration of alkenes, N_2O_4 is added to 1,2-dimethylcyclohexene **93**, which leads to the corresponding dinitro compound with a high ratio of the trans form of **95** (>30:1). Catalytic hydrogenation of the produced compound with $Pd(OH)_2$ on carbon affords a quantitative yield of (*d*,*l*)-1,2-diamino-1,2-dimethylcyclohexane **96**. The latter is resolved into pure enantiomers via co-recrystallisation with mandelic acid (Scheme 30).[186] The stereoselectivity may be rationalised with the help of Shechter's proposed free-radical addition mechanism of N_2O_4 to alkenes, with a free and relatively long-lived tertiary radical **94** undergoing the less hindered axial attack by NO_2 to afford **95** (Scheme 30).[177]

A synthesis of nitroolefins from olefins and N_2O_4 via the addition of two NO_2 groups and elimination of HNO_2 was developed by Seifert.[187,188] A similar pathway was suggested for the reaction of 1-isopropenylcarborane **97** with N_2O_4 to give the dinitro and nitronitrito intermediate **98**. When **98** is treated with silica gel, the corresponding nitroolefin **99** and β-nitroalcohol **100** are obtained (Scheme 31).[189]

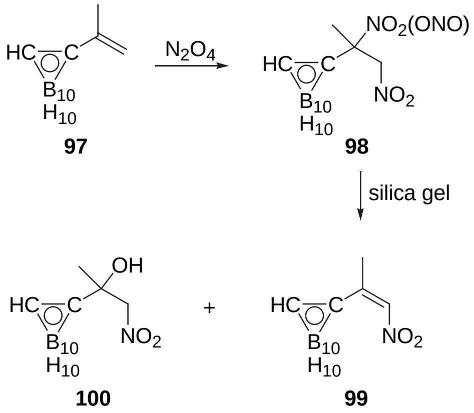
Treatment of α-acylstilbenes with N_2O_4 yields the corresponding *Z*-α-acyl-β-nitrostilbenes; chemical or electrochemical reduction of these stilbenes leads to trisubstituted isoxazoles in good yields (Scheme 32).[190]



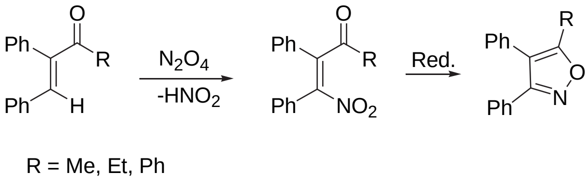
Scheme 28.



Scheme 30.



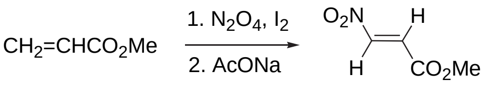
Scheme 31.



Scheme 32.

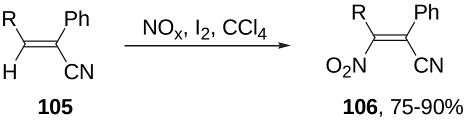
By applying the *Kyodai* method to the styrene derivative **101** in dichloromethane at 0 to −20 °C the corresponding isomeric nitro-nitrato adducts **102** and **103** were obtained in excellent combined yield.[191] The β-nitro-α-nitrato adduct **103** easily eliminates nitric acid by the action of a weak base such as sodium hydrogen carbonate or alumina, giving the corresponding β-nitrostyrene **104** in good yield (Scheme 33).

Methyl 3-nitroacrylate, which is a very important reagent in organic synthesis, has been prepared by the reaction of methyl acrylate with N_2O_4 in the presence of iodine, followed by subsequent treatment with sodium acetate (Scheme 34).[192] It is most likely that NO_2 and iodine are added in the first step, whilst HI is eliminated with base (AcONa) in the second step.



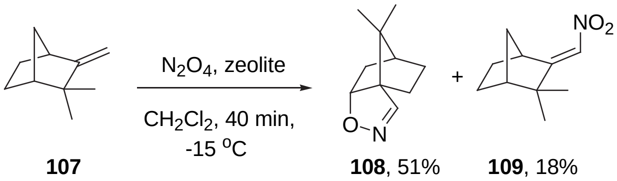
Scheme 34.

In a similar reaction, α,β-unsaturated nitriles **105** are treated with nitrogen oxides in the presence of iodine in carbon tetrachloride at −5 °C to exclusively give the corresponding nitroolefins **106** with *Z*-geometry about the double bond in yields of 75–90% (Scheme 35).[193]

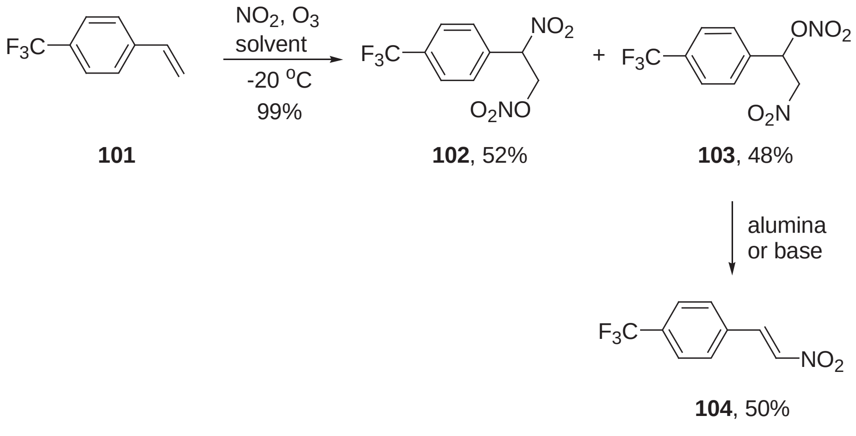


Scheme 35.

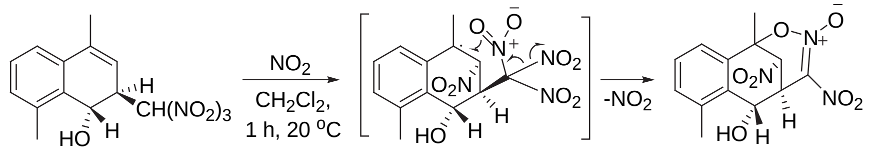
The interaction of camphene **107** with N_2O_4 in the presence of zeolites leads to a mixture of isoxazoline **108** in 51% yield and the nitrovinylcamphene adduct **109** in 18% yield (Scheme 36).[194]



Scheme 36.



Scheme 33.



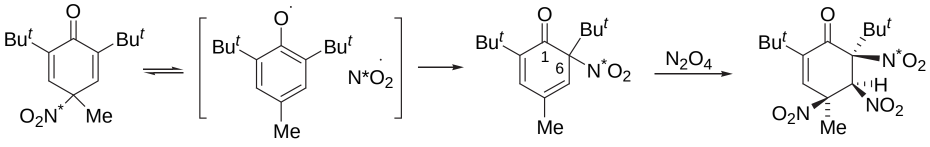
110 **111** **112**

Scheme 37.

Nitration concurrent with intramolecular cyclisation has been reported for the trinitro compound **110** in a solution containing dilute NO_2 to produce the nitronic ester **112** in quantitative yield via the formation of the radical nitro intermediate **111** (Scheme 37).[195] The reaction is light sensitive and should be performed in the dark.

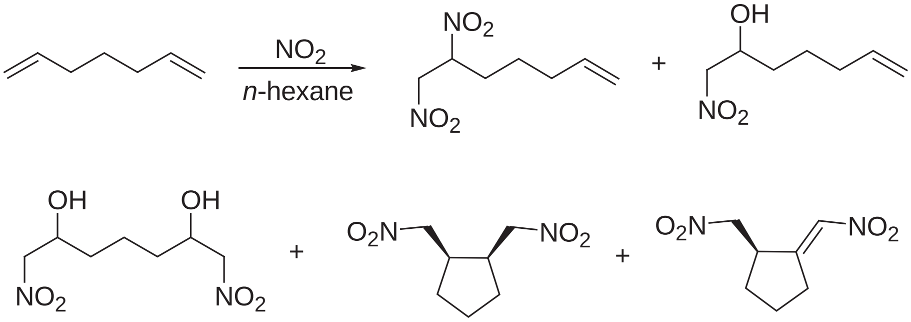
Hartshorn et al.[196] performed an extensive study on the mechanism of addition of N_2O_4 to phenol derivatives. They reported that the hindered trinitro compound **115** is obtained via the migration of N^*O_2 from the 4-position to the 6-position.[197] They demonstrated this migration reaction by the addition of ^{15}N-labelled N_2O_4 to 2,6-di-*tert*-butyl-4-methyl-4-nitrocyclohexa-2,5-dienone **113** with subsequent addition of NO_2 to carbons 4 and 5 of **114** (Scheme 38).

The reaction of conjugated alkenes with nitrogen dioxide has also been investigated and it was shown that the reactivity of the conjugated dienes is greater than that of mono alkenes.[198–200] In this way, Ridd et al. reported the reaction of nitrogen dioxide with conjugated dienes in organic solvents to produce 1,4-dinitro compounds and 1,4-nitro alcohols as the major products.[201] With the unconjugated hepta-1,6-diene, addition can be controlled to occur at both double bonds, but when 2 equiv of nitrogen dioxide is added very slowly, the main products derive from addition to one double bond and cyclisation to form *cis*- and *trans*-1,2-bis(nitromethyl)cyclopentane (Scheme 39).[201]



113 **114** **115**

Scheme 38.



Scheme 39.

Significant evidence suggests that the presence of molecular oxygen alters the course of the olefin–dinitrogen tetroxide addition–elimination reaction. It was reported[202–204] that oxygen greatly increases the yield of β-nitroalkyl nitrates (minor products in the absence of oxygen) and concurrently reduces the yield of dinitro adducts. This effect is enhanced with increasing the oxygen concentration.[205] In addition, oxygen is consumed at a measurable rate by the olefin and nitrogen dioxide solution in this manner.[206] The reaction of olefins with N_2O_4 in the presence of O_2 was investigated in nonpolar media at 0 °C and it resulted in the formation of β-nitroalkyl peroxynitrates. These materials are moderately stable at 0 °C, but rapidly decompose at room temperature to the corresponding α-nitro ketones (Scheme 40).[207]

Anodic oxidation of N_2O_4 to NO_2^+ is achieved in a solution of acetonitrile; this reagent effectively nitrates a range of organic substrates including aromatics, silylenol ethers, alkenes and dienes to the corresponding nitroaromatics, α-nitro ketones, vicinal nitroamides and nitroacetamides.[208–210]

In the case of the nitration of hydrazone derivatives, 2,4-diphenylhydrazones are rapidly oxidised by nitrogen dioxide to the nitroazo compound **116**, in good yields (Scheme 41).[211]

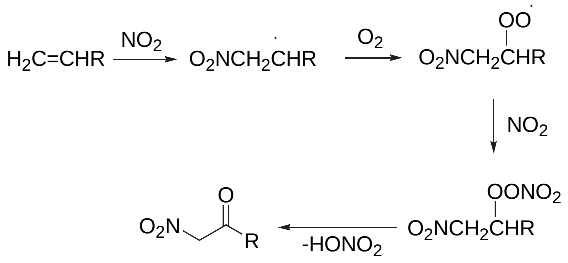
Only a few reports on the reaction of N_2O_4 and alkynes are found in the literature. It has been reported that the addition of N_2O_4 to acetylenes yields *cis*- and *trans*-dinitroolefins.[212,213] N_2O_4 and metal acetylides yield *E*- and *Z*-1,2-dinitroalkenes.[214]

3. Nitrosation reactions

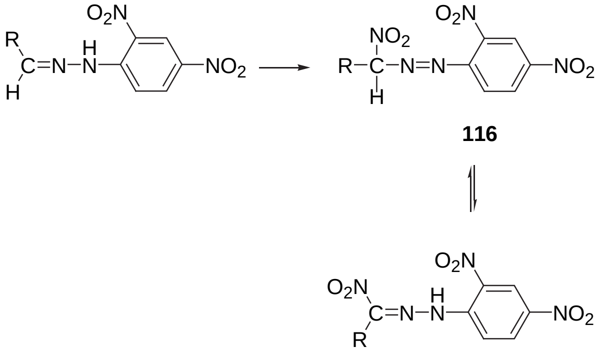
Nitroso compounds such as *C*-, *N*-, *O*- and *S*-nitroso analogues serve as potential nitric oxide donors and will be considered in this section. The chemistry and biochemistry of nitric oxides have been considered to be a very important research area in recent years.[1,215] Some related nitrosation reactions such as diazotisation are also covered.

3.1. C-Nitrosation

Kochi's group performed an interesting study in which they found that quinone dioximes are converted into the monomeric

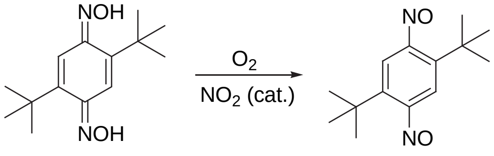


Scheme 40.



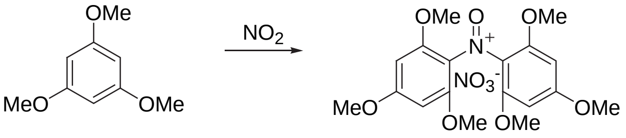
Scheme 41.

dinitrosobenzenes with O_2 in the presence of a catalytic amount of nitrogen dioxide (Scheme 42).[216]



Scheme 42.

1,3,5-Trimethoxybenzene gives bis(2,4,6-trimethoxyphenyl) nitrosonium nitrate **117** in quantitative yield as a result of the initial nitrosation step followed by coupling of the two aromatic moieties through the nitrosonium ion (Scheme 43).[217]

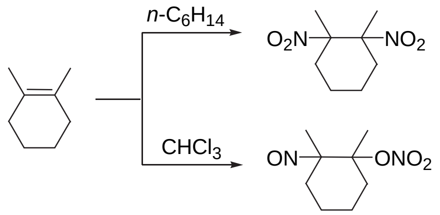


117

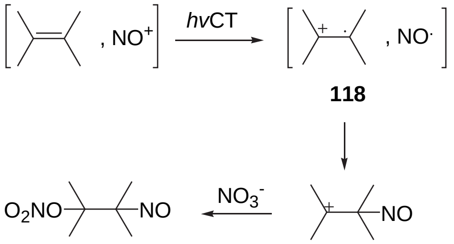
Scheme 43.

Alkenes can yield nitroso nitrates at low temperature with liquid ethane/propane as the solvent.[218] Recently, Ridd et al. have shown that the reaction with hexenes in *n*-hexane yields a dinitro compound as the major product with smaller amounts of nitronitrite and nitroalcohol, whereas, in chloroform, the main product is the nitrosonitrate (Scheme 44).[219]

Complexes of different alkenes with N_2O_4/SbF_5 were investigated by Bosch and Kochi.[220] The photochemical activation of these complexes leads to the generation of the corresponding radical cations. Thus, irradiation of 2,3-dimethylbut-2-ene and N_2O_4 in a matrix at the frequency corresponding to the charge-transfer band (νCT) at 75 K affords a radical cation pair of the type **118** (Scheme 45).[220,221] The subsequent reaction of the radical cation of 2,3-dimethylbut-2-ene with nitric oxide gives rise to the 1-nitroso-2,3-dimethylbut-2-yl cation, which reacts with the NO_3^- anion to form nitrosonitrate.



Scheme 44.



Scheme 45.

A similar reaction was initiated by the addition of a small quantity of nitrogen dioxide, which produced β-nitroalkyl radicals that were detected by electron paramagnetic resonance (EPR) measurements.[222] These radicals were then captured by nitric oxide to give the nitrosonitroalkane. The reactions of alkenes with nitrogen oxides and other nitrosating (and nitrating) agents have been reviewed in 2003.[223]

Metal acetylides **119** with N_2O_4 yield nitrosoacetylenes **120** and/or 1-acetylenyl nitrites **121** (Scheme 46).[214]

$$\underset{\mathbf{119}}{R{-}C{\equiv}CM} \xrightarrow{N_2O_4} \underset{\mathbf{120}}{R{-}C{\equiv}C\text{-}NO} \text{ and/or } \underset{\mathbf{121}}{R{-}C{\equiv}C\text{-}ONO}$$

M = metal

Scheme 46.

The reaction of acetylated glycals with N_2O_4, depending on the reaction conditions, can give either acetylated 2-deoxy-2-nitroso-α-D-aldopyranosyl nitrates as dimers or acetylated 2-nitroglycals.[224]

3.2. N-Nitrosation

Apart from the wide range of biological applications of *N*-nitroso compounds, they have also been used as reagents and intermediates for the introduction of various important materials.[225–230] Although other *N*-nitrosating agents are used, N_2O_4 is one of the most common reagents for the production of these materials.[227,231–235]

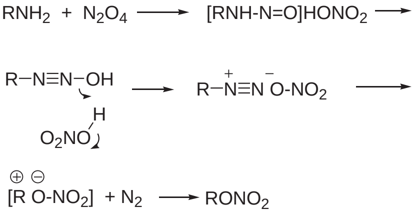
The reaction of N_2O_4 with primary aromatic amines usually gives the diazonium nitrite but the corresponding aliphatic compounds give a variety of nitrosation products for alkylammonium nitrites, alkyl nitrites, and alkenes.

The kinetics of the nitrosation reaction of aniline by N_2O_4 in non-aqueous solvents with electron-donating atoms, e.g., acetonitrile or ethyl acetate, was reported.[236] The reaction is first order with respect to N_2O_4 and zero order with respect to aniline in each of the donor solvents added.

The mechanism of nitrosation for primary and secondary amines by gaseous N_2O_4 and N_2O_3 in aqueous alkaline solutions was studied by Challis et al.[235,237] In 1977, Challis and Kyrtopoulos demonstrated that the formation of nitrosamines from various amines and NO_2 under neutral and basic conditions was 2000-fold faster than the corresponding reaction with H_2O in pH 7–14 to yield nitrites and nitrates.[238]

The preparation of nitrato compounds via the nitrosation–deamination of amines in the presence of N_2O_4 is shown in Table 12 and has been reported by Wudl and Lee. They found that this process is strongly dependent on the reaction media (Table 12).[239]

Table 12
Deamination of $PhCHMeNH_2$ during nitrate production

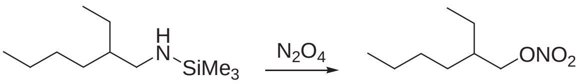


Solvent	Temp (°C)	Yield (%)
THF	−60	80–90
Et_2O	−60	70
CH_2Cl_2	−65	15[a]
CH_3CN	−30	40
H_2O	0	3[b]
CH_3CO_2H	25	Trace[c]
DMF	−30	44[d]

[a] Major products nitroamine, alkylammonium nitrate and alkylammonium nitrite.
[b] Alcohol (7%), 4% ketone, and 86% alkylammonium salts (recovered as pure amine).
[c] Acetate (50%).
[d] Formate ester (15%), 9% alcohol.

Barton and Narang showed that N_2O_4 converts primary amines into the corresponding nitrato esters.[240] Addition of an amidine base was found to improve the yield of the nitrate ester and significantly reduce the formation of olefins.

In a related study, Wudl and Lee found that the treatment of *N*-2-ethylhexyl-*N*-trimethylsilylamine with N_2O_4 affords 2-ethylhexyl nitrate in fair yields (Scheme 47).[241]



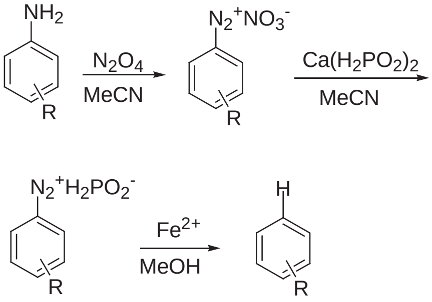
Scheme 47.

Deamination of the amines via N-nitrosation in acetonitrile at −20 °C, followed by treatment with calcium hypophosphite in the presence of methanol and a catalytic amount of iron(II) sulfate at room temperature, results in the reductive removal of the amino group, giving the corresponding arenes in moderate-to-good yield (Scheme 48).[242]

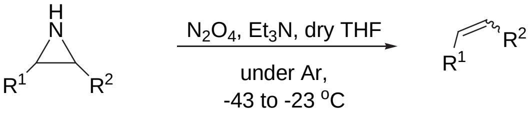
Various aziridines react with N_2O_4 in the presence of Et_3N in dry THF to give the corresponding ethylenes in good-to-excellent yields at −23 °C (or −43 °C) in 10 min under an argon atmosphere (Scheme 49).[243]

Treatment of sulfonamides **122** with N_2O_4 leads to the formation of sulfonate esters **123** via nitrosation and decomposition of *N*-nitrososulfonamides (Scheme 50).[244]

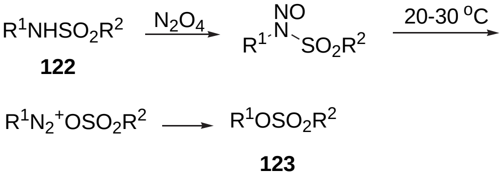
N-Sulfinylamines react with N_2O_4 according to the mechanism presented in Scheme 51 and are converted into aryldiazonium nitrates.[245]



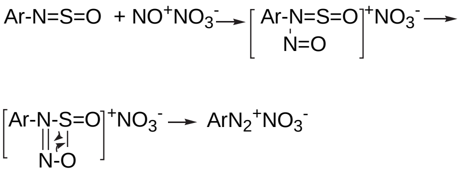
Scheme 48.



Scheme 49.

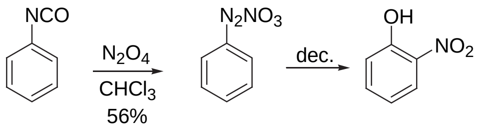


Scheme 50.



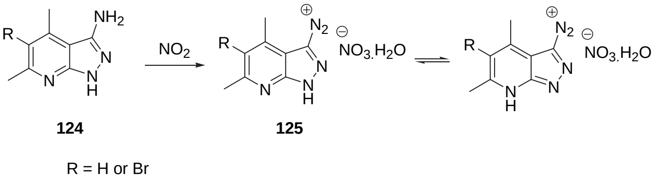
Scheme 51.

Phenyl isocyanate, in chloroform, forms benzenediazonium nitrate in 56% yield (Scheme 52).[246] The latter decomposes slowly, if left in the chloroform solution, to form a tar, from which *o*-nitrophenol was isolated.



Scheme 52.

Kaupp and his group used gaseous NO_2 in the quantitative diazotisation of solid aromatic amines.[247–249] They also developed the diazotisation of **124** with NO_2 in solvent-free conditions (Scheme 53).[250] In this study, the coupling of **125** with (thio)

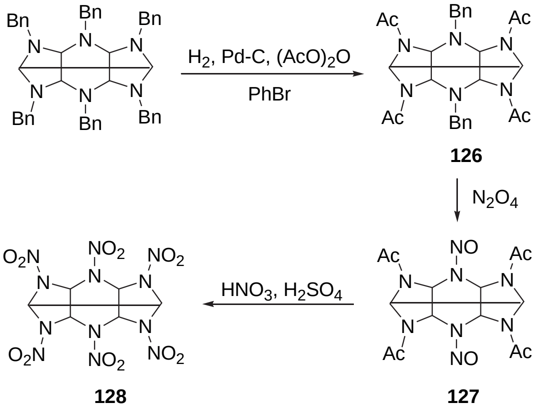


Scheme 53.

barbituric acids, acetoacetanilides, β-naphthol and 2,6-dimethylphenol was investigated.

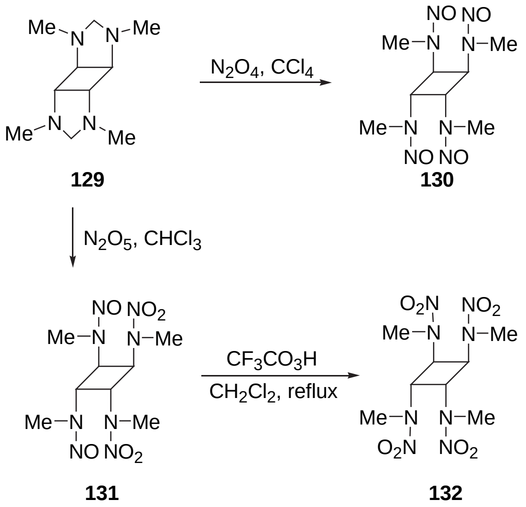
Scribner reported the synthesis of anhydrous diazonium salts from Schiff bases.[251] There are a few reports describing the nitrosolytic dealkylation of tertiary amines upon treatment with N_2O_4.[252–254]

The synthesis of the highly energetic molecule **128**, involving nitrosation of **126** in acetic acid, and nitration of **127** by means of a mixture of HNO_3 and H_2SO_4, was investigated by Latypov et al. (Scheme 54).[255]



Scheme 54.

In the process of nitrosation dealkylation of the tertiary amine **129**, *N*,*N*,*N*′,*N*″-tetramethyl-*N*,*N*,*N*′,*N*″-tetranitroso-1α,2α,3β,4β-cyclobutanetetramine **130** was produced and, via a similar reaction with N_2O_5, formed the dinitrodinitroso derivative **131** (Scheme 55).[256] The latter was converted into the tetranitro compound **132** in the presence of trifluoroperacetic acid.

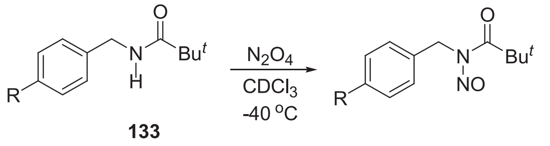


Scheme 55.

It was found that, when *N*-4-R-benzylpivalamides **133** are functionalised with N_2O_4 in $CDCl_3$ at −40 °C, the rate of the nitrosation reaction is increased with electron-donating groups, whereas electron-withdrawing groups decelerate the rate of N-nitrosation (Table 13).[257] In a similar fashion, the nitrosation reaction is accelerated in polar solvents, but is slower in solvents of lower polarity.

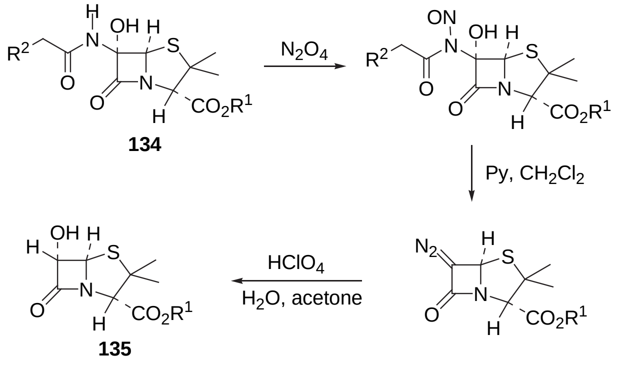
Hydroxypenicillins **135** are formed when their amides **134** are treated with N_2O_4 followed by reaction with a Lewis base and then an acid (Scheme 56).[258,259]

Table 13
Kinetic data for N-nitrosation of **133**[a]



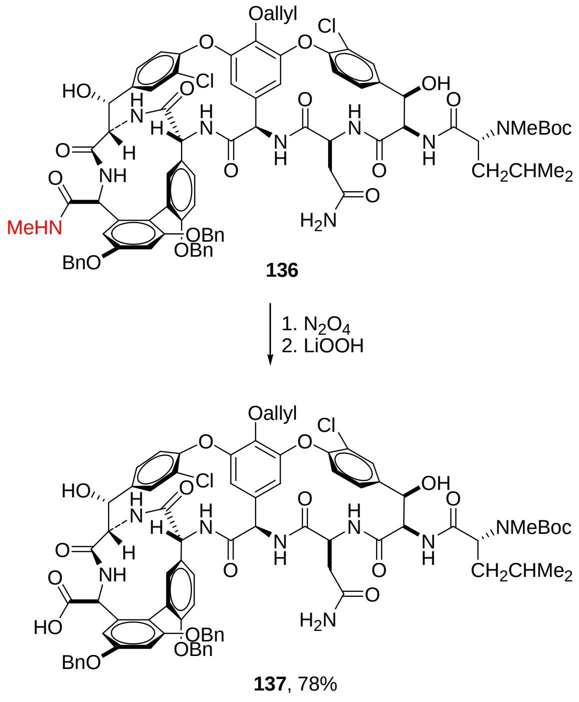
R	k ($\times10^{-2}$ s^{-1})	$t_{1/2}$ (min)	σ_p
MeO	3.33	21	−0.27
Me	2.04	34	−0.14
H	1.23	57	0.00
CF_3	0.344	202	0.53
NO_2	0.179	388	0.78

[a] [Nitrosamide] ~ 0.045 M.



Scheme 56.

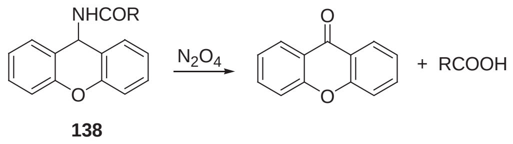
Evans et al. developed a mild method for the saponification of secondary amides **136** to **137** involving N-nitrosation cleavage of the resultant nitrosamide with lithium hydroperoxide (Scheme 57).[260]



Scheme 57.

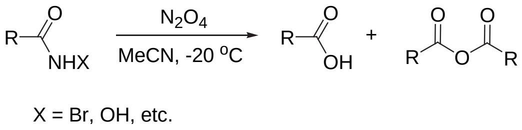
9-Acylamidoxanthenes **138** were converted into both carboxylic acids and xanthone.[261] The reaction is proposed as an alternate approach to carboxylic acid preparation when direct nitrosation of an amide fails. The reaction is shown not to proceed by the usual nitrosoamide decomposition mechanism since the nitrosation of *N*-(9-xanthyl)benzamide-carbonyl-^{18}O produced xanthone containing no oxygen-18, whilst the benzoic acid contained all of the oxygen-18. Mechanistic studies were hampered, owing to the xanthone forming from several different substrates (Table 14).

Table 14
Nitrosation of 9-acylamidoxanthenes **138**



R	Acid	Yield (%)	Xanthone (%)
C_6H_4Me	*p*-Toluic	55	78
OEt	Ethylbicarbonic	95	99
Ph	Benzoic	60	75
1-Naphthyl	1-Naphthoic	50	78
CH_2Ph	Phenylacetic	42	80
$CH(t\text{-}Bu)_2$	Di-*tert*-butylacetic	62	99
CPh_3	Triphenylacetic	40	99

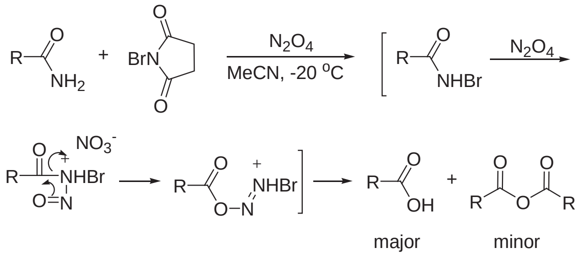
Facile functional-group transformation of carboxamides to acids is achieved with N_2O_4, even related compounds such as *N*-bromoamides and hydroxamic acids are also converted into the corresponding acids and anhydrides (Scheme 58).[262]



Scheme 58.

In a similar study, Kim et al. converted a large variety of benzamides into benzoic acids with N_2O_4 in the presence *N*-bromosuccinimide (NBS) (Table 15).[263]

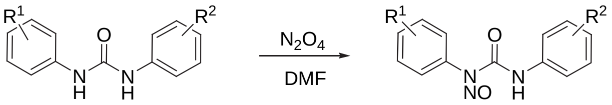
Table 15
Deamination of amides with N_2O_4 and *N*-bromosuccinimide



Amides	NBS (equiv)	N_2O_4 (equiv)	Time (h)	Acid[a] (%)	Anhydride[b] (%)
$PhCONH_2$	1.2	1.8	0.5	96	2
$PhCONH_2$	None	4.0	3.0	86	—[b]
p-Me–$PhCONH_2$	1.2	1.8	0.5	92	6
p-Me–$PhCONH_2$	None	4.0	3.0	85	—[b]
p-Cl–$PhCONH_2$	1.2	1.8	0.5	94	2
p-Cl–$PhCONH_2$	None	4.0	3.0	85	—[b]
o-Me–$PhCONH_2$	1.2	1.8	0.5	94	Trace
p-NO_2–$PhCONH_2$	1.2	2.0	0.5	93	4
p-NO_2–$PhCONH_2$	1.2	2.0	0.5	92	2
p-Br–$PhCONH_2$	1.2	1.8	0.5	95	Trace
p-MeO–$PhCONH_2$	1.2	1.8	0.5	96	Trace

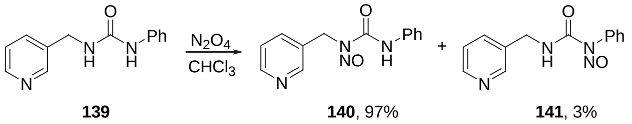
[a] Isolated yield.
[b] Not checked.

The effect of substituent on the nitrosation reaction of 1,3-diarylureas with NOCl, N_2O_4 and N_2O_3 was studied by Miyahara and his group (Scheme 59).[68]



Scheme 59.

It was found that 1-phenyl-3-(3-pyridyl)urea **139** is largely selective for the *N*-nitroso derivative **140** related to **141** (Scheme 60).[264]



Scheme 60.

In addition, the efficient formation of other nitrosoureas, namely **142**,[265] **143**[266] **144**,[267] **145**,[268] **146**,[269] **147**,[270] was reported from the reaction of the corresponding urea-sugars (Fig. 4). The produced nitrosoureas exhibit antitumour activities.

The synthesis and characterisation of *N*-nitrosopeptides[271–273] and *N*-nitrosolactams[274] in the presence of N_2O_4 at room temperature have been reported.

In an alternative approach, Kim et al. provided an efficient method for the synthesis of azides from hydrazines at low temperature (Table 16).[275]

An alternative form of N_2O_4 as $[NO^+ \cdot Crown \cdot H(NO_3)_2^-]$ has been used by Zolfigol et al. for the nitrosation of secondary amines under mild and homogeneous conditions (Scheme 61).[5] An attractive advantage is that the 18-Crown-6 can be recycled and reused.

N-Nitrosation of secondary amines with N_2O_4/pyridine or N_2O_4/triethylamine complexes has been examined (Scheme 62).[276]

Iranpoor et al. have reported N_2O_4 supported on charcoal (Charcoal/N_2O_4)[277] or polyvinylpyrrolidone (PVP/N_2O_4)[278] as heterogeneous, stable and convenient nitrosating agents. The solid support can be recycled. These workers were able to introduce nitroso groups into a large variety of amines, *N*-alkyl amides and *N*-alkylureas. They also converted tertiary amines into the corresponding *N*-nitroso derivatives with a stoichiometric amount of reagents. Dealkylation was achieved with excess of the nitrosating agents (Scheme 63). Selective N-nitrosation of different amines, amides and ureas has also been studied using these reagents (Table 17).[277]

The selective N-nitrosation versus O-nitrosation and oxidation of the hydroxyl group is shown in Scheme 64.[277]

Rudkevich et al. have reported N_2O_4 encapsulated in calix[4] arenes, which were used as selective nitrosation agents (Scheme 65).[279,280]

The same workers also prepared a novel class of stable, mild and size–shape-selective nitrosating agents for secondary amides. These are based on the reversible entrapment and release of reactive nitrosonium species by polymer-[281] or solid-supported calix [4]arenes (Scheme 66).[282]

3.3. O-Nitrosation

Alkyl nitrites or nitrite esters have been known for a long time and are effective nitrosation agents, under diverse reaction conditions.

White reported the effect of temperature on the nitrosation reaction of alkoxide ions in CH_2Cl_2.[283] Whereas at 0 °C the alkyl nitrite is formed, at 80 °C the alkyl nitrate is the main product.

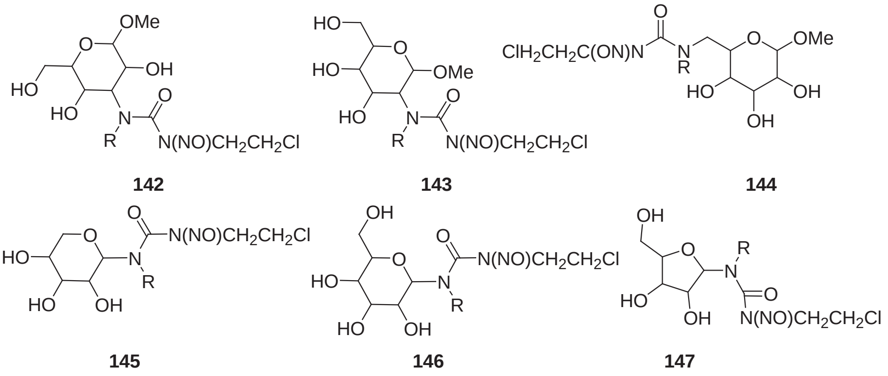
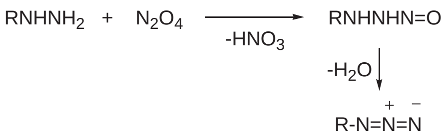
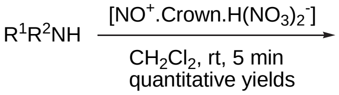


Fig. 4. Structure of nitrosourea-sugars.

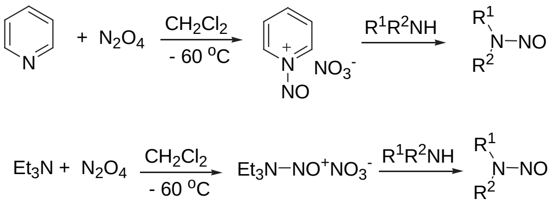
Table 16
Conversion of hydrazines into azides



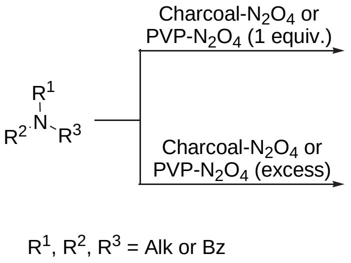
Run	Hydrazine	Temp (°C)	Time (min)	Isolated yield (%)
1	$PhCONHNH_2$	−30	10	91
2	$4\text{-}MePhSO_2NHNH_2$	−20	10	95
3	$PhNHNH_2$	−20	20	87
4	2-Furyl-$CONHNH_2$	−25	20	86
5	*p*-Ph$(CONHNH_2)_2$	−10	10	92
6	$4\text{-}NO_2\text{–}PhCONHNH_2$	−30	10	89
7	4-Cl–$PhCONHNH_2$	−40	20	84
8	2,4-di$NO_2\text{–}PhNHNH_2$	−30	10	90
9	$4\text{-}NO_2\text{–}PhNHNH_2$	−30	10	95



Scheme 61.



Scheme 62.



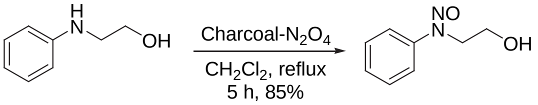
Scheme 63.

Similarly, NO_2 almost exclusively yielded alkyl nitrites in the reaction with alcohols.[284,285]

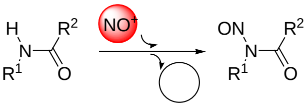
Polynitrito esters (Fig. 5) may be achieved by dissolving cellulose in a solution of N_2O_4 and dimethylformamide.[286]

Table 17
Selective N-nitrosation by PVP/N_2O_4 or charcoal/N_2O_4

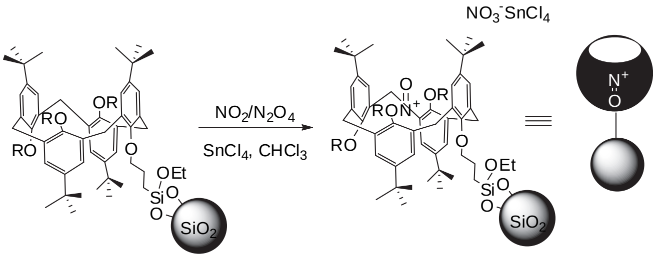
Substrate	Product	Time (min)	GC yield (%)
i-Pr_2NH	*i*-Pr_2NNO	30	98
PhNHMe	PhNHMe		95
Et_2NH	Et_2NNO	30	100
Et_3N	Et_3N		99
Et_2NH	Et_2NNO	20	100
MeCONHMe	MeCONHMe		95
MeCONHMe	MeCON(NO)Me	240	98
MeCONHPh	MeCONHPh		100
MeCONHMe	MeCON(NO)Me	240	95
$MeCONH_2$	$MeCONH_2$		100



Scheme 64.



Scheme 65.



Scheme 66.

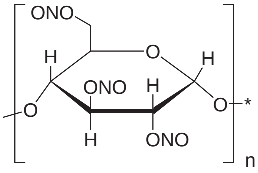
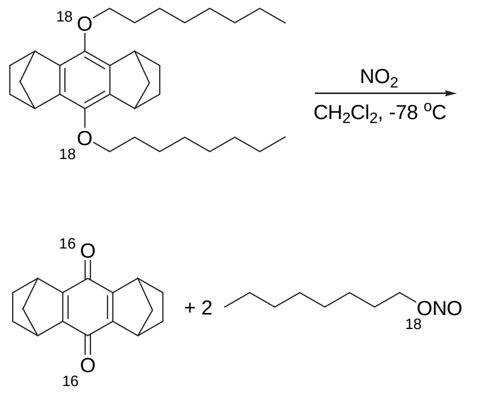


Fig. 5. Structure of polynitroso cellulose.

In the reaction of hydroquinone dialkyl ethers with NO_2, the corresponding quinone and alkyl nitrite were isolated in an inert solvent at room temperature, or even lower temperatures (Scheme 67).[287]



Scheme 67.

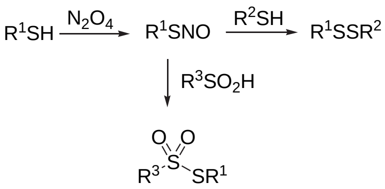
In a stimulating study, Pryor et al. reported a new method for the nitrosation of hydroperoxides with N_2O_4 in which the pernitrite ester is isolated as the major product.[288]

3.4. S-Nitrosation

One of the problems encountered in the synthesis of *S*-nitrosothiols is their low stability and their ease of conversion into the corresponding disulfides, due to the oxidative ability of the reaction media.[289]

The use of gaseous N_2O_4 in an inert solvent at low temperature quantitatively converts thiols into their corresponding *S*-nitrosothiols.[290,291] Additionally, the successful synthesis of thionitrites from thiols was reported with PVP/N_2O_4,[292] and $[NO^+(18\text{-crown-6})H(NO_3)_2^-]$.[293]

Oae and his group found that treatment of sulfinic acid or thiols with N_2O_4 yields unsymmetrical thiolsulfonates and disulfides, respectively (Scheme 68).[291,294] They also prepared symmetrical thiolsulfonates or disulfides from thiols and N_2O_4,[295,296] $[NO^+(18\text{-crown-6})H(NO_3)_2^-]$,[269] or $Cu(NO_3)_2{\cdot}N_2O_4$.[297]

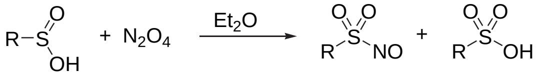


Scheme 68.

Pryor et al. postulated a mechanism for this reaction involving the homolytic dissociation of the RS–NO bond to RS and NO radicals followed by coupling of two RS radicals to form the dimer RSSR (Eq. 4).[298]

$$\text{RS-N=O} \longrightarrow \text{RS}^{\cdot} + {}^{\cdot}\text{NO} \longrightarrow \text{RSSR} \qquad \textbf{(4)}$$

Several sulfonyl nitrites are isolated as brown unstable crystals from sulfinic acids and N_2O_4. Sulfonic acid is formed as a by-product (Scheme 69).[299,300]



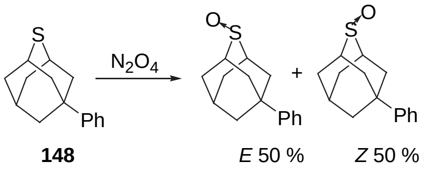
Scheme 69.

4. Oxidation with N_2O_4

4.1. Oxidation of sulfur

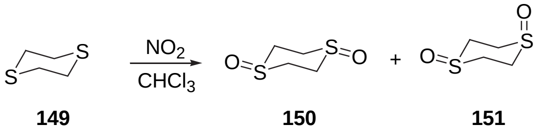
Gaseous N_2O_4 is known to be a useful reagent for the oxidation of sulfides to sulfoxides.[301–305] Various alkyl and aryl thioethers (R_2S) are readily converted in high yields into sulfoxides in the presence of dioxygen and catalytic amounts of nitrogen dioxide.[306] The oxidation of methyl phenyl sulfide by dinitrogen tetroxide has been investigated spectrophotometrically.[307] The reaction follows the equation: Rate=$k[N_2O_4]^{0.5}[RR^1S]$. A mechanism was proposed for this oxidation reaction, which involves the dissociation of N_2O_4 to NO_2 radicals acting as the oxidising species.[307] Photooxidation of dimethyl sulfide (DMS) with NO_2[308,309] and in the presence of oxidant scrubbers[310] was also studied.

The stereochemical oxidation of 5-phenyl-2-thiaadamantane **148** was investigated by Mukherjee and Le Noble. They reported a 50:50 *E*/*Z* distribution for the corresponding sulfides that are formed (Scheme 70).[311]



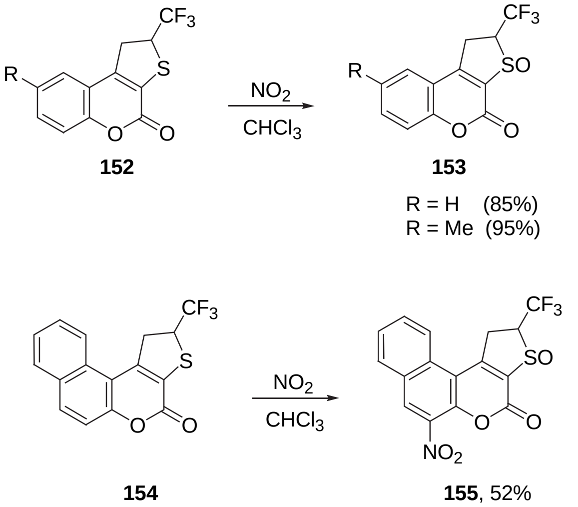
Scheme 70.

Oxidation of 1,4-dithiane **149** to 1,4-dithiane α-disulfoxide (trans isomer) **150** 93–94% and a small amount of 1,4-dithiane β-disulfoxide (cis isomer) **151** 6–7% (Scheme 71) is observed in the presence of N_2O_4, but 1,3,5-trithiane decomposes readily with dinitrogen tetroxide.[312]



Scheme 71.

Coumarins **152** are oxidised to the corresponding sulfoxides **153** in $CHCl_3$ with an excess of NO_2 at room temperature over 4 days in high yields with almost complete chemoselectivity, but coumarin **154** directly gives the nitrosulfoxide **155** under the same conditions (Scheme 72).[313]



Scheme 72.

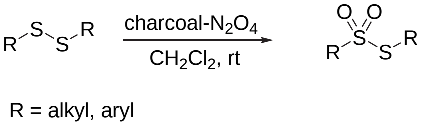
Other forms of N_2O_4 such as acylated silica gel/N_2O_4,[314] [$NO^+\cdot$18-Crown-6$\cdot H(NO_3)_2^-$],[296] $Cu(NO_3)_2\cdot N_2O_4$ and 2Fe $(NO_3)_3\cdot 3N_2O_4$ are efficient oxidants for the selective and quantitative conversion of sulfides into the sulfoxides.[315]

PVP/N_2O_4[292] and charcoal/N_2O_4[6] systems have also been efficiently employed for this purpose. The results of selective oxidation of sulfides with charcoal/N_2O_4 are presented in Table 18.[6]

Table 18
Selective oxidation of binary mixtures of sulfides with charcoal/N_2O_4

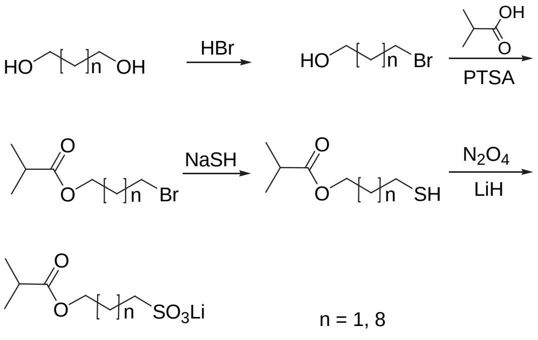
Entry	Substrate	Product	Time (min)	Conversion (%)
1	Et_2S	Et_2SO	20	100
	PhSMe	PhSMe		100
2	*n*-Bu_2S	*n*-Bu_2SO	30	100
	i-PrSPh	*i*-PrSPh		95
3	*n*-Bu_2S	*n*-Bu_2SO	45	100
	PhSEt	PhSEt		92
4	*n*-Bu_2S	*n*-Bu_2SO	45	100
	$PhSCH_2Ph$	$PhSCH_2Ph$		96
5	$(4\text{-MeOPh})_2S$	$(4\text{-MeOPh})_2SO$	30	100
	Ph_2S	Ph_2S		98

Selective oxidation of disulfides to thiosulfonates was also performed with charcoal/N_2O_4. Over-oxidation does not occur at room temperature (Scheme 73).[6]



Scheme 73.

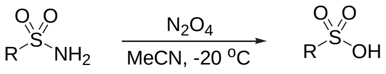
The use of N_2O_4 as a non-aqueous oxidising agent for the synthesis of sulfonic acids has been patented.[316] Kramer and Röder have also described the oxidation of simple aliphatic thiols with the same system.[317] They then, successfully applied this method for the synthesis of a new lyotropic liquid crystal **156** (Scheme 74).



156

Scheme 74.

Kim et al. reported that thiophenol and *para*-methylthiophenol in the presence of excess N_2O_4 (6 equiv) are oxidised to benzenesulfonic acid and *para*-methylbenzenesulfonic acid, respectively, at room temperature.[295] They have also demonstrated that sulfonamides react with N_2O_4 to produce the corresponding sulfonic acids (Scheme 75).[262]



Scheme 75.

4.2. Carbon oxidation

N_2O_4 is frequently used for the oxidation of carbon atoms in various substrates. The most common reaction appears to be the oxidation of alcohols to aldehydes.[318,319] Modified oxidation systems for various classes of hydroxy compounds have been reported with powerful oxidising agents such as charcoal/N_2O_4,[277] 2Fe $(NO_3)_3\cdot 3N_2O_4$ and $Cu(NO_3)_2\cdot N_2O_4$.[320] Secondary fluoro alcohols are oxidised by nitrogen dioxide at 400 °C to give the corresponding fluoro ketones.[321] N_2O_4 has also been employed for the conversion of hydroxyl functional groups into carbonyl groups in mannan and cellulose.[322]

Bozell et al. investigated the oxidation of *para*-substituted phenols to the corresponding benzoquinones in moderate-to-high yield with a catalytic amount of NO_2 (in situ generation from $NaNO_2$ and H^+) in the presense of O_2 in MeOH. Little or no oxidation occurs under an argon atmosphere.[323] Substrates of lower reactivity gave quinones when treated with a stoichiometric amount of NO_2 in CCl_4, but nitration of the aromatic ring became a significant side reaction (Scheme 76).

Kochi has shown that NO_2 oxidation of hydroquinone dialkyl ethers to quinones occurs via a radical cation that results from the reaction of the substrate with the NO_2 disproportionation product $NO^+NO_3^-$.[69,287] The oxidation of hydroquinone was also investigated by the same group.[324,325] The capacity of NO_2 to oxidise 1,2,10-trihydroxyanthracene was studied by Arens et al.[326]

Mehta has used a solution of NO_x in dichloromethane for the deprotection of rigid-cage thioacetals and thioketals **157** to the corresponding carbonyl compounds **158** (Scheme 77).[327]

An SiO_2/N_2O_4 system (N_2O_4 impregnated onto silica gel),[328] [$NO^+\cdot$crown$\cdot H(NO_3)_2^-$],[296] $Fe(NO_3)_3\cdot 1.5N_2O_4$ and $Cu(NO_3)_2\cdot N_2O_4$[329] were used as alternative and powerful oxidation agents for the conversion of cyclic dioxalanes and dithianes (ketones protected as thioethers) into the parent carbonyl compounds. It was suggested that the deprotection of dithianes proceeds via the nitrosation of sulfur, as proposed in Scheme 78.[296]

Nitrogen dioxide also converts ketals into ketones in the presence of silica gel under neutral, anhydrous and mild conditions (Scheme 79).[330]

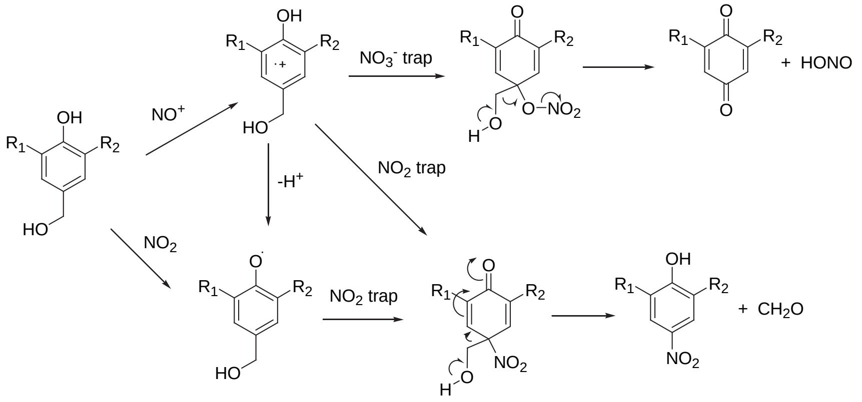
In a similar manner, carbonyl groups were regenerated from oximes and hydrazones at −40 °C in aprotic solvents in excellent yields, as presented in Table 19.[331]

α-Oximinoketones when subjected to treatment with N_2O_4 are converted into diketones (Scheme 80).[331] Cleavage of oximes through nitrosation with N_2O_4 also furnishes the desired α-keto-esters.[332,333]

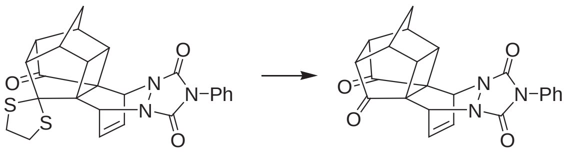
Regeneration of the original aldehydes from their corresponding 1,1-diacetates may be achieved with [$NO^+\cdot$crown$\cdot H(NO_3)_2^-$].[334] This is an effective deprotecting agent, which is not prone to any over-oxidation at room temperature and produces quantitative yields according to Zolfigol and his group (Scheme 81).

It was shown that NO_2 in water is a useful reagent for the transformation of various alkyl methyl ethers into carbonyl compounds under mild conditions with moderate-to-good yields (Scheme 82).[335] A similar observation was reported by using NO_2 in the presence of O_3, without water. This method, however, requires prolonged reaction times.

A large variety of silyl ether groups and *THP* ether groups can be converted into carbonyl groups in aprotic solvents with $Fe(NO_3)_3\cdot 1.5N_2O_4$ and $Cu(NO_3)_2\cdot N_2O_4$.[329] The ethers are efficiently oxidised to the corresponding aldehydes or ketones in the presence of silica gel under an atmosphere of nitrogen dioxide.[336] Firouzabadi et al. employed N_2O_4/charcoal for the same transformation.[337] They observed a high selectivity for the oxidation of benzylic ethers and trimethylsilyl ethers in the presence of *THP* ethers (Table 20).

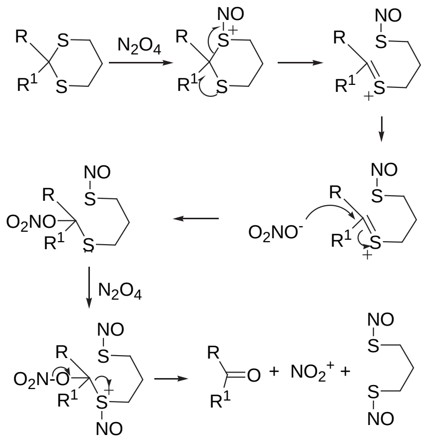


Scheme 76.

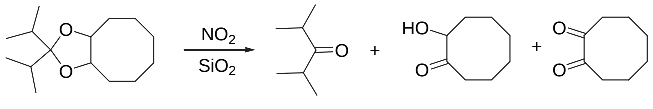


157 **158**

Scheme 77.



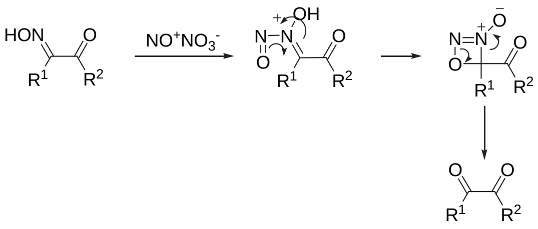
Scheme 78.



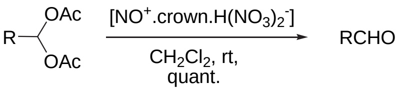
Scheme 79.

Table 19
Conversion of hydrazones into their carbonyl group with N_2O_4

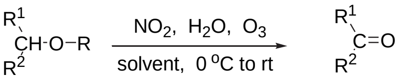
Run	R^1	R^2	Temp (°C)	Time (min)	Isolated yield (%)
1	p-NO_2Ph	H	0	30	94
2	p-ClPh	H	−40	10	95
3	p-Tolyl	H	−35	10	94
4	Ph	Me	−40	10	91
5	Ph	Et	−35	10	92
6	Ph	Ph	−40	10	85
7	$(Ph)_2CH$	Ph	−40	10	94



Scheme 80.



Scheme 81.



Scheme 82.

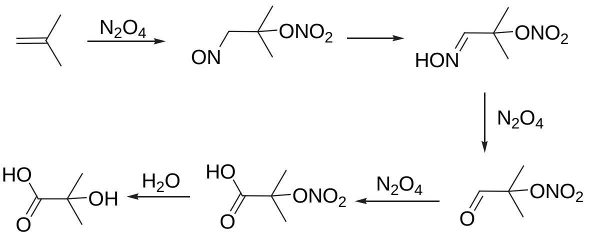
Table 20
Selective oxidation of different binary ethers

Run	Substrates	Products	Time (h)	Conversion (%)
1	4-$MePhCH_2O$*TMS*	4-MePhCHO	1	98
	$PhCH_2O$*THP*	$PhCH_2O$*THP*		99
2	4-$ClPhCH_2O$*TMS*	4-ClPhCHO	1	98
	4-NO_2PhCH_2O*THP*	4-NO_2PhCH_2O*THP*		100
3	PhCH(Me)O*TMS*	PhCOMe	2	92
	$PhCH_2O$*THP*	$PhCH_2O$*THP*		98
4	$(PhCH_2)_2O$	PhCHO	6	95
	$PhCH_2O$*THP*	$PhCH_2O$*THP*		96
5	$PhCH_2OMe$	PhCHO	5	92
	$C_6H_{13}CH(Me)O$*THP*	$C_6H_{13}CH(Me)O$*THP*		99

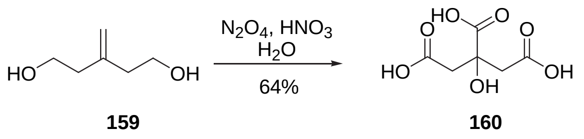
The oxidation of 2-methylpropene with N_2O_4 to produce 2-hydroxy-2-methylpropanoic acid is presented in Scheme 83.[338,339] The formation of nitrato acids[340] and nitrate esters of α-hydroxy acids has also been reported.[341]

Citric acid **160** is formed in 64% yield by the reaction of 3-methylene-1,5-pentanediol **159** with N_2O_4 in aqueous HNO_3 (Scheme 84).[342]

The oxidation of benzylic groups to the corresponding carboxylic acid functionality was achieved by means of a combination of nitrogen oxides, O_2 and SeO_2.[343] Substrates examined for this investigation included alkylnaphthalenes and alkylpyridines. The

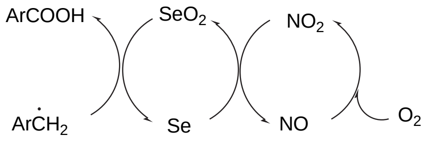


Scheme 83.



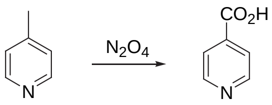
Scheme 84.

aldehyde appears to be an intermediate in the reaction. Mechanistic studies suggest that the rate-determining step is hydrogen-atom abstraction by NO_2 to form the benzyl radical. Selenium dioxide subsequently oxidises this radical to the desired product (Scheme 85).



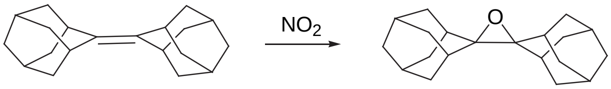
Scheme 85.

Aerobic oxidation of methylquinolines was successfully achieved by the use of *N*-hydroxyphthalimide/$Co(OAc)_2$/$Mn(OAc)_2$ as catalyst in the presence of a small amount of nitrogen dioxide as initiator.[344] γ-Picoline reacts with dinitrogen tetroxide to yield isonicotinic acid (Scheme 86).[345]



Scheme 86.

Nojima et al. irradiated a mixture of cyclohexene and NO_2 in air with a xenon lamp and isolated cyclohexene oxide in 50% yield.[346] Epoxidation of diadamantylidene and related hindered olefins with stoichiometric and catalytic amounts of NO_2 was reported in the absence of light by Bosch and Kochi (Scheme 87).[347,348]

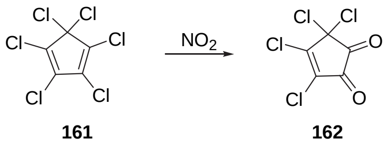


Scheme 87.

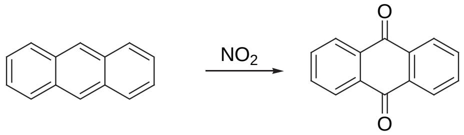
The stereoselective photooxidation of alkenes to epoxides with NO_2, excited by red light in a cryogenic matrix, was performed.[349–351]

Hexachlorocyclopentadiene **161** undergoes a novel reaction with nitrogen dioxide at 60 °C to afford tetrachloropentene-1,2-dione **162** in 90% yield (Scheme 88).[352]

Rodriguez and Tijero performed a kinetic study of the oxidation of anthracene to anthraquinone with nitrogen dioxide in acetic acid (Scheme 89).[353]

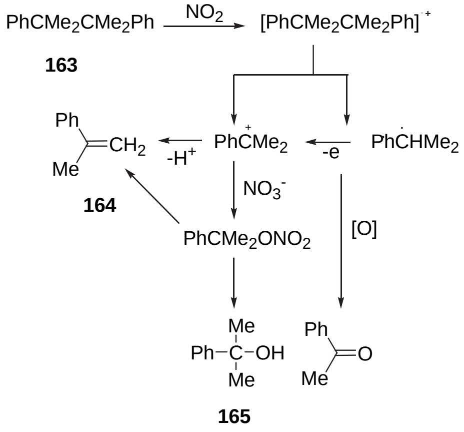


Scheme 88.



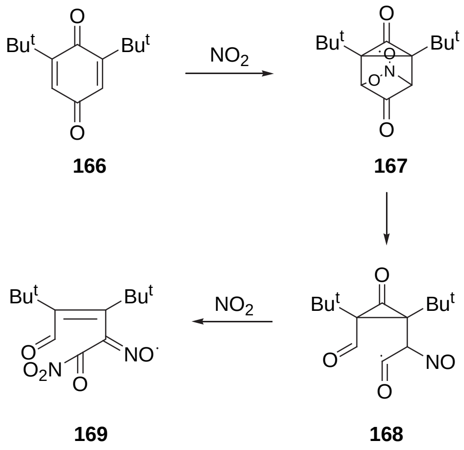
Scheme 89.

The use of NO_2/N_2O_4 in the oxidation of more complex alkenes has caused C–C bond cleavage, unlike the situation for 2-methylpropene. In this regard, it was shown that bicumenes readily form a cation radical, which undergoes facile cleavage of the central C–C bond, giving one cumyl cation and one cumyl radical species.[354] Bicumene **163** was stable towards nitrogen dioxide in a dilute dichloromethane solution at −20 °C. When ozone was introduced into this solution at the same temperature, however, the hydrocarbon **163** was rapidly cleaved to produce 2-phenylpropene **164**, α-cumyl alcohol **165** and acetophenone (Scheme 90).



Scheme 90.

The formation of oxynitroxyl radicals **167** was observed by EPR in the course of the exposure of *p*-benzoquinone **166** to nitrogen dioxide. This process involves the addition of nitrogen dioxide to the double-bond system of quinones (Scheme 91). Thermal conversion of oxynitroxyl radicals leads to the formation of acyl(alkyl) nitroxyl **168** and iminoxyl **169**, radicals along with other minor nitration products.[355]



Scheme 91.

The effects of the catalytic action of $NOBF_4$ and NO_2 in CH_2Cl_2/CF_2COOH mixtures and aryls were investigated. It was found that they are efficient catalysts for the synthesis of certain biaryls via an oxygen-promoted oxidative dimerisation step (Table 21).[356]

Table 21
$NOBF_4$ and NO_2 in biaryl coupling of 1-methoxynaphthalene[a]

$$2ArH + 2NO^+ \longrightarrow ArAr + 2NO + 2H^+$$
$$2NO + 2H^+ + 0.5O_2 \longrightarrow 2NO^+ + H_2O$$

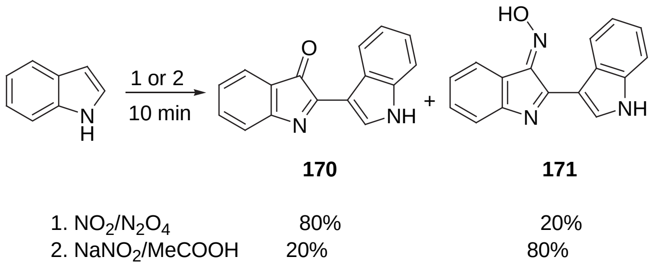
Source of NO_x[b]	ArH/NO_x	Conditions[c]	ArAr (mmol)
$NOBF_4$	20	Argon	0.02
$NOBF_4$	20	Air	0.48
$NOBF_4$	20	Oxygen	0.24
$NOBF_4$	100	Air	0.27
NO_2	20	Argon	0.01
NO_2	20	Air	0.35

[a] Reaction of 1.00 mmol of 1-methoxynaphthalene for 20 min with 0.01–0.05 mmol of $NOBF_4$ (NO_2) in 8 ml of CH_2Cl_2/2 ml of CF_3COOH in different atmospheres at 20 °C. Reactions performed in 25 ml Erlenmeyer flasks with magnetic stirring.

[b] $NOBF_4$ initially dissolved in CF_3COOH; NO_2 initially dissolved in CH_2Cl_2.

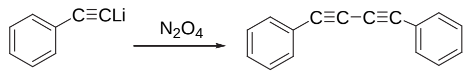
[c] Gentle stream of Ar; balloon filled with O_2; or drying tube to furnish ambient air.

The reaction of indole with nitrogen dioxide leads to 2-(indol-3-yl)-3*H*-indol-3-one **170** as the main product together with small amounts of 2-(indol-3-yl)-3*H*-indol-3-oxime **171**, whereas the major product obtained when the same indole is reacted with nitrous acid is the oxime **171** (Scheme 92).[53]



Scheme 92.

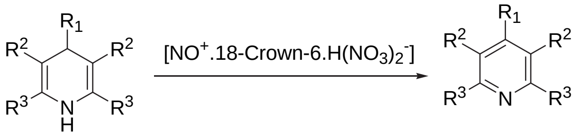
N_2O_4-initiated oxidative coupling of lithium phenylacetylide **172** that yields diphenylbutadiyne **173** is a highly important model of C^{sp}–C^{sp} bond formation (Scheme 93).[214]



172 **173**

Scheme 93.

Dehydrogenation of dihydropyridines and their conversion into the corresponding pyridine derivatives at room temperature with quantitative yields have been explored by the group of Zolfigol (Scheme 94).[357]

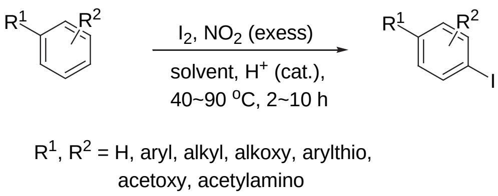


Scheme 94.

5. N_2O_4/NO_2-facilitated halogenation reactions

Aromatic halogen compounds have been used for over a century as important chemicals or intermediates in organic synthesis. Iodoarenes are valuable intermediates in the synthesis of a wide variety of organic compounds via reactions involving C–C bond formation by transition metals.[358]

Noda and Kashima have used excess nitrogen dioxide for the iodination of some activated aromatic compounds with molecular iodine in the presence of a catalyst (Scheme 95).[359]



Scheme 95.

After this breakthrough, a practical system was reported for the direct and regioselective iodination and bromination of benzene, naphthalene and other activated aromatic compounds using molecular iodine, bromine and their sodium salts in the presence of metal nitrate adducts of N_2O_4 supported on charcoal (Table 22).[360]

Table 22
para-Iodination of anisole with I_2 in presence of 0.25 M ratio of metal nitrate complexes of N_2O_4 in CH_2Cl_2 at room temperature

Entry	Reagent	Time (h)	Conversion (%)
1	$Fe(NO_3)_3 \cdot 1.5N_2O_4$ complex/charcoal	2	98
2	$Zn(NO_3)_2 \cdot 2N_2O_4$ complex/charcoal	24	57
3	$Cu(NO_3)_2 \cdot N_2O_4$ complex/charcoal	24	Trace

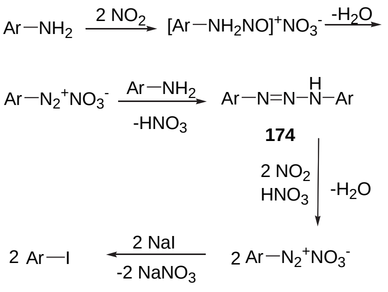
$2Fe(NO_3)_3 \cdot 3N_2O_4$/charcoal-facilitated iodination results[360] for arenes have been compared with other reported methods using NO_2[359] gas and $SiO_2/Fe(NO_3)_3 \cdot 9H_2O$ (Table 23).[361]

Table 23
Comparison of iodination of aromatic compounds by NO_2/I_2 and different methods

Substrate	Products	Time (h)/yield (%)/temp (°C)		
		A	B	C
Toluene	4-Iodotoluene	4/60/60	—/—/—	15/56/20
	2-Iodotoluene	4/40/60	—/—/—	15/37/20
Diphenyl ether	4,4′-Diiodo diphenyl ether	10/90/40	28/80/20	2/83/20
Benzene	Iodobenzene	—/—/—	48/0/20	24/74/20
Anisole	4-Iodoanisole	6/95/70	3.5/95/20	2/96/20

A: NO_2. B: $SiO_2/Fe(NO_3)_3 \cdot 9H_2O$ (Silfen). C: $2Fe(NO_3)_3 \cdot 3\,N_2O_4$/charcoal.

Diazotisation of arylamines followed by the addition of sodium iodide successfully gives the aryl iodides under non-aqueous conditions in acetonitrile at −20 °C (Scheme 96).[362] In order to get an insight into the pathway of this reaction, the progress of diazotisation was monitored by ^1H NMR using 4-methylaniline as the substrate. On the basis of the observations, a one-pot conversion of the arylamine into the corresponding aryl iodide was depicted, as shown in Scheme 96. Thus, under polar non-aqueous conditions, the diazotisation of aromatic amines with NO_2 proceeds via two distinct stages involving a triazene **174** as the intermediate (Scheme 96).[362]

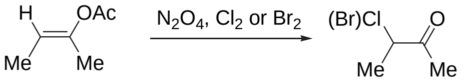


Scheme 96.

The process was developed by Kaupp et al. in the gas–solid state and using KI instead of NaI.[249]

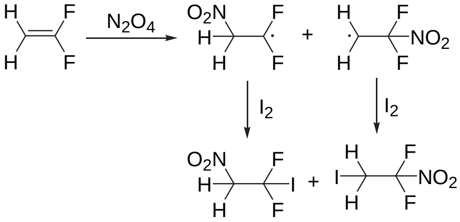
A simple method for the iodination of aromatic compounds, using I^- as the iodine source with O_2, and catalytic amounts of $NO^+BF_4^-$ as the oxidant, has been reported.[363] In this study, it was found that mesitylene is efficiently iodinated with the $NH_4I/O_2/NO_2$ system in 98% yield.

The use of N_2O_4 for the halogenation of acyl enol ethers with Cl_2 and Br_2 was reported and the α-chloro and α-bromo ketones are, respectively, produced (Scheme 97).[364]



Scheme 97.

Olefins are converted into the β-iodoalkyl nitrates and β-nitroalkyl iodides with a mixture of N_2O_4 and I_2, depending on the type of olefin used.[365,366] The reaction with 1,1-difluoroethylene gave two novel isomeric adducts, 1,1-difluoro-1-iodo-2-nitroethane **175** (predominantly) and 1,1-difluoro-2-iodo-1-nitroethane **176** (Scheme 98).[367] An unusual and facile conversion of the former isomers (**175** and **176**) with alcohols to yield the novel fluoronitro ethers $ROCF_2CH_2NO_2$ (R=Me– or Et–) was also described.[367]

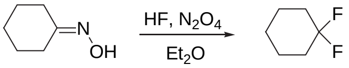


175 **176**

Scheme 98.

The reaction of dienes with a mixture of nitrogen dioxide and iodine was reported to give some dinitro compounds as side products, the major products being iodonitro compounds.[368]

Oximes with HF in the presence of N_2O_4 are converted into geminal-difluoroalkanes (Scheme 99).[369]



Scheme 99.

6. Miscellaneous reactions

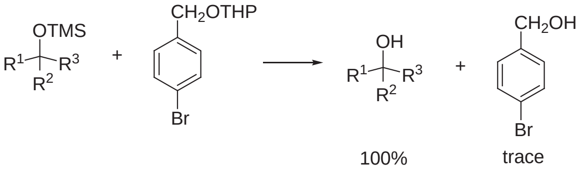
Trimethylsilyl ethers (TMS ethers) and tetrahydropyranyl ethers (THP eters) in the presence of N_2O_4 in CH_2Cl_2 at −10 °C produced only the parent alcohols.[329] In another study, similar observations were reported for N_2O_4 impregnated on silica gel, even with an excess of reagent.[370] In a competitive reaction between trimethylsilyl ethers and tetrahydropyranyl ethers with the same reagents, only trimethylsilyl ethers were selectively cleaved to alcohols, whilst the tetrahydropyranyl ethers were recovered intact (Table 24).

Three isomers of phenylglyoxime were oxidised to the corresponding phenylfurazan oxide **177** in separate reactions with dinitrogen tetroxide (Scheme 100).[371]

4-Substituted-1,2,4-triazole-3,5-diones (TADs) **179** are readily obtained from bisurazol **178** and $[NO^+\cdot 18\text{-crown-6}\cdot H(NO_3)_2^-]$.[372] The same reaction was reported with N_2O_4,[373] and PEG/N_2O_4,[374] in quantitative yields (Scheme 101).

Table 24

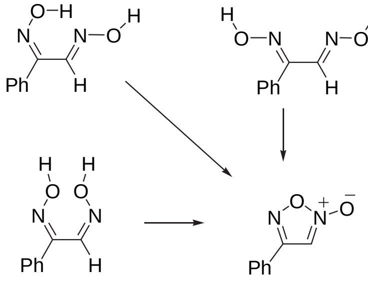
Comparative reaction between TMS and THP ethers in presence of N_2O_4/SiO_2 system at room temperature in CH_2Cl_2[a]



Entry	Substrate	TMS ether/THP ether/N_2O_4/SiO_2	Time (min)
1	4-BrPhCH$_2$OTMS 4-BrPhCH$_2$OTHP	1:1:300[b]	10
2	Ph$_2$CH$_2$OTMS 4-BrPhCH$_2$OTHP	1:1:300[b]	25
3	PhCH$_2$(CH$_3$)$_2$CH$_2$OTMS 4-BrPhCH$_2$OTHP	1:1:300[b]	40

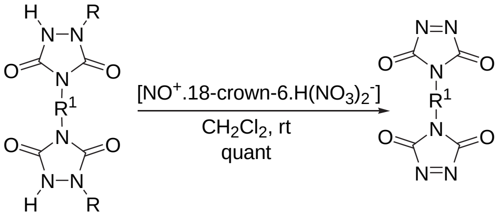
[a] Detected by GC.

[b] mmol/mmol/mg.



177

Scheme 100.



178 **179**

R = Na and R^1 = 4,4'-Ph-CH$_2$-Ph-

R = Na and R^1 = -(CH$_2$)$_6$-

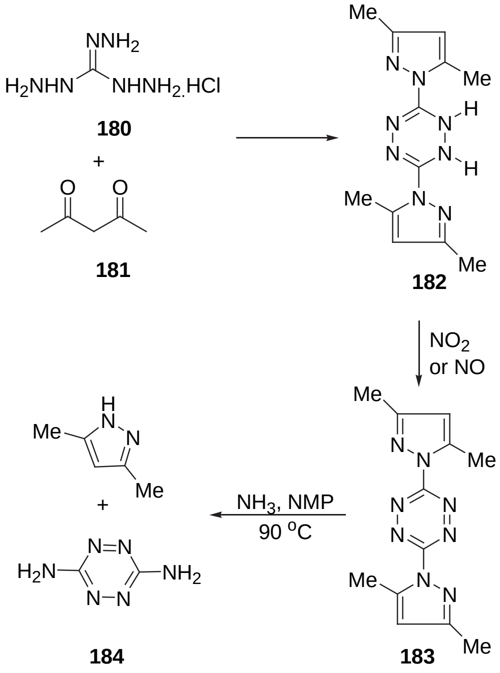
Scheme 101.

Treatment of triaminoguanidine monohydrochloride **180** with 2,4-pentane dione **181** gives 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazine **182** in 80–85% yields. Oxidation of **182** with nitric oxide or nitrogen dioxide to 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazine **183** followed by ammonolysis of **183** gives 3,6-diamino-1,2,4,5-tetrazine **184** in quantitative yield (Scheme 102).[375]

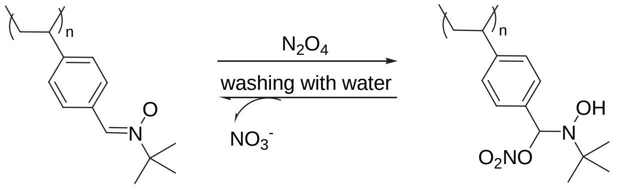
Spin-trapping agents have been reported that are able to absorb N_2O_4. The spin-trapping agent is converted into the nitrate derivative (Scheme 103).[376–378]

Dinitrogen tetroxide was found to be an efficient reagent for the preparation of the oxamidinium dication **186** from tetraaminoethylene **185** in *n*-hexane (Scheme 104).[379]

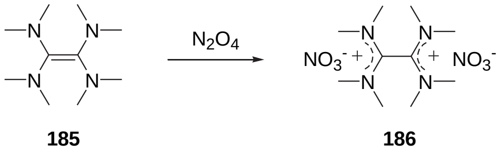
Some other reactions such as the N-nitration of morpholine in aqueous solution,[380] the oxidation of phosphites to phosphates[381–383] and a kinetic investigation of the isomerisation of *cis*- and *trans*-alkenes were reported.[384,385] The reaction of ylidenetriphenylphosphoranes with NO_2 was also examined and different products were produced depending on the structure and the reaction conditions.[386]



Scheme 102.



Scheme 103.



Scheme 104.

7. Conclusions

Dinitrogen tetroxide is a long-stablished reagent that has been widely applied in many organic reactions as a nitrating, nitrosating and oxidisting agent. The diversity this reagent has been dramatically expanded by the introduction of solid beds such as mineral materials, and polymeric compounds. New N_2O_4 systems, which are easily handled and with unprecedented reactivities have become readily available. The versatility of the reagent is based on the dissociation characterics of N_2O_4 in different media. Depending on the nature of the reaction conditions, it can either undergo homolytic or heterolytic cleavage. Other advances in terms of improved selectivity and reactivity of N_2O_4 have been achieved by means of oxidants, solvents and catalysts. Some of these additives have provided powerful systems such as NO_2/O_3, NO_2/O_2, and NO_2/zeolites, which were successfully applied in organic transformations. Successful applications of acidic ionic liquids with the dual role of solvent and catalyst have also been discovered.

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