# THE NITRO GROUP IN ORGANIC SYNTHESIS

Noboru Ono

WILEY-VCH

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# SERIES FOREWORD

In the organic nitro chemistry era of the fifties and early sixties, a great emphasis of the research was directed toward the synthesis of new compounds that would be useful as potential ingredients in explosives and propellants.

In recent years, the emphasis of research has been directed more and more toward utilizing nitro compounds as reactive intermediates in organic synthesis. The activating effect of the nitro group is exploited in carrying out many organic reactions, and its facile transformation into various functional groups has broadened the importance of nitro compounds in the synthesis of complex molecules.

It is the purpose of the series to review the field of organic nitro chemistry in its broadest sense by including structurally related classes of compounds such as nitroamines, nitrates, nitrones, and nitrile oxides. It is intended that the contributors, who are active investigators in various facets of the field, will provide a concise presentation of recent advances that have generated a renaissance in nitro chemistry research.

Henry Feuer
Purdue University

# PREFACE

The purpose of this book is to emphasize recent important advances in organic synthesis using nitro compounds. Historically, it was aromatic nitro compounds that were prominent in organic synthesis. In fact they have been extensively used as precursors of aromatic amines and their derivatives, and their great importance in industrial and laboratory applications has remained.

This book is not intended to be a comprehensive review of established procedures, but it aims to emphasize new important methods of using nitro compounds in organic synthesis.

The most important progress in the chemistry of nitro compounds is the improvement of their preparations; this is discussed in chapter 2. Environmentally friendly methods for nitration are emphasized here.

In recent years, the importance of aliphatic nitro compounds has greatly increased, due to the discovery of new selective transformations. These topics are discussed in the following chapters: Stereoselective Henry reaction (chapter 3.3), Asymmetric Micheal additions (chapter 4.4), use of nitroalkenes as heterodienes in tandem [4+2]/[3+2] cycloadditions (chapter 8) and radical denitration (chapter 7.2). These reactions discovered in recent years constitute important tools in organic synthesis. They are discussed in more detail than the conventional reactions such as the Nef reaction, reduction to amines, synthesis of nitro sugars, alkylation and acylation (chapter 5). Concerning aromatic nitro chemistry, the preparation of substituted aromatic compounds via the $S_NAr$ reaction and nucleophilic aromatic substitution of hydrogen (VNS) are discussed (chapter 9). Preparation of heterocycles such as indoles, are covered (chapter 10).

Noboru Ono
Matsuyama, Ehime

# ACKNOWLEDGMENTS

Mr. Satoshi Ito, a graduate student in my group, has drawn all figures. It would have been impossible to complete the task of writing this book without his assistance. I would like to dedicate this book to the late Dr. Nathan Kornblum whom I met 30 years ago at Purdue University. Since then I have been engaged in the chemistry of nitro compounds.

It is a pleasure to express my gratitude to all persons who contributed directly or indirectly to the accomplishment of the task. Dr. Henry Feuer advised me to write this monograph and also provided many helpful suggestions, for which I thank him. Thanks to professors Node, Vasella, Ballini, Ohno and Ariga, who kindly sent me their papers. I also express my gratitude to Dr. H. Uno for his careful proofreading. Finally, thanks to my wife Yoshiko and daughter Hiroko for their constant encouragement.

Professors Kornblum and Ono.

# ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| AIBN | α,α-azobisisobutyronitrile |
| Ar | aryl |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| BINAP | 1,1′-bisnaphthalene-2,2′-diyl-bisdiphenylphosphine |
| BINOL | 1,1′-bi-2-naphthol |
| Boc | *tert*-butoxycarbonyl |
| Bn = Bzl | benzyl |
| Bu | butyl |
| BuLi | *n*-butyllithium |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| CTAB | cetyltrimethylammonium bromide |
| Cbz | benzyloxycarbonyl |
| DBN | 1,8-diazabicyclo[4.3.0]nonene-5 |
| DBU | 1,8-diazabicylo[5.4.0]undecene-7 |
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD | diethylazodicarboxylate |
| DMAP | 4-*N*,*N*-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMI | 1,3-dimethyl-2-imdazolizinone |
| DMSO | dimethyl sulfoxide |
| dba | dibenzylideneacetone |
| d.e. | diastereomeric excess |
| d.s. | diastereoselectivity |
| dppe | 1,2-bis(diphenylphosphino)ethane |
| dppp | 1,3-bis(diphenylphosphino)propane |
| dppb | 1,4-bis(diphenylphosphino)butane |
| dppf | 1,1′-bis(diphenylphosphino)ferrocene |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| E | electrophiles |
| Et | ethyl |
| e.e. | enantiomeric excess |
| HMDS | hexamethyldisilazane |
| Im | 1-imidazolyl |
| LDA | lithium diisopropylamide |
| L-Selectide | lithium tri-*sec*-butyl borohydride |
| MCPBA | *m*-chloroperbenzoic acid |

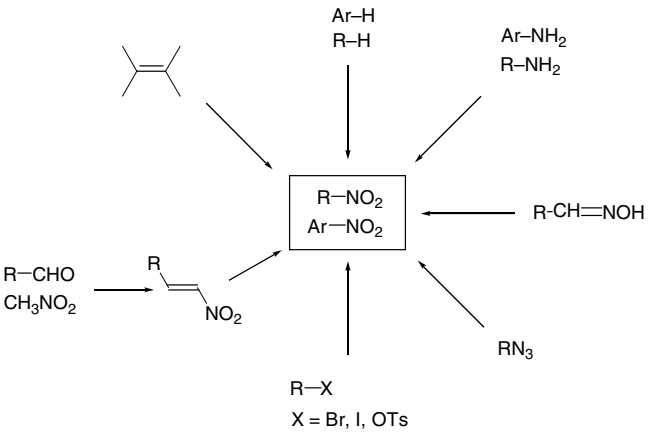
| | |
|---|---|
| Me | methyl |
| MEM | 2-methoxyethoxymethyl |
| MOM | methoxymethyl |
| NBS | *N*-bromosuccinimide |
| NMO | *N*-methylmorpholine *N*-oxide |
| Nu | nucleophiles |
| PCC | pyridinium chlorochromate |
| Phth | phthaloyl |
| PMB | *p*-methoxybenzyl |
| PNB | *p*-nitrobenzyl |
| TBDMS | *tert*-butyldimethylsilyl |
| TMG | tetramethylguanidine |
| TBAF | tetrabutylammonium fluoride |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydro+furan |
| Tf | trifluoromethanesulfonyl |
| THP | tetrahydropyranyl |
| Tr | trityl |
| TMEDA | tetramethylethylenediamide |
| TMS | trimethylsilyl |
| Tol | *p*-tolyl |
| Ts | *p*-tolenesulfonyl, tosyl |
| SET | single electron transfer reaction |

# 1

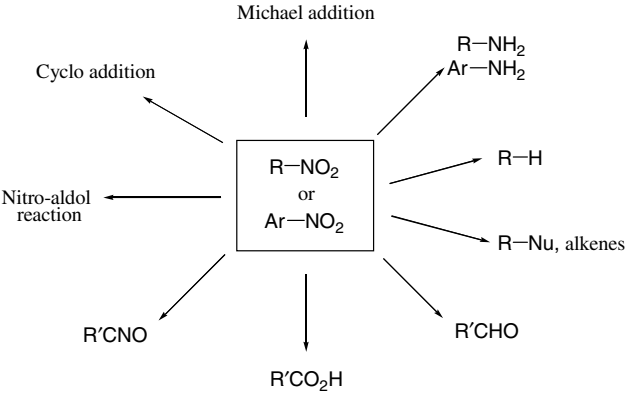
# INTRODUCTION

The remarkable synthetic importance of nitro compounds has ensured long-standing studies of their utilization in organic synthesis. Historically, nitro compounds, especially aromatic nitro compounds, are important for precursors of azo dyes and explosives. Of course, the importance of nitro compounds as materials for dyes and explosives has not been changed; in addition, they have proven to be valuable reagents for synthesis of complex target molecules. The versatility of nitro compounds in organic synthesis is largely due to their easy availability and transformation into a variety of diverse functionalities.

Preparation and reaction of nitro compounds are summarized in Schemes 1.1 and 1.2. Although there are many excellent books and reviews concerning nitro compounds, as listed in the references, the whole aspect of synthetic utility of nitro compounds has not been documented. This book has paid special emphasis to newly developing areas of nitro compounds such as radical reaction of nitro compounds, the stereoselective nitro-aldol reaction, and environmentally friendly chemistry (green chemistry). The control of the stereochemistry of the reactions involving nitro compounds is a quite recent progress. Furthermore, the reactions of nitro compounds have been regarded as non-selective and dangerous processes. However, clean




**Scheme 1.1.** Preparation of nitro compounds




**Scheme 1.2.** Reaction of nitro compounds

synthesis, synthesis in water or without solvents, the use of a fluorous phase, waste minimization, and highly selective reactions have been devised in many cases using nitro compounds. Such recent progresses are described in this book.

General reviews for preparation of nitro compounds[1] and for the reaction of nitro compounds[2–5] are listed in the references.

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# 2

# PREPARATION OF NITRO COMPOUNDS

## 2.1 NITRATION OF HYDROCARBONS

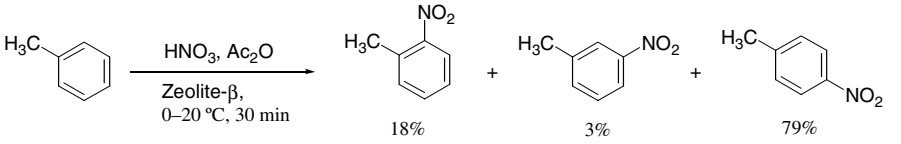
### 2.1.1 Aromatic Compounds

Aromatic nitration is an immensely important industrial process. The nitro aromatic compounds are themselves used as explosives and act as key substrates for the preparation of useful materials such as dyes, pharmaceuticals, perfumes, and plastics. Therefore, nitration of hydrocarbons, particularly of aromatic compounds, is probably one of the most widely studied organic reactions.[1,2] The classical nitration method usually requires the use of an excess of nitric acid and the assistance of strong acids such as concentrated sulfuric acid. Although this process is still in use in industries, nitrations are generally notoriously polluting processes, generating nitrogen oxide (NOx) fumes and large quantities of waste acids. Although many methods to improve the classical nitration method have been reported,[1,2] there is a great need for new nitration methods that can overcome such problems. Nitration has been well documented in the book by Olah, in which the following nitrating agents are discussed:[1] (a) $HNO_3$ + acid catalyst ($H_2SO_4$, $H_2PO_4$, polyphosphoric acid, $HClO_4$, HF, $BF_3$, $CH_3SO_3H$, $CF_3SO_3H$, $FSO_3H$, Nafion-H); (b) $RONO_2$ + acid catalyst ($H_2SO_4$, $AlCl_3$, $SnCl_4$, $BF_3$); (c) $RCO_2NO_2$; (d) $NO_2Cl$ + acid catalyst ($AlCl_3$, $TiCl_4$); (e) $N_2O_5$ or $N_2O_4$ + acid catalyst ($H_2SO_4$, $HNO_3$, $AlCl_3$ et al.); (f) $NO_2^+BF_4^-$, $NO_2^+PF_6^-$; and (g) *N*-nitropyridinum salts.

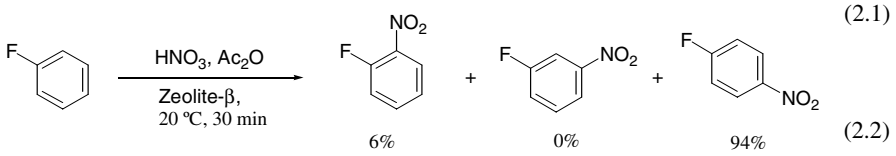
A new nitration process, that is environmentally friendly, has been the focus of recent research. Clark has pointed out that aromatic nitration, a particularly wasteful and hazardous industrial process, has benefited relatively little from the environmentally friendly catalytic methods.[3] An environmentally friendly nitration process requires high regioselectivity (*ortho* to *para*) and avoidance of excess acids to minimize waste. The use of solid acid catalysts is potentially attractive because of the ease of removal and recycling of the catalyst and the possibility that the solid might influence the selectivity.[3] The use of Nafion-H and other polysulfonic acid resins reduces the corrosive nature of the reaction mixture, although it does not improve regioselectivity.[4] A new class of solid acid catalyst systems, a high surface-area Nafion resin entrapped within a porous silica network, has been developed to mono-nitrate benzene in 82% conversion.[5] Copper nitrate supported on montmorillonite K-10 nitrates toluene in the presence of acetic anhydride to produce high *para* selectivity.[6] Nitration of benzocy-

clobutene using acetyl nitrate generated in situ by a continuous process in the presence of montmorillonite K-10 clay gives 3-nitrobicyclo[5.4.0]-1,3,5-triene in 60% yield.[7,8] High *para* selectivity (95%) is reported in the nitration of toluene catalyzed by zeolite ZSM-5 and alkyl nitrate.[9] The selective nitration of 4-hydroxbenzaldehyde to give the 3-nitro derivative has been achieved using iron(III) nitrate and a clay in quantitative yield.[10]

Smith and coworkers have screened the solid catalysts for aromatic nitration, and found that zeolite β gives the best result. Simple aromatic compounds such as benzene, alkylbenzenes, halogenobenzenes, and certain disubstituted benzenes are nitrated in excellent yields with high regioselectivity under mild conditions using zeolite β as a catalyst and a stoichiometric quantity of nitric acid and acetic anhydride.[11] For example, nitration of toluene gives a quantitative yield of mononitrotoluenes, of which 79% is 4-nitrotoluene. Nitration of fluorobenzene under the same conditions gives *p*-fluoronitrobenzene exclusively (Eqs. 2.1 and 2.2)



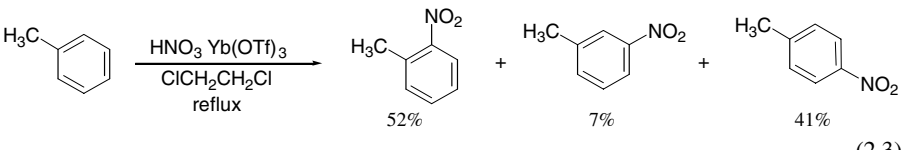

(2.1)




(2.2)

To avoid excessive acid waste, lanthanide(III) triflates are used as recyclable catalysts for economic aromatic nitration. Among a range of lanthanide(III) triflates examined, the ytterbium salt is the most effective. A catalytic quantity (1–10 mol%) of ytterbium(III) triflate catalyzes the nitration of simple aromatics with excellent conversions using an equivalent of 69% nitric acid in refluxing 1,2-dichloromethane for 12 h. The only by-product of the reaction is water, and the catalyst can be recovered by simple evaporation of the separated aqueous phase and reused repeatedly for further nitration.[12]

However, this catalyst is not effective for less reactive aromatics such as *o*-nitrotoluene. In such cases, hafnium(IV) and zirconium(IV) triflates are excellent catalysts (10 mol%) for mononitration of less reactive aromatics. The catalysts are readily recycled from the aqueous phase and reused (Eqs. 2.3 and 2.4).[12]

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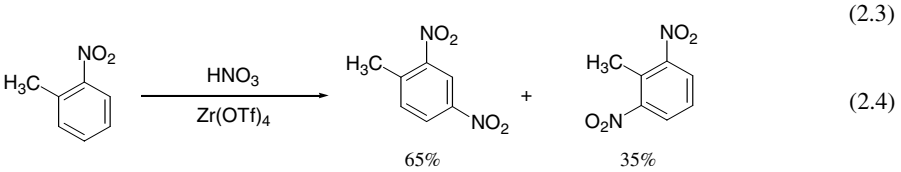
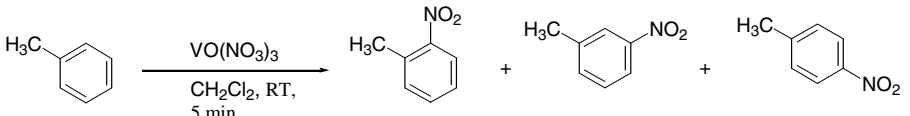



(2.4)

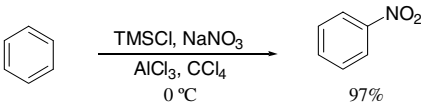
Phenols are easily mononitrated by sodium nitrate in a two-phase system (water-ether) in the presence of HCl and a catalytic amount of $La(NO_3)_3$.[13] Various lanthanide nitrates have been used in the nitration of 3-substituted phenols to give regioselectively the 3-substituted 5-nitrophenols.[14]

Vanadium oxytrinitrate is an easy to handle reagent that can be used to nitrate a range of substituted aromatic compounds in dichloromethane at room temperature, leading to >99% yields of nitration products (Eq. 2.5).[16]




(2.5)

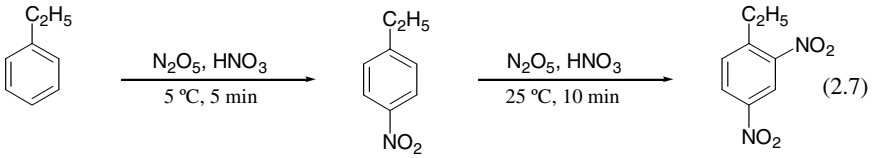
A novel, mild system for the direct nitration of calixarenes has been developed using potassium nitrate and aluminum chloride at low temperature. The side products of decomposition formed under conventional conditions are not observed in this system, and the *p*-nitrocalixarenes are isolated in 75–89% yields.[17] Such Friedel-Crafts-type nitration using nitryl chloride and aluminum chloride affords a convenient system for aromatic nitration.[18] Nitryl chloride was previously prepared either by the oxidation of nitrosyl chloride or by the reaction of chlorosulfonic acid with nitric acid. However, these procedures are inconvenient and dangerous. Recently, a mixture of sodium nitrate and trimethysilyl chloride (TMSCl) has been developed as a convenient method for the in situ generation of nitryl chloride (Eq. 2.6).




(2.6)

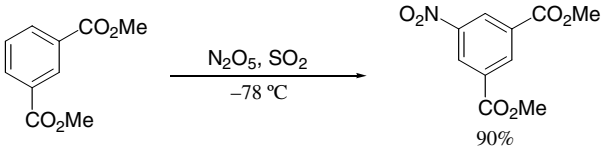
Nitration with dinitrogen pentoxide ($N_2O_5$) has increased in its importance as an environmentally cleaner alternative to conventional procedures. It might become the nitration method of the future. Dinitrogen pentoxide can be produced either by ozone oxidation of dinitrogen tetraoxide ($N_2O_4$) or electrolysis of $N_2O_4$ dissolved in nitric acid.[19]

Dinitrogen pentoxide (prepared by the oxidation of $N_2O_4$ with $O_3$) in nitric acid is a potent nitration system. It can be used for nitrating aromatic compounds at lower temperatures than conventional system. It is also convenient for preparing explosives that are unstable in nitrating media containing sulfuric acid (Eq. 2.7).[20]




(2.7)

Dinitrogen pentoxide in liquid sulfur dioxide has been developed as a new nitration method with a wide potential for aromatic nitration, including deactivated aromatics, as shown in Eq. 2.8.[21] Electrophilic aromatic substitution of the pyridine ring system takes place under forcing conditions with very low yields of substituted products. Thus, nitration of pyridine with $HNO_3/H_2SO_4$ gives 3-nitropyridine in 3% yield. Bakke has reported a very convenient procedure for the nitration of pyridine using $N_2O_5$. Pyridines are nitrated in the β-position by the reaction with $N_2O_5$ in $MeNO_2$ followed by treatment with an aqueous solution of sodium bisulfate (Eq. 2.9). The reaction proceeds via the *N*-nitropyridinium ion.[22]

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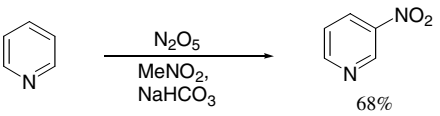
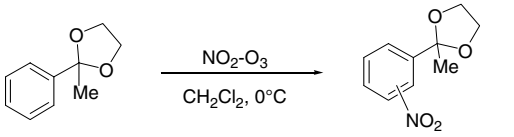


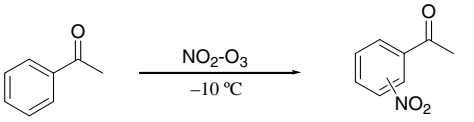

(2.9)

Nitrogen dioxide, in the presence of ozone, is a good nitrating system for various aromatics.[23] Suzuki and coworkers have proposed a mechanism that proceeds in a dual mode, depending on the oxidation potential of the aromatic substrate; nitrogen dioxide reacts with ozone to form nitrogen trioxide, which oxidizes the aromatic substrate to form a radical cation, an intermediate in the ring substitution. In the absence of an appropriate oxidizable substrate, the nitrogen trioxide reacts with another nitrogen dioxide to form dinitrogen pentoxide, which is a powerful nitrating agent in the presence of an acid. The mechanism of this nitration is well discussed in Ref. 27. This method has several merits over the conventional ones. As the reaction proceeds under neutral conditions, acid-sensitive compounds are nitrated without decomposition of acid-sensitive groups.[24a] The regioselectivity of this nitration process differs from that of the conventional nitration process, in that, for example, substrates bearing an electron-withdrawing group are preferentially nitrated in the *ortho*-position (Eqs. 2.10 and 2.11).[25]




58% (*o*:*m*:*p* = 22:19:59)

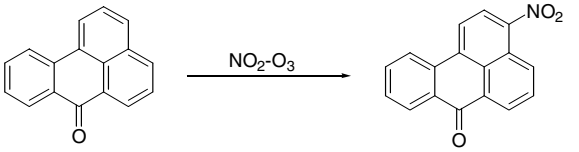
(2.10)




*o*- 52%, *m*- 48%

(2.11)

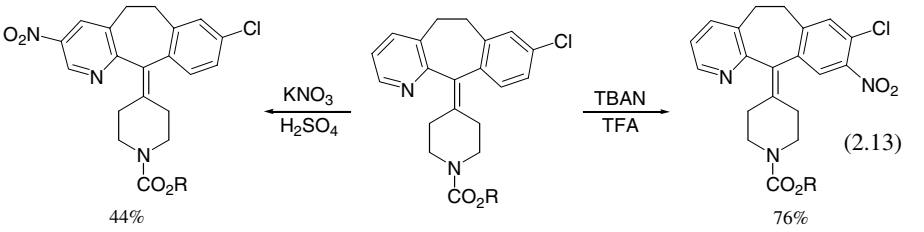
Reaction of benzanthrone with nitrogen dioxide alone or in admixture with ozone gives a mixture of nitrated products including 3-nitrobenzanthrone, which is a new class of powerful direct-acting mutagens of atmospheric origin (Eq. 2.12).[26]




(2.12)

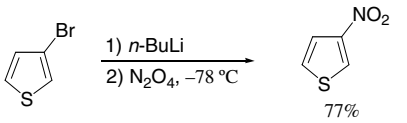
The regioselectivity of aromatic nitration depends on the conditions of nitration. Discussion of the regiochemistry of nitration is voluminous and is beyond the scope of this book; Ref. 1 and other appropriate references should be utilized for this discussion. Some recent interesting related topics are described here. The regiochemistry on the nitration of naphthalenes with various nitrating agents is compared. Unusually high 1-nitro-to-2-nitro isomer ratios are observed in the nitration with $NO_2$ and $O_3$, which proceeds via radical cation intermediates.[27] In a practical synthesis of polycyclic aromatics, regioselectivity of nitration is important. Classical nitration of azatricyclic systems using potassium nitrate and sulfuric acid yield mainly 9-nitro derivatives via the ionic process. However, the use of tetrabutylammonium nitrate (TBAN) and trifluoroacetic anhydride (TFAA) gives exclusively the 3-nitro derivatives. It is

suggested that the nitrating species in this case is the nitrosyl radical, generated from the homolytic decomposition of the TBAN/TFAA adduct (Eq. 2.13).[28] The easily prepared dinitrogen tetroxide complexes of iron and nickel nitrates have been shown to selectively mono- or dinitrate phenolic compounds in high yields.[29] It is well recognized that $NO_2$ is a very reactive radical taking part in atmospheric chemistry. Atmospheric reactions of polycyclic aromatic hydrocarbons forming mutagenic nitro derivatives have also been investigated.[30]

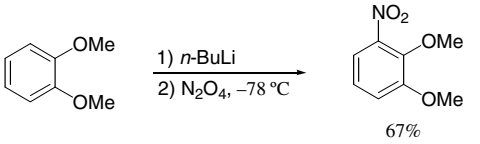



(2.13)

Recently, nitration of organolithiums and Grignards with $N_2O_4$ has been developed for the preparation of certain kinds of nitro compounds (Eqs. 2.14 and 2.15).[31] The success of this process depends on the reaction conditions (low temperature) and the structure of substrates. For example, 3-nitrothiophene can be obtained in 70% overall yield from 3-bromothiophene; this is far superior to the older method. 3-Nitroveratrole cannot be prepared usefully by classical electrophilic nitration of veratrole, but it can now be prepared by direct *ortho*-lithiation followed by low-temperature $N_2O_4$ nitration. The mechanism is believed to proceed by dinitrogen tetroxide oxidation of the anion to a radical, followed by the radical's combination.




(2.14)




(2.15)

Nitration of aromatic compounds published in recent years is summarized in Table 2.1.

### 2.1.2 Alkanes

In contrast to the nitration of aromatic hydrocarbons, saturated aliphatic hydrocarbons are inert toward conventional nitrating agents under ambient conditions. Under forced conditions, they undergo cleavage of the C-C bond to give a complex set of oxidation products and lower nitroalkanes. The nitration in the gas phase has been used in industry since the 1940s, producing nitromethane, nitroethane, 1-nitropropane, 2-nitropropane, 1-nitrobutane and 2-nitrobutane.[1] Although this method is important for the preparation of nitroalkanes in industry, it is not practical for the laboratory preparation of nitroalkanes. Electrophilic nitration of alkanes is a more difficult process than aromatic nitration due to the fast formation of byproducts. Olah has reported nitration of adamantane with nitronium salts in aprotic solvents at ambient temperature, but the yield of 1-nitroadamantane is only 10%.[32] Since then, many attempts of nitration of adamantane have been tried, and the yield has been improved to 60–70% by using purified nitrile-free nitromethane as a solvent.[33] This reaction proceeds by electrophilic substi-

**Table 2.1 Nitration of aromatic compounds**

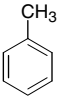
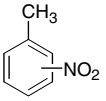
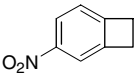
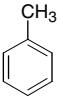
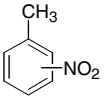
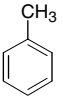
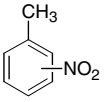
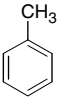
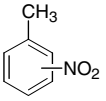
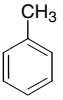
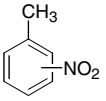
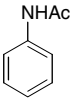
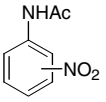
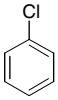
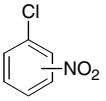
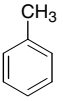
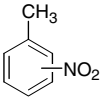
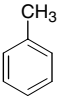
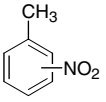
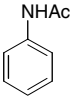
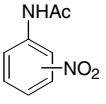
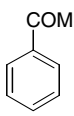
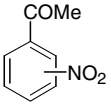
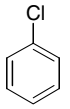
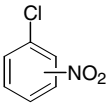
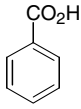
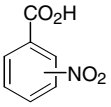
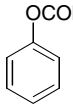
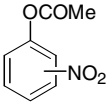
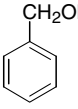
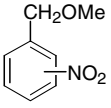
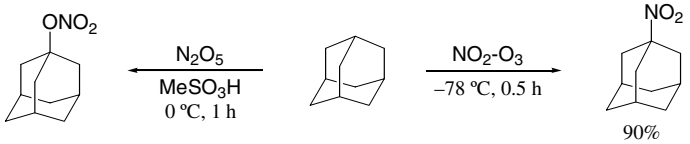
| Substrate | Reagent | Condition | Product | Yield | (%)[a] | Ref. |
|---|---|---|---|---|---|---|
|  | $HNO_3$, $Ac_2O$, K-10 | $CCl_4$ reflux |  | *o*-31<br>*m*-2<br>*p*-67 | (75–98) | 6 |
|  | $HNO_3$, $Ac_2O$, K-10 | $CCl_4$ reflux |  | | (60) | 8 |
|  | $HNO_3$, $Ac_2O$, Zeolite β | 0–20 °C 30 min |  | *o*-18<br>*m*-3<br>*p*-79 | (99) | 11 |
|  | $HNO_3$, $Yb(Otf)_3$ (10 mol%) | $ClCH_2CH_2Cl$ reflux |  | *o*-52<br>*m*-7<br>*p*-79 | (95) | 12 |
|  | $HNO_3$, $Me_3SiCl$ $AlCl_3$ | $CCl_4$ 0 °C, 1 h |  | *o*-42<br>*m*-3<br>*p*-55 | (90) | 15 |
|  | $VO(NO_3)_3$ | $CH_2Cl_2$ RT, 6 min |  | *o*-50<br>*m*-3<br>*p*-47 | (99) | 16 |
|  | $VO(NO_3)_3$ | $CH_2Cl_2$ RT, 15 min |  | *o*-46<br>*p*-54 | (85) | 16 |
|  | $VO(NO_3)_3$ | $CH_2Cl_2$ RT, 20 min |  | *o*-43<br>*p*-57 | (99) | 16 |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$ 0 °C, 1 h |  | *o*-51<br>*m*-6<br>*p*-43 | (99) | 24b |
|  | $NO_2$, $O_3$ pyridine (3 equiv) | $CH_2Cl_2$ 0 °C, 2 h |  | *o*-22<br>*m*-66<br>*p*-13 | (21) | 24b |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$ 0 °C, 2.5 h |  | *o*-81<br>*p*-19 | (98) | 24c |

**Table 2.1 Continued**

| Substrate | Reagent | Condition | Product | Yield | (%)[a] | Ref. |
|---|---|---|---|---|---|---|
|  | $NO_2$, $O_3$ | $CH_2Cl_2$<br>–10 °C, 4 h |  | *o*-52<br>*m*-48 | (99) | 24a |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$<br>0 °C, 3 h |  | *o*-43<br>*m*-1<br>*p*-56 | (97) | 27 |
|  | $NO_2$, $O_3$ | $ClCH_2CH_2Cl$<br>0 °C, 1.5 h |  | *o*-29<br>*m*-69<br>*p*-2 | (98) | 24d |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$<br>0 °C, 2 h |  | *o*-60<br>*p*-40 | (100) | 24e |
|  | $NO_2$, $O_3$ | $CH_2Cl_2$<br>0 °C, 2 h |  | *o*-69<br>*m*-4<br>*p*-27 | (99) | 24f |

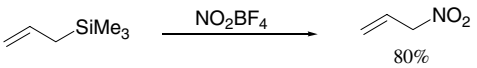
[a] *o*-, *m*-, *p*-ratio and yield.

tution at single bonds. On the other hand, radical nitration of adamantane using $N_2O_5$ gives a mixture of several compounds arising from the N- and O-attacks at the secondary and tertiary positions.[34] Selective N- and O-functionalization of adamantane has been reported. In the presence of ozone at –78 °C, nitrogen dioxide selectively reacts with adamantane at the bridgehead position to give the nitrated product, whereas, in the presence of methanesulfonic acid at 0 °C, $N_2O_5$ reacts with this hydrocarbon at the same position to give the nitrooxylated product (Eq. 2.16).[35]

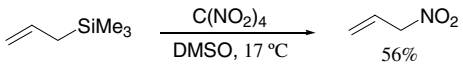



(2.16)

Nitrodesilylation (Eq. 2.17)[36] and nitrodestanylation (Eq. 2.18)[37] are efficient methods for the preparation of some kinds of nitroalkanes from readily available alkylsilanes or allylstannanes. Similar nitration also takes place at the vinylic positions (see Eq. 2.36 in Section 2.1.4).



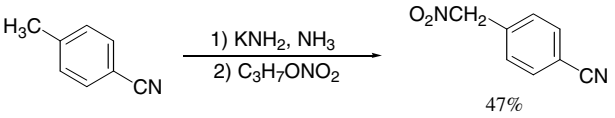

(2.17)



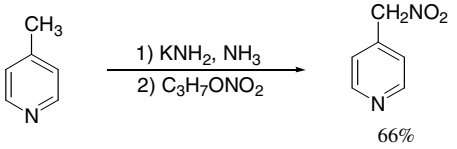

(2.18)

### 2.1.3 Activated C-H Compounds

The nitration of active methylene compounds generally proceeds via the reaction of carbanionic intermediates with an electrophilic nitrating agent such as alkyl nitrate (alkyl nitrate nitration). Details of this process are well documented in the reviews.[38] The alkyl nitrate nitration method has been used extensively for the preparation of arylnitromethanes. The toluene derivatives, which have electron-withdrawing groups are nitrated with alkyl nitrates in the presence of $KNH_2$ in liquid ammonia (Eqs. 2.19 and 2.20).[39]

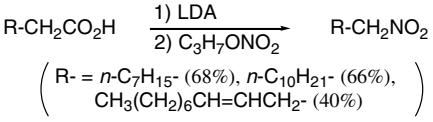



(2.19)

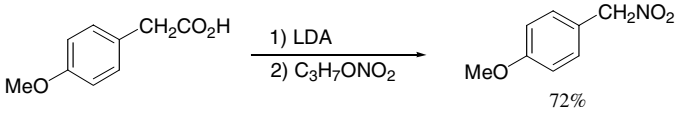



(2.20)

Nitration of delocalized carbanions with alkyl nitrates in the presence of bases provides a useful method for the preparation of nitro compounds. As a typical example, cyclopentanone, cyclohexanone, and cyclooctanone react with amyl nitrate in the presence of potassium *t*-butoxide in THF at a low temperature (–30 °C) to give α,α-dinitrocycloalkanones in 35–72% yield. The products are converted into α,ω-dinitroalkanes. Thus, the potassium salt of 2,6-dinitrocyclohexanone is converted to 1,5-dinitropentane in 78% yield on treatment with acid. In a similar way, 1,5-dinitropentane and 1,4-dinitrobutane are prepared in about 70% yield.[40] Dianions derived from carboxylic acids are nitrated to give nitroalkanes in 45–68% yield (Eq. 2.21).[41] Arylnitromethanes are readily prepared by this method (Eq. 2.22).[42] This method is useful for the preparation of arylnitromethanes with electron-rich aryl groups, which are generally difficult to prepare by nitration of the corresponding halides.

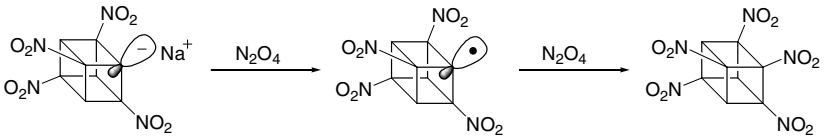



(2.21)



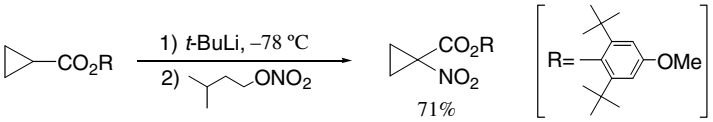

(2.22)

The sodium salts of 1,3,5,7-tetranitrocubane and 1,2,3,5,7-pentanitrocubane can be nitrated successfully with $N_2O_4$ in THF at low temperature. These reactions proceed by $N_2O_4$ oxidation of the anion to the radical and its combination with $NO_2$ (Eq. 2.23).[43] Such highly nitrated cubanes are predicted to be shock-insensitive, very dense, high-energy compounds with great potential as explosives and propellants.




(2.23)

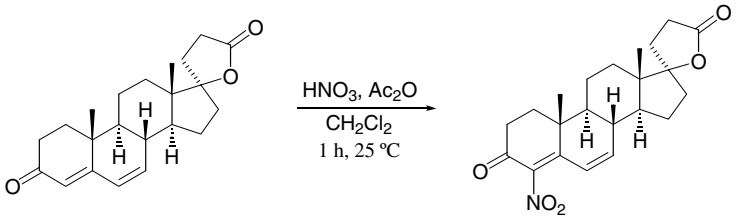
1-Nitrocyclopropane-1-carboxylate is prepared in 71% yield by nitration of the enolate derived from the cyclopropane carboxylate with isoamyl nitrate (Eq. 2.24). It is a precursor of α-amino acid, containing a cyclopropane ring.[44]




(2.24)

### 2.1.4 Alkenes

Nitration of alkenes gives conjugated nitroalkenes, which are useful and versatile intermediates in organic synthesis. Nitroalkenes are generally prepared either by nitration of alkenes or dehydration of 2-nitro alcohols formed via the Henry reaction (see Section 3.2.1). Nitration of alkenes with $HNO_3$ gives nitroalkenes in moderate yields, but this process has not been used for organic synthesis in a laboratory because of the lack of selectivity and decomposition of alkenes. Early references are found in Ref. 1. Nitration of the steroid canrenone using nitric acid and acetic anhydride occurs at the 4-position in 52% yield (Eq. 2.25).[45] This regiochemistry is noteworthy; early papers on nitration of the steroids with $HNO_3$ report the nitration at the 6-position.[46]

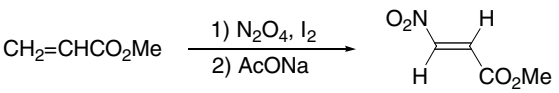



(2.25)

A convenient preparative method for conjugated nitroalkenes has been developed based on the reaction of nitrogen oxides. Nitric oxide (NO) is commercially available and used in the industry for the mass production of nitric acid. Nitric oxide is currently one of the most studied molecules in the fields of biochemistry, medicine, and environmental science.[47] Thus, the reaction of NO with alkenes under aerobic conditions is of a renewed importance.[48]

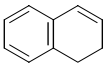
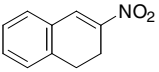
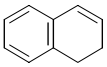
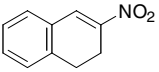
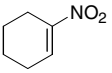
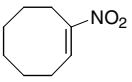
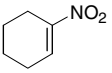
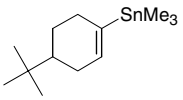
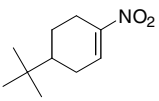
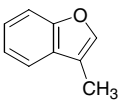
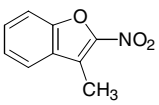
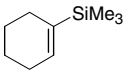
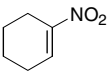
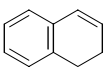
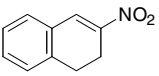
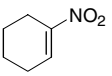
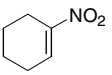
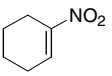
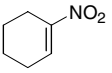
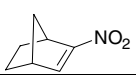
There are many reports for nitration of alkenes using various nitrating agents, which proceeds via an ionic or radical addition process.[49] Nitration of cyclohexene with acetyl nitrate gives a mixture of β-and γ-nitrocyclohexenes, 1,2-nitroacetate, and 1,2-nitronitrate. This reaction is not a simple ionic or radical process; instead, [2+2] cycloaddition of nitryl cation is proposed.[50]

Two important methods for the preparation of nitroalkenes are reported in Collective Volume 6 in Organic Synthesis. Methyl 3-nitroacrylate, which is a very important reagent for organic synthesis, is prepared by the reaction of methyl acrylate with $N_2O_4$ in the presence of iodine, which is followed by the subsequent treatment with sodium acetate (Eq. 2.26).[51] The reaction of alkenes with nitrogen oxides in the presence of oxygen gives a mixture of vicinal nitro nitrates and dinitro compounds, which are precursors of nitroalkenes. Thus, 1-nitrocyclooctene is prepared in 63–64% yield by the reaction of cyclooctene and $N_2O_4$ in the presence of $O_2$ (Table 2.2).[52]




(2.26)

**Table 2.2 Preparation of cyclic nitroalkenes via nitration**

| Cyclic alkenes | Reagent | Product | Yield (%) | Ref. |
|---|---|---|---|---|
|  | NO<br>$Al_2O_3$ |  | 86 | 53 |
|  | NO<br>H-zeolite |  | 76 | 54 |
|  | NO<br>H-zeolite |  | 86 | 54 |
|  | 1) $N_2O_4$, $O_2$<br>2) $Et_3N$ |  | 63 | 52 |
|  | 1) PhSeBr, $AgNO_2$<br>$HgCl_2$<br>2) $H_2O_2$ |  | 81 | 66 |
|  | $C(NO_2)_4$, DMSO |  | 94 | 37 |
|  | 1) *t*-BuLi/THF<br>$Me_3SnCl$<br>2) $C(NO_2)_4$,<br>DMSO |  | 72 | 72 |
|  | $AcONO_2$ |  | 73 | 73 |
|  | 1) $KNO_2$,<br>18-crown-6, $I_2$,<br>THF<br>2) pyridine |  | 90 | 64 |
|  | $NaNO_2$<br>$Ce(NH_4)_3(NO_3)_6$<br>AcOH |  | 96 | 56 |
|  | $NaNO_2$, $NaNO_3$<br>anodic oxidation |  | 41 | 59 |
|  | $NaNO_2$, $I_2$<br>$HOCH_2CH_2OH$ |  | 72 | 63 |
|  | 1) $NaNO_2$, $HgCl_2$<br>2) NaOH |  | 92 | 74 |
|  | 1) $NaNO_2$, $HgCl_2$<br>2) NaOH |  | 90 | 74 |