REVIEW

Some Aspects of the Chemistry of Nitro Compounds

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Dedicated with respect and admiration to Professor *Dieter Seebach*

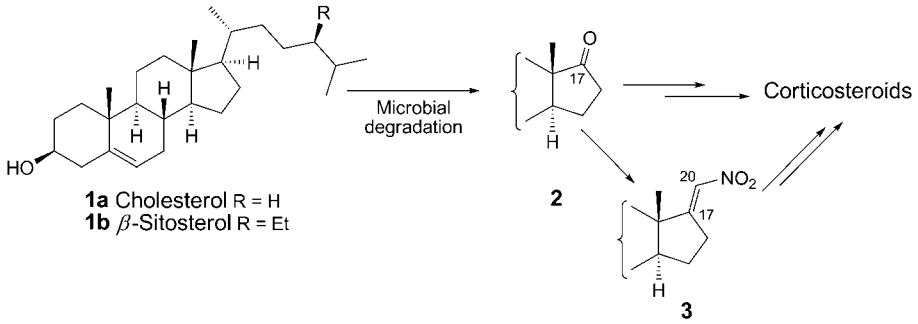
The present brief account relates our discovery of new reactions revolving around the chemistry of the NO_2 group. It covers the condensation of $MeNO_2$ with hindered ketones, and the synthesis of pyrroles, triazoles, and enamides. It also describes new transformations of allylic nitro compounds, such as their conversion to allylic sulfones and unsaturated lactones, their sigmatropic rearrangement into allylic nitrites and thence into allylic alcohols, as well as their use in a short synthesis of nitroestrone derivatives. This is followed by an unusual reduction method furnishing unsubstituted amines (RR′C=NH) under conditions where these hydrolytically labile species can be captured inter- or intramolecularly. Finally, a mechanistic study of a strange alkyne-forming reaction, first reported by *Abidi* and later shown by *Corey* and co-workers to proceed through allylic nitro intermediates, ultimately led to a practical and powerful synthesis of alkynes starting from β-keto esters.

Introduction. – My early fascination with the chemistry of the NO_2 group was indirectly responsible for my first encounter with Professor *Dieter Seebach*, nearly 30 years ago, in March 1983. He was the plenary speaker at the *'Journée de Printemps'* of the French Chemical Society, and I was an invited speaker, just fresh out of my Ph.D. and trembling at the prospect of speaking in front of a large audience. I presented on that day work related to the synthesis and modification of nitro steroids, and Professor *Seebach*'s group at the time was heavily involved in the study of silyl nitronates and dianions derived from nitro compounds, so we had a natural topic for discussion on our way to lunch. Our paths crossed a few times after that, and he never failed to give words of encouragement. The present brief account, relating some aspect of NO_2 chemistry we developed over the years, is an homage to his immense contributions to this and numerous other areas of chemistry.

From Nitro Steroids to Pyrroles. – The first synthetic problem we tried to solve using the chemistry of the NO_2 group concerned the side chain of the corticosteroids. In the 1970s, the microbiological degradation of the saturated side chain of abundant sterols such as cholesterol (**1a**) and especially β-sitosterol (**1b**), a waste product from soybean, became industrially feasible and opened a powerful and practical access to various 17-ketosteroids **2** [1]. The sudden availability of such elaborate, yet relatively cheap raw materials prompted the search for alternative, industrially viable processes

for the manufacture of clinically important corticostereroids starting from 17-ketosteroids. The efficient introduction of the missing corticosteroid side chain thus became a major synthetic challenge (*Scheme 1*).

Scheme 1. *Corticosteroids from Abundant Sterols*



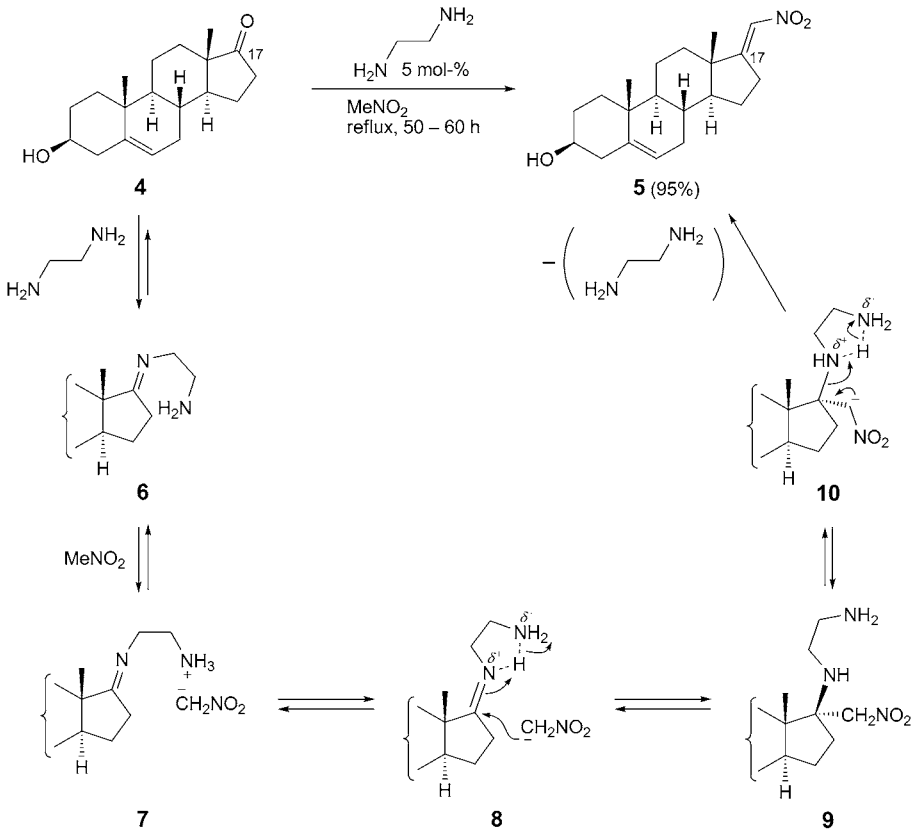
One of the approaches we considered hinged on accomplishing a *Knoevenagel* type condensation of $MeNO_2$ on a 17-ketosteroid to give nitro alkene **3** and then applying the rich chemistry of the NO_2 group to further elaborate the side chain. A study of the existing literature, however, clearly indicated that such condensations were far from trivial. While the formation of nitrostyrenes and their heteroaromatic analogs by reaction of $MeNO_2$ with aromatic or heteroaromatic aldehydes is easily accomplished using a variety of amine catalysts, the corresponding condensation even with simple ketones, let alone hindered 17-ketosteroids, is generally problematic and inefficient [2].

Indeed, when dehydroepiandrosterone (**4**) was subjected to several typical condensation conditions, only traces at best of the desired nitro alkene **5** were observed. After months of failure, it occurred to us that converting an inoperative intermolecular condensation into a *pseudo*-intramolecular reaction by using ethane-1,2-diamine as the catalyst would perhaps overcome the poor reactivity of the sterically hindered 17-ketone.

Indeed, the use of catalytic amounts of ethane-1,2-diamine in neat refluxing $MeNO_2$ accomplished the desired transformation quite efficiently [3a][3b] (*Scheme 2*). The condensation of the diamine leads to imine **6**, which still contains a dangling free amine that is capable of partially deprotonating $MeNO_2$ to afford aminium salt **7**. Electrostatic attraction now ensures that the nitronate is close to the imine group and able to react in an essentially intramolecular manner, most likely *via* structure **8**, where the iminyl N-atom is partially protonated and, therefore, more receptive to a nucleophilic attack by the nitronate anion. Regeneration of the diamine catalyst is also assisted through intermediates **9** and **10**. In this transformation, which may be viewed as an early example of organocatalysis, the ethane-1,2-diamine acts like a 'microenzyme', facilitating every step of the process.

With the desired nitro steroid **5** in hand, various corticosteroid derivatives could then be elaborated using standard reactions of the NO_2 group [3a][3b]. Thus, a *Henry* reaction with aqueous HCHO, followed by acetylation, furnished allylic nitro steroid **11** in nearly quantitative yield. The NO_2 group could be reduced with aqueous $CrCl_2$ to

Scheme 2. *Condensation of $MeNO_2$ with a 17-Ketosteroid*

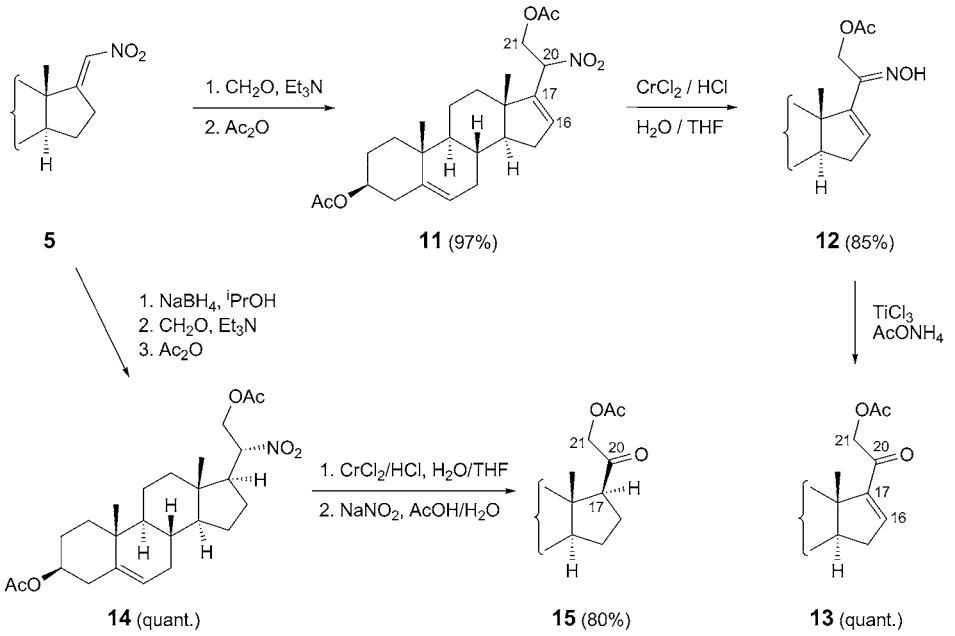


give oxime **12**. This reduction is complete upon mixing of the components: the beautiful sky-blue color of the chromous salt instantaneously changes to the stunning emerald green of Cr^{III}. Finally, the oxime was cleaved into the desired 20-ketosteroid **13** with aqueous $TiCl_3$. The nitro alkene in steroid **5** could also be reduced with $NaBH_4$ before subjecting it to the *Henry* reaction. The resulting intermediate **14** was then converted to the corresponding 20-ketosteroid **15** in high yield (*Scheme 3*).

The diamine-mediated condensation of $MeNO_2$ with ketones opens a practical access to various nitro alkenes [3]. Numerous ketones can now be made to react with $MeNO_2$. The analogous condensation with $EtNO_2$ and higher nitro alkanes is much less efficient, but moderate yields can sometimes be secured with more reactive ketones such as cyclohexanones. *N*-Methylethylenediamine, and the unsymmetrical *N*,*N*-dimethylethylenediamine are equally effective as catalysts, but not the symmetrical *N*,*N*′-dimethylethylenediamine congener [3b][1]). This indicates that a primary amine is

[1]) The use of *N*,*N*-dimethylethylenediamine as catalyst for the condensation was later 'rediscovered' [3c].

Scheme 3. *Construction of Corticosteroid Side Chains*

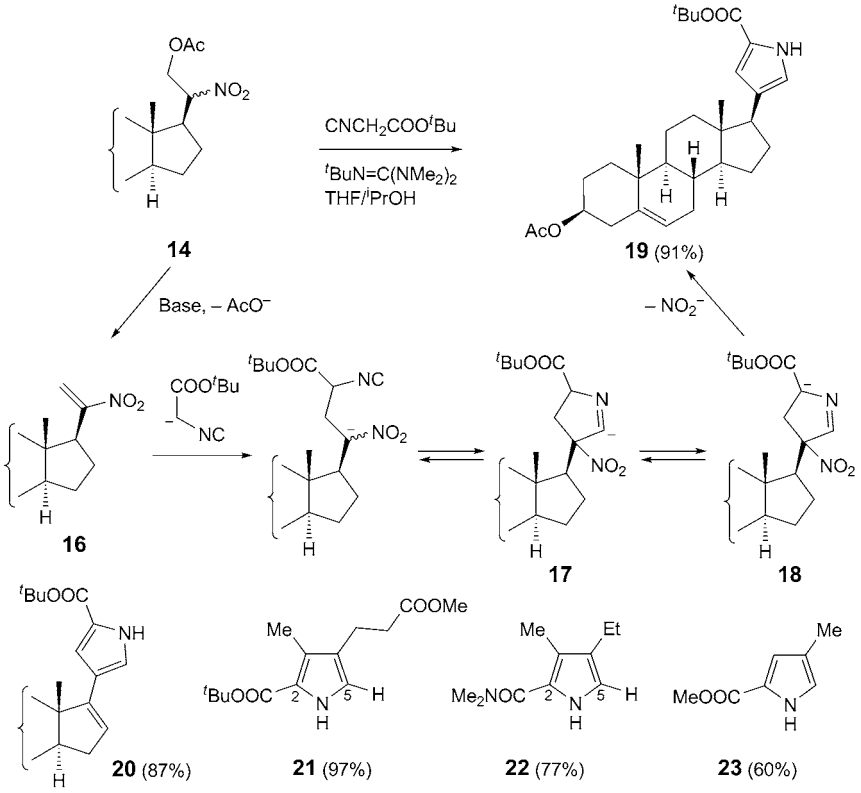


necessary for imine formation, but that the second amine, whose role is to act as a base, may be primary, secondary, or tertiary.

In another approach to the corticosteroid side chain, we used a strategy involving condensation of dimethyl α-isocyanoethylphosphonate with 17-ketosteroids [4]. It seemed, therefore, interesting to examine the reaction of α-isocyano carbanions with the strongly electrophilic nitro alkenes, which can be generated *in situ* from nitro acetates such as **14**. We were delighted to find that exposure of **14** to *tert*-butyl α-isocyanoacetate in the presence of a strong organic base gives rise to pyrrole carboxylate **19** in high yield [5]. The reaction proceeds, as depicted in *Scheme 4*, by a rapid *Michael* addition of the α-isocyanoacetate carbanion to nitro alkene **16**, followed by a reversible ring closure of the resulting adduct into anion **17**. This latter intermediate is in equilibrium with its isomer **18**, from which a NO_2^- anion is expelled to give **19** after a simple prototropic shift.

A few further examples from our work are depicted in the lower part of *Scheme 4*. Pyrrole **20** is derived from nitro steroid **11** and contains a vinyl substituent. The simpler pyrrole **23** is the trail marker pheromone of the Texas leaf-cutting ant, *Atta texana* (BUCKLEY). Pyrroles **21** and **22** contain at C(3) and C(4) substituents that are often found in natural porphyrins. Indeed, pyrroles obtained by this route constitute ideal building blocks for porphyrin synthesis. They are unsubstituted at C(5), allowing couplings to other pyrroles, and C(2) can be temporarily shielded by a (*tert*-butoxy)carbonyl (Boc) group, which is easily removed by treatment with acid. They may also be substituted by an amido group as in **22**. Conversion of the amide to the *Vilsmaier* salt enables easy attachment of further pyrrole units and the construction of

Scheme 4. *Synthesis of 1*H*-Pyrroles from Nitro Alkenes*

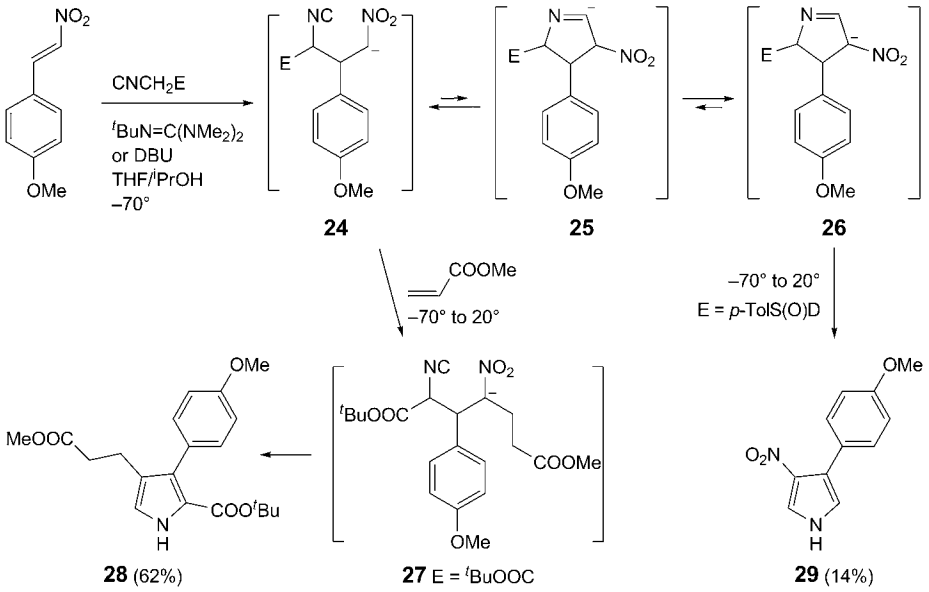


porphyrins by what is called the oxo-bilane route. Both the Boc and the carboxamido substituents are difficult to introduce by other methods.

The cyclization of the nitronate onto the isocyano group is reversible and, in the case of a *primary* nitronate such as **24** (*Scheme 5*), aromatization by elimination of a nitrite is hampered by the formation of highly stabilized anion **26**. At low temperature, the cyclization into **25** appears to be slow enough to allow *Michael* addition to an electrophilic alkene such as methyl acrylate. This leads to a secondary nitronate **27**, which readily cyclizes to give finally pyrrole **28** in what may be viewed as a multicomponent variant [5b]. The presence of stabilized anion **26**, when the temperature is raised, could be demonstrated by starting with *p*-toluenesulfonylmethyl isocyanide (TsMIC) as the isocyano component. This leads to intermediate **26**, with E = *p*-TolS(O)O, which can aromatize by elimination of *p*-toluenesulfinate to give nitropyrrole **29**, albeit in low yield (14%).

The aforementioned approach to pyrroles, either directly from nitro alkenes or from their nitro acetate precursors, is general, convergent, and atom-economical. The nitro acetate precursors are usually more convenient to handle in the aliphatic series than the corresponding nitro alkenes; they are also readily available by *Henry* addition

Scheme 5. *Multicomponent Synthesis of 1*H*-Pyrroles*



of a nitro alkane to an aldehyde followed by acetylation [2a]. In some cases, the two steps can be combined through the use of 4-(dimethylamino)pyridine (DMAP) as both the base for the *Henry* reaction and the promoter for the acetylation [5b].

Over the years, hundreds of pyrroles have been prepared by what is now called the *Barton–Zard* reaction [6]. This reaction is in fact a direct application of the observations of *Schöllkopf* [6a][6b], whose earlier fundamental contributions are not only more extensive but also surprisingly underappreciated. It would be appropriate and fair to perpetuate his memory by adding his name to this powerful pyrrole synthesis[2]).

Further Reactions of Nitro Alkenes. – We exploited the high electrophilic character of nitro alkenes and the ability of the NO_2 group to undergo β-elimination as a nitrite anion to perform a double addition of cyanide [3b]. This is showcased by the conversion of steroid nitro acetate **14** to dicarbonitrile **30** upon heating with NaCN in DMSO at 80° (*Scheme 6*). In this reaction sequence, the CN^- acts alternately as a base and as a nucleophile. All the intermediates shown may be isolated if desired, simply by modifying the experimental conditions. In the context of corticosteroids side-chain synthesis, this transformation is of no particular importance; however, it could represent a mild, versatile route to various substituted succinic acid derivatives **31** through hydrolysis of the CN groups.

The experience we gained in the chemistry of nitro alkenes served us to unravel a strange observation made by *Zefirov et al.* over 40 years ago [8]. The Russian group

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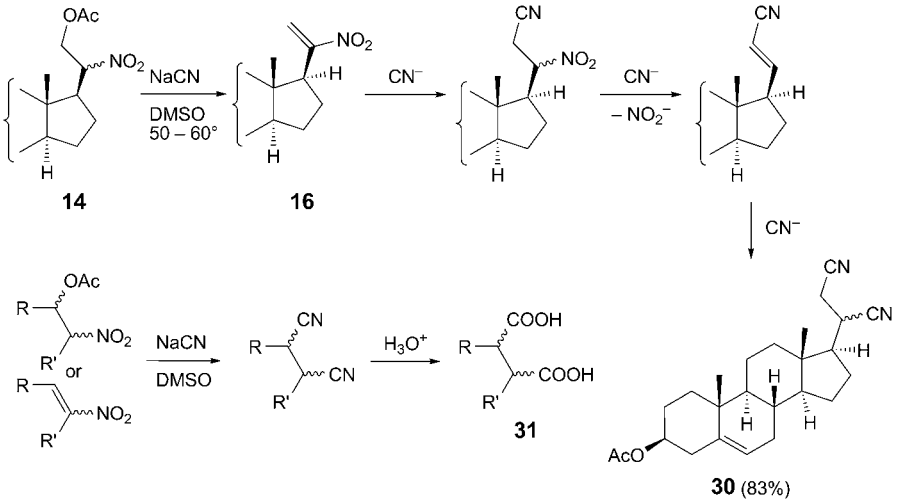
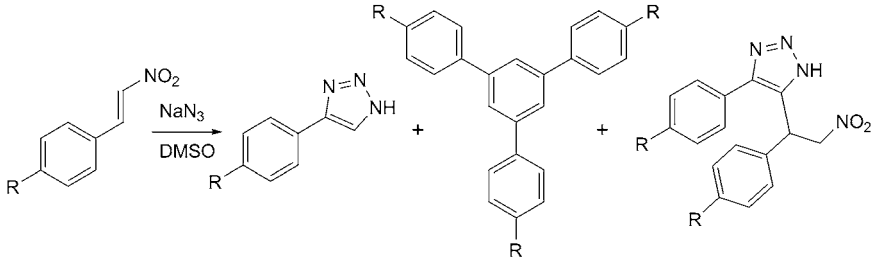
[2]) This modification has just been introduced [7].

Scheme 6. *Synthesis of 1,2-Dicarbonitriles*



reported that reaction of nitro-styrenes **32a**–**32c** with NaN_3 in DMSO *at room temperature* gave the corresponding triazoles **33a**–**33c** in *ca.* 60% yield, along with 'considerable quantities' of 1,3,5-triarylbenzenes **34a**–**34c** (*Scheme 7*). No other compounds were reported. The formation of the symmetrical triarylbenzenes clearly requires the condensation of *three nitrostyrene molecules.* It seemed to us surprising that a reaction could lead, in comparable yields, to a simple triazole, on one hand, and to a product resulting from a complex trimerization on the other, without the formation of significant side products. We, therefore, decided to have a fresh look at this reaction [9].

Scheme 7. *Synthesis of 1,2,3-Triazoles from Nitro Alkenes*



32a R = H
32b R = Cl
32c R = Br

33a R = H
33b R = Cl
33c R = Br

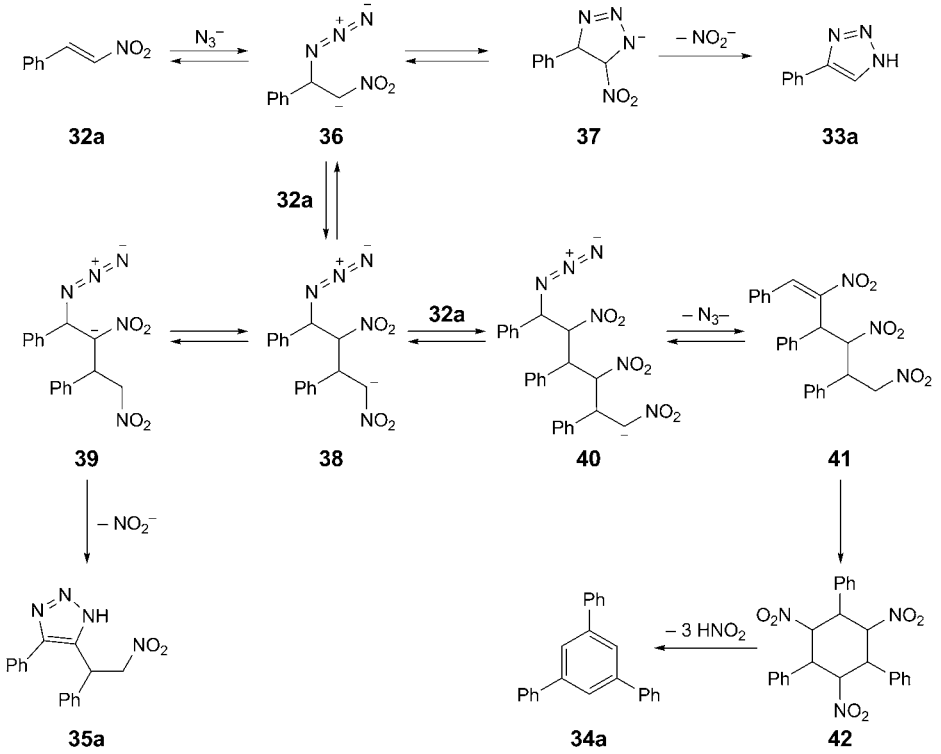
34a R = H
34b R = Cl
34c R = Br

35a R = H
35b R = Cl
35c R = Br

We first tried to reproduce the reaction relying on the scant experimental information provided in the original communication [9]. Stirring nitro-styrene **32a** with NaN_3 in DMSO *at room temperature* produced only a small yield of triazole **33a** but did not give any 1,3,5-triphenylbenzene (**34a**). The main product, isolated from a relatively

complex reaction mixture, was triazole **35a** (*Scheme 8*). Various modifications in the experimental procedure did not cause any significant change, except when the temperature was modified. At 80°, 4-phenyltriazole (**33a**) and 1,3,5-triphenylbenzene (**34a**) were formed in 24 and 13% yield, respectively, but triazole **35a** was still the major product and could be isolated in 40% yield.

Scheme 8. *Mechanism for the Formation of 1,2,3-Triazoles from Nitro Alkenes*

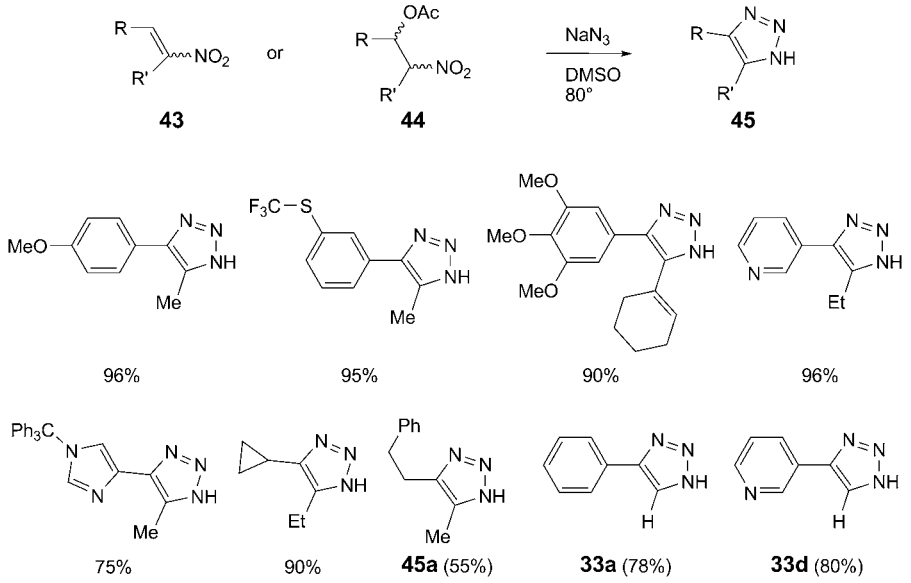


How the Russian group could obtain aryltriazoles **33a**–**33c** and 1,3,5-triarylbenzenes **34a**–**34c**, in apparently good yield, without observing the formation of the corresponding substituted triazoles **35a**–**35c** is still a mystery. Nevertheless, a plausible mechanistic manifold could be put forward to rationalize these results (*Scheme 8*). Conjugate addition of azide to the nitro-styrene gives rise to adduct **36**, which only sluggishly undergoes cyclization into triazole **33a**. The inefficient ring closure of *primary* nitronate **36** to give **37** allows a second *Michael* addition to nitro-styrene to take place to give another primary nitronate intermediate **38**, which is in equilibrium with its isomeric *secondary* nitronate **39**. The latter is able to cyclize more efficiently to give substituted triazole **35a**. This situation is analogous to that discussed in connection with the multicomponent pyrrole synthesis in *Scheme 5*. Intermediate nitronate **38** can participate in a further *Michael* addition to nitro-styrene to give primary nitronate **40**, and this can undergo elimination of azide to furnish nitro alkene **41**. Internal *Michael*

addition and elimination of three molecules of HNO_2 from the resulting trinitrocyclohexane **42** finally generates the observed symmetrical 1,3,5-triphenylbenzene (**34a**).

With this information in hand, it became possible to devise conditions leading to high yields of triazoles **45**, starting either directly from nitro alkenes **43** or from their nitro acetate precursors **44** [9]. Some representative examples are given in *Scheme 9*. In the case of substituted nitro alkenes **43** or nitro acetates **44** ($R' \neq H$), mere heating at 80° with NaN_3 in DMSO furnishes high yields of the desired triazoles. This reflects the efficiency of ring closure of the corresponding *secondary* nitronates. All triazoles were obtained from the nitro alkenes, except triazole **45a**, which originated from the corresponding nitro acetate **44** ($R = PhCH_2CH_2$; $R' = Me$). For *unsubstituted* nitro alkenes **43** or nitro acetates **44** ($R' = H$), slow addition of the NO_2 component to a hot solution of NaN_3 in DMSO favors the desired but more sluggish *unimolecular* ring closure (*e.g.*, **36** to **33a** in *Scheme 8*) over the undesired *bimolecular* conjugate addition to a second molecule of nitro alkene leading to more complex triazoles such as **35a**. In this manner, monosubstituted triazoles **33a** and **33d** were obtained in 78 and 80% yield, respectively (*Scheme 9*).

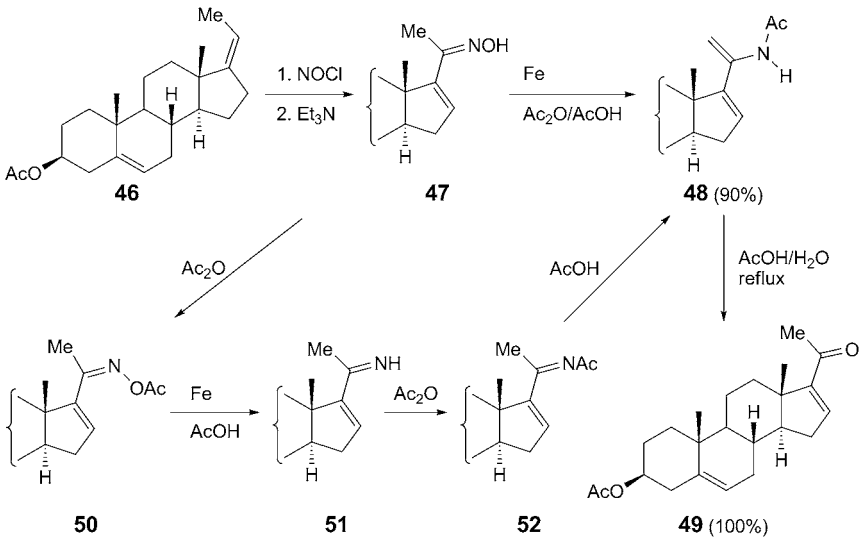
Scheme 9. *Examples of 1,2,3-Triazoles from Nitro Alkenes*



In yet another route to corticosteroids from 17-ketosteroids [10], we prepared pregnene **46** from the 17-ketosteroid precursor by a *Wittig* reaction, converted it to oxime **47** with NOCl and base, then used a combination of Fe powder, AcOH, and Ac_2O to convert the oxime to dienyl-acetamide **48**, which could be readily hydrolyzed to the pregnadienolone **49** (*Scheme 10*). Oxime **47** itself is not rapidly reduced by the weak reducing combination of Fe and AcOH, in contrast to the oxime acetate **50**. The reduction furnishes imine **51**, which is protected from hydrolysis by the presence of Ac_2O and captured by the same reagent to give *N*-acetyl imine **52**. This intermediate is

impervious to the mild reducing agent and simply tautomerizes in the acidic medium into the more stable *N*-dienyl-acetamide **48**. This reduction represents a convenient general route for the conversion of oximes to *N*-enyl-acetamides. It has since been extensively used in the literature, since enamides can be readily reduced enantioselectively using chiral homogeneous catalysts [11].

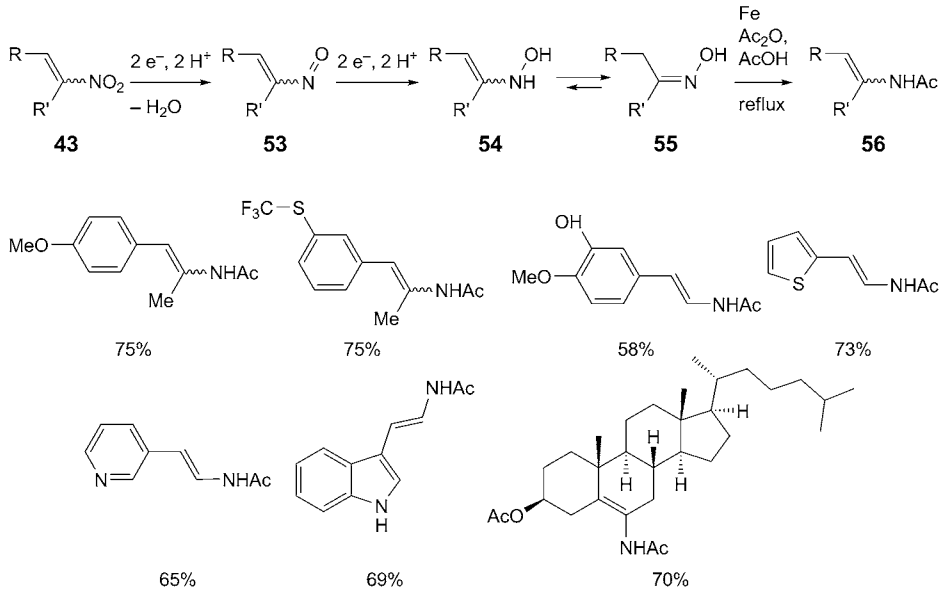
Scheme 10. *Reduction of Oximes into Ene-acetamides*



By considering the intermediates involved in the reduction of nitro compounds, it seemed reasonable to expect that the same combination of Fe powder, AcOH, and Ac_2O used above would convert nitro alkenes to *N*-enyl-acetamides. Dissolving metals reduction of the NO_2 group proceeds usually through the intermediate hydroxylamines [2a]. In the case of nitro alkenes **43**, the corresponding vinyl hydroxylamines **54** would tautomerize rapidly to the oximes **55** and should, therefore, be converted to *N*-enyl-acetamides **56** in the same way (*Scheme 11*). In the event, a variety of nitro alkenes were smoothly transformed into the desired *N*-enylacetamides, as shown by the examples assembled in *Scheme 11* [12]. The process applies to nitro alkenes derived from aromatic or heteroaromatic aldehydes as well as to purely aliphatic members. Electron-poor heteroaromatic rings, such as pyridines, are not affected by the mild reducing conditions. Other carboxylic acid/carboxylic anhydride combinations may be applied, if enamides other than *N*-enyl-acetamides are desired. The direct conversion of nitro alkenes to enamides had not hitherto been reported, and the present method constitutes a convenient entry into a class of very useful synthetic intermediates.

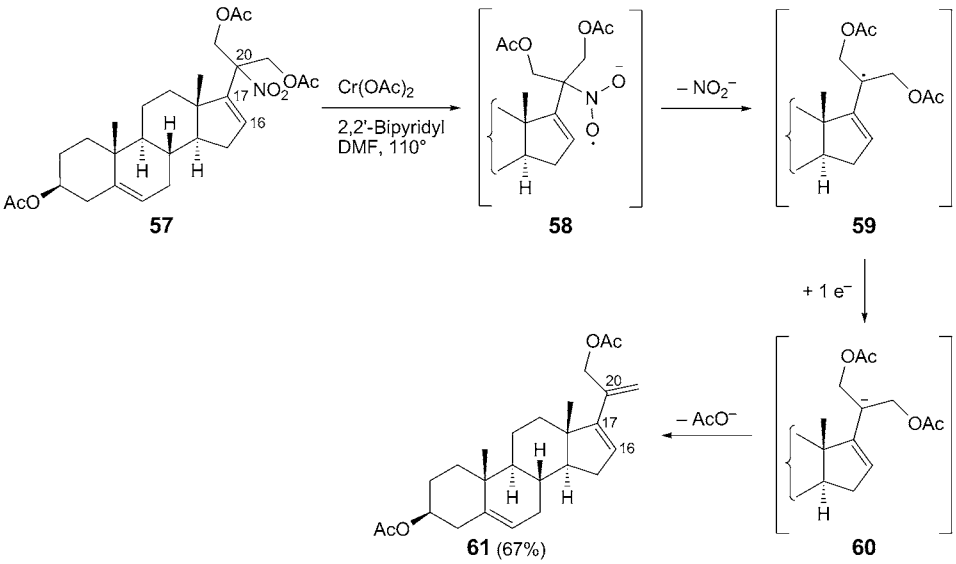
Fun with Allylic NO_2 Derivatives. – The first step in the reduction of nitro compounds with dissolving metals or low-valent metallic salts is a one-electron transfer leading to a radical anion. This species then undergoes a second electron transfer, protonation, and loss of H_2O to give a nitroso intermediate (*e.g.*, **53** in *Scheme 11*). It seemed possible to divert this reduction process by contriving a situation where the

Scheme 11. *Formation of Ene-acetamides from Nitro Alkenes*



radical anion would undergo fragmentation before the second electron-transfer step. The transformation we specifically had in mind is outlined in *Scheme 12* starting with nitro triacetate **57**, a compound easily prepared from nitro steroid **5** through a double

Scheme 12. *Formation of a Diene from Nitro Acetates*



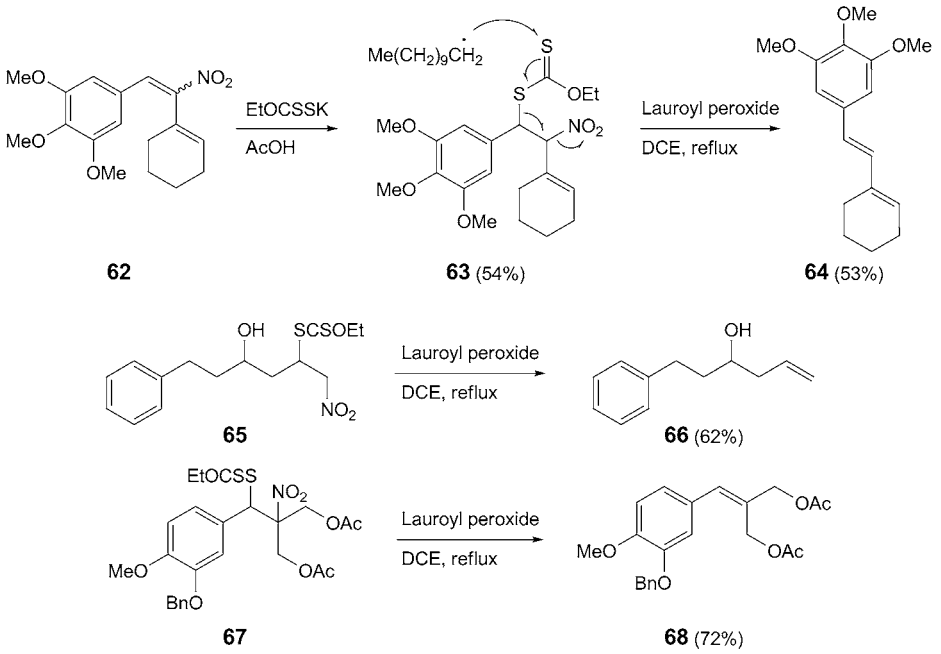
Henry addition with HCHO and acetylation. Electron transfer would lead to radical anion **58**, which could undergo fragmentation to give stabilized tertiary allylic radical **59**. A second electron transfer would furnish the corresponding carbanion **60** and cause the expulsion of an acetate anion to give diene **61**.

It took us considerable experimentation to find the right reducing system to accomplish this transformation: with powerful reducing agents, further reduction of the radical anion **58** took place before the fragmentation could happen; with weaker reducing species, the second electron transfer leading to anion **60** was too slow to compete with dimerization of radical **59** [13]. With Ti^{III} reducing agents, for instance, over-reduction of the NO_2 group to the amine was observed, whereas with $Cr(OAc)_2$ in toluene, THF, or MeCN, we isolated steroid dimers in modest yields. The latter observation was nonetheless encouraging, since, at least, it established the feasibility of the fragmentation of the radical anion **58**. Moreover, by using the more basic DMF as the solvent, we started observing significant amounts of the desired diene **61**. Finally, addition of 2,2′-bipyridyl further enhanced the reducing ability of the $Cr(OAc)_2$ and suppressed most of the unwanted dimeric products. Under these conditions, diacetoxy nitro steroid **57** furnished diene **61** in 67% yield. This transformation is not of very broad generality in terms of tolerance for substituents and is sometimes capricious, but nevertheless provides access to a family of synthetically useful dienes.

A different, more versatile approach to dienes as well as to alkenes hinges on the fast extrusion of NO_2 from a β-nitroalkyl radical [14]. We took advantage of the ease of addition of a xanthate salt to nitro alkenes under mild *acidic* conditions to form β-nitro xanthates, as exemplified by the conversion of nitro alkene **62** into nitro xanthate **63** (*Scheme 13*). The need for acidic conditions is to avoid a *retro-Michael* reaction giving back the nitro alkene. Upon exposure of **63** to lauroyl peroxide (3 equiv.) in refluxing 1,2-dichloroethane (DCE), the elimination proceeded as anticipated to furnish diene **64** in a synthetically useful yield. The undecyl radical, produced by the thermal decomposition of lauroyl peroxide, attacks the thiocarbonyl S-atom of the xanthate causing its fragmentation and concomitant β-elimination of the NO_2 group. Mono-, di-, and trisubstituted alkenes can be obtained by this combination of conjugate addition of a xanthate salt and homolytic fragmentation. Two further examples are displayed in *Scheme 13* involving the conversion of nitro xanthates **65** and **67** into alkenes **66** and **68** under the same mild conditions.

The easy homolytic extrusion of NO_2 and the ready availability of allylic nitro compounds led us to examine another transformation involving radicals, namely the possibility of producing allylic sulfones by the radical chain process outlined in *Scheme 14*. This conception took its inspiration from earlier studies by *Whitham* and co-workers on the reaction of sulfonyl radicals with allyl sulfones [15]. In the event, the allylic NO_2 group could indeed be replaced by a sulfone in synthetically useful yields when heated under air with $PhSO_2Na$ in aqueous AcOH, as indicated by the examples in *Scheme 14* [16]. In the case of primary and unhindered secondary allylic nitro substrates, the initial sulfone undergoes a radical chain allylic rearrangement to give the more stable isomeric allyl sulfone, where the sulfone occupies the same position as the initial NO_2 group. This is illustrated by the conversion of 1-(nitromethyl)dodec-1-ene (**69**) into allylic phenyl sulfone **71** *via* intermediate phenyl sulfone **70** and by the formation of allylic phenyl sulfone **73** from 1-(1-nitroethyl)cyclohex-1-ene (**72**).

Scheme 13. *Formation of Dienes and Alkenes from Nitro Alkenes*

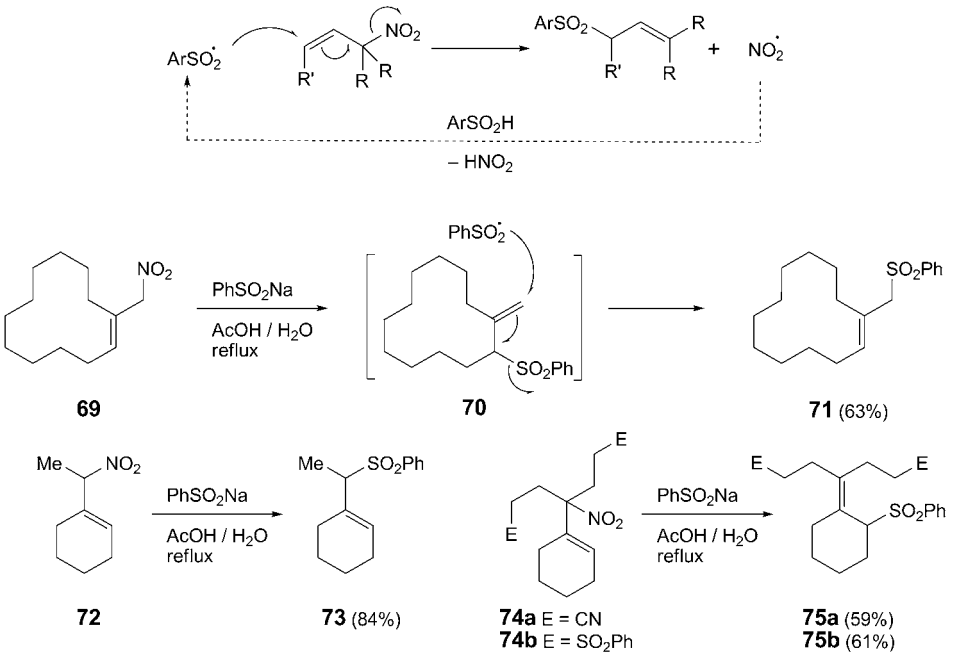


Tertiary allylic nitro derivatives invariably gave the 'normal' sulfones as shown by the synthesis of **75a** and **75b** from the corresponding nitro-alkene precursors **74a** and **74b**.

In the course of this work, we made an interesting observation: the reaction of triacetoxy nitro steroid **57** furnished not only the expected sulfone **76a** but also significant amounts of hydroxy derivative **76b** (*Scheme 15*) [16]. It was surprising in the first place that hydrolysis of the acetate should occur in a medium rich in AcOH ($AcOH/H_2O$ 3 :2); but if acid-catalyzed hydrolysis was indeed taking place, why should it only affect the side-chain acetates and not the acetate in ring *A*? The most plausible explanation is that, in addition to the radical process, a solvolytic pathway is operating leading to intermediate **77**. Quenching by the sulfinate at the 16α-position gives rise to sulfone **76a**, whereas attack by H_2O furnishes alcohol **78**, which, in turn, reacts with the toluenesulfinate to give sulfone **76b**. In principle, the allylic sulfone products **76a** and **76b** are also capable of undergoing solvolysis in a medium of high dielectric constant such as aqueous AcOH and the steps must, therefore, be reversible, as shown. As would be expected, the solvolysis is made especially easy in this particular case because an allylic tertiary cationic species is generated.

Corroboration for this rationale emerged from a second experiment involving nitro diester **79**, which gave rise to lactone **81** (*Scheme 16*), *both in the presence and in the absence of* $PhSO_2Na$ [16]. The formation of the lactone ring can only be the result of a solvolysis leading to stabilized tertiary allylic cationic species **80**. This transformation was easily extended to secondary derivatives, thus expanding its scope considerably.

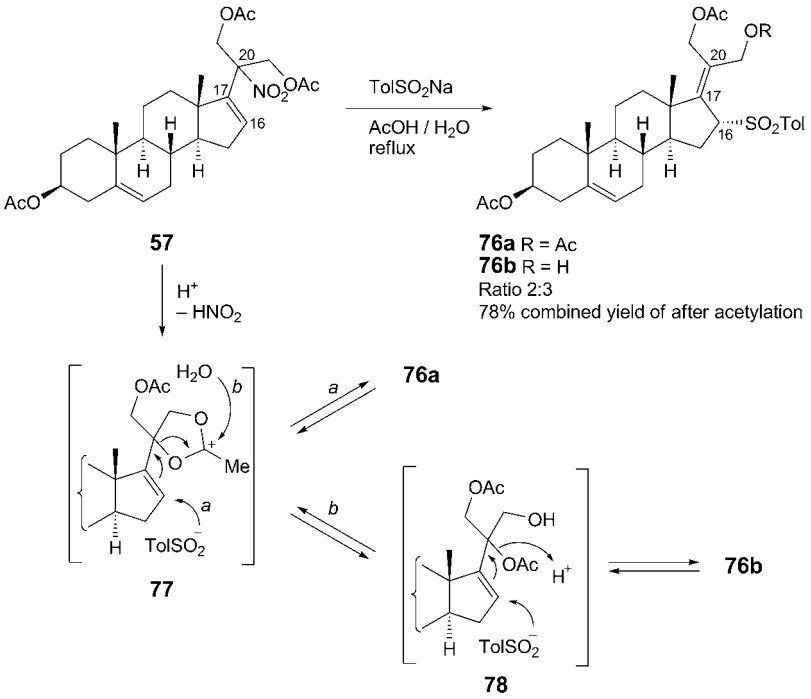
Scheme 14. *Synthesis of Allyl Sufones*



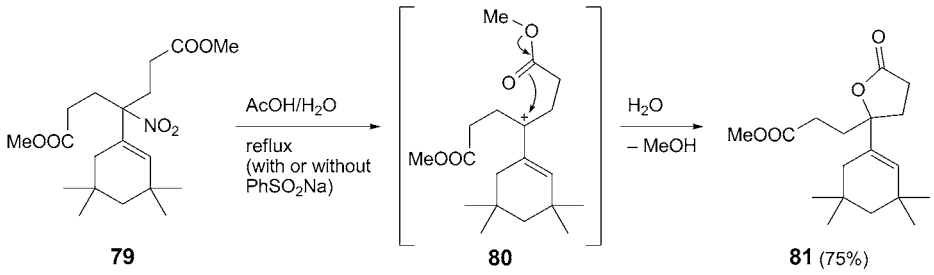
The precursors are readily prepared by *Michael* addition of nitro alkenes to acrylates, providing access to allylic γ-lactones with a variety of substitution patterns. Allylic γ-lactones are deceptively simple structures that are, in fact, only tediously accessible by existing routes. They offer numerous possibilities for synthesis, in particular, when associated with the powerful *Claisen* rearrangement. For example, reaction of lactone **83**, derived from nitro ester **82**, with a combination of Ph_3P and CCl_4 in refluxing THF affords in moderate yield dichloro-enol ether **84**, which readily rearranges upon heating into dichloro-cycloheptenone **85** (*Scheme 17*; yields in parentheses are based on recovered starting material) [17]. Interestingly, treatment of this dichloro ketone with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in hot MeOH induces an unusual *Favorskii* rearrangement leading to ring contraction and the formation of cyclohexa-1,4-diene **86** in good yield. This route complements nicely more conventional approaches to cyclohexa-1,3-dienes, since the disposition of the skipped diene is different from the one normally expected from a *Birch* reduction of the corresponding aromatic carboxylic acid.

Sigmatropic rearrangements are fascinating and rather elegant chemical transformations that appear under a variety of guises. Allylic sulfoxides undergo the well-known and reversible thermal *Mislow–Braverman–Evans* [2,3]-sigmatropic transposition into the corresponding allylsulfenates (*Scheme 18*) [18]. The corresponding rearrangement of allylic selenoxides is also widely used in synthesis and often proceeds spontaneously at or even below room temperature. Much less common is the *Meisenheimer* [2,3]-sigmatropic rearrangement of allylic amine oxides **87** into allylic

Scheme 15. *Unexpected Acetate Hydrolysis*



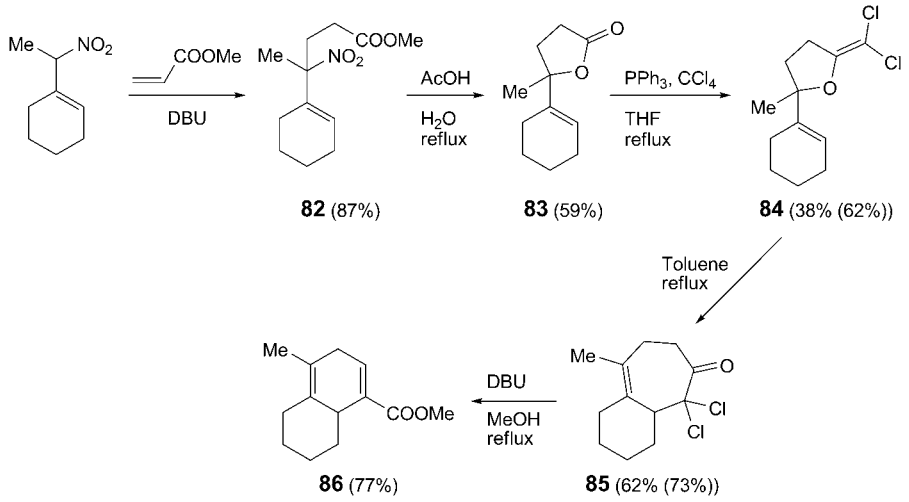
Scheme 16. *Formation of an Unsaturated γ-Lactone*



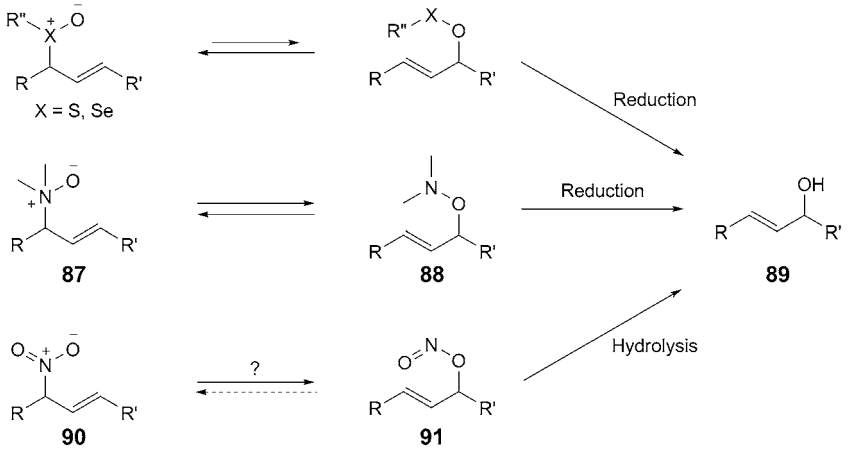
hydroxylamines **88** [19]. In both of these transformations, a reduction step is required to produce the final allylic alcohol **89** (in the case of selenates, a fast disproportionation takes place within the reaction medium, and no additional reducing agent is needed). Allylic nitro compounds **90** bear a structural kinship with amine oxides, and the possibility of inducing a similar thermal [2,3]-sigmatropic rearrangement looked enticing, as it would furnish first allylic nitrite **91** then allylic alcohol **89** by simple hydrolysis.

Indeed, this transformation proved feasible, but required relatively high temperatures. This explains perhaps why it was not observed in the past. Nevertheless, heating

Scheme 17. *Synthesis of Cycloheptanones and Cyclohexa-1,3-dienes*



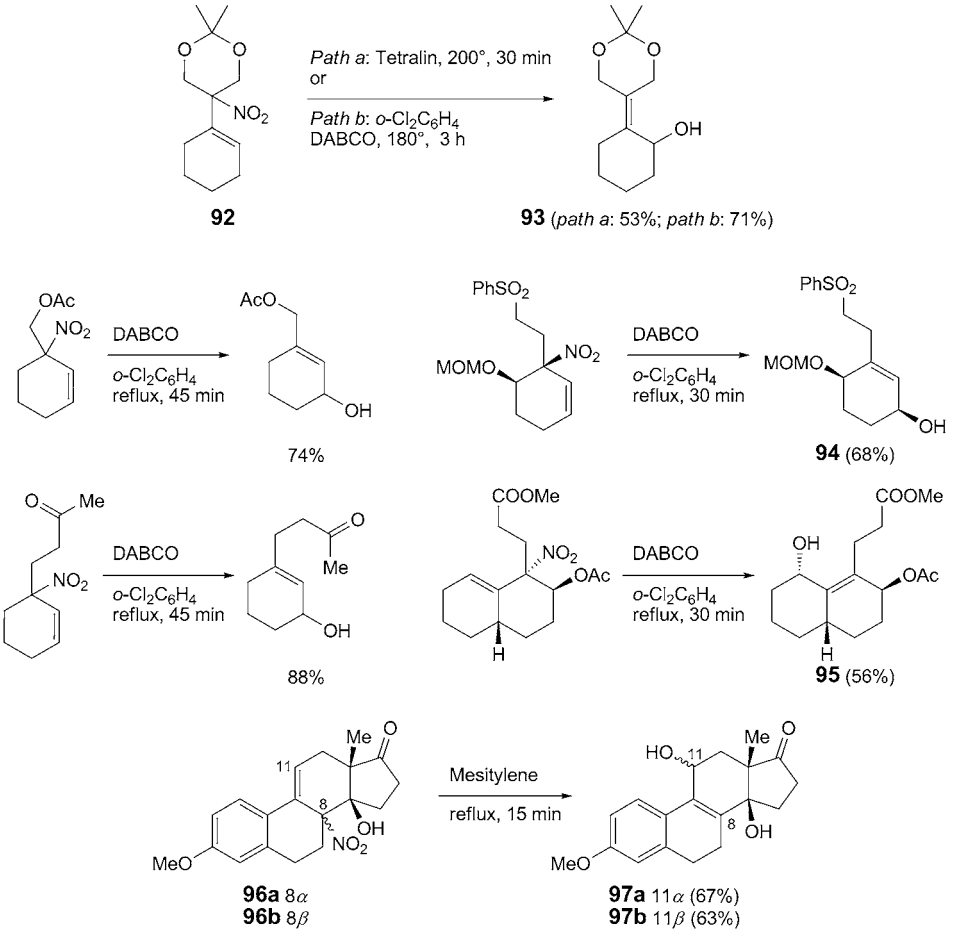
Scheme 18. *Sigmatropic Rearrangements*



various allylic nitro compounds to temperatures ranging from 160° to 200° furnishes the corresponding rearranged allylic alcohols, as seen by the examples collected in *Scheme 19* [20]. The reaction is limited to secondary and tertiary NO_2 derivatives, with the latter rearranging more easily. Primary allylic nitro compounds decompose at the temperatures needed to trigger the rearrangement.

Dehydration of the allylic alcohols (or the corresponding nitrites) into dienes at the elevated temperatures needed to promote the rearrangement is the main side reaction. We later found that addition of 1,4-diazabicyclo[2.2.2]octane (DABCO) protected the allylic alcohol produced by neutralizing any acid or acidic sites (*e.g.*, the silica surface of the glass vessel) and increased the yields significantly [20b]. This is shown in the

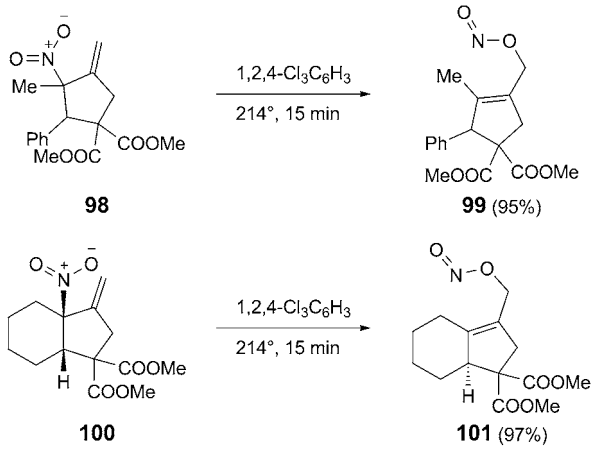
Scheme 19. *Allylic Alcohols from Allylic Nitro Compounds*



generation of allylic alcohol **93** from nitro-alkene precursor **92** in the presence and absence of DABCO. Most of the earlier examples would have certainly benefited from these modified conditions. The stereoselective formation of allylic alcohols **94** and **95** from their respective precursors constitutes a strong evidence for the suprafacial sigmatropic rearrangement. Additional corroborating evidence for the sigmatropic nature of the reaction arose from the observation that the two epimeric nitro steroids **96a** and **96b** (*Scheme 19*) furnish the corresponding allylic alcohols **97a** and **97b** stereospecifically upon heating with no cross-over products formed, in line with a suprafacial process [21].

At the scale at which these reactions were carried out, the nitrite intermediates were simply hydrolyzed on the silica-gel columns, and the desired alcohols were isolated directly. Very recently, *Bonne* and co-workers [22] succeeded in isolating

Scheme 20. *Formation of Allylic Nitrites*

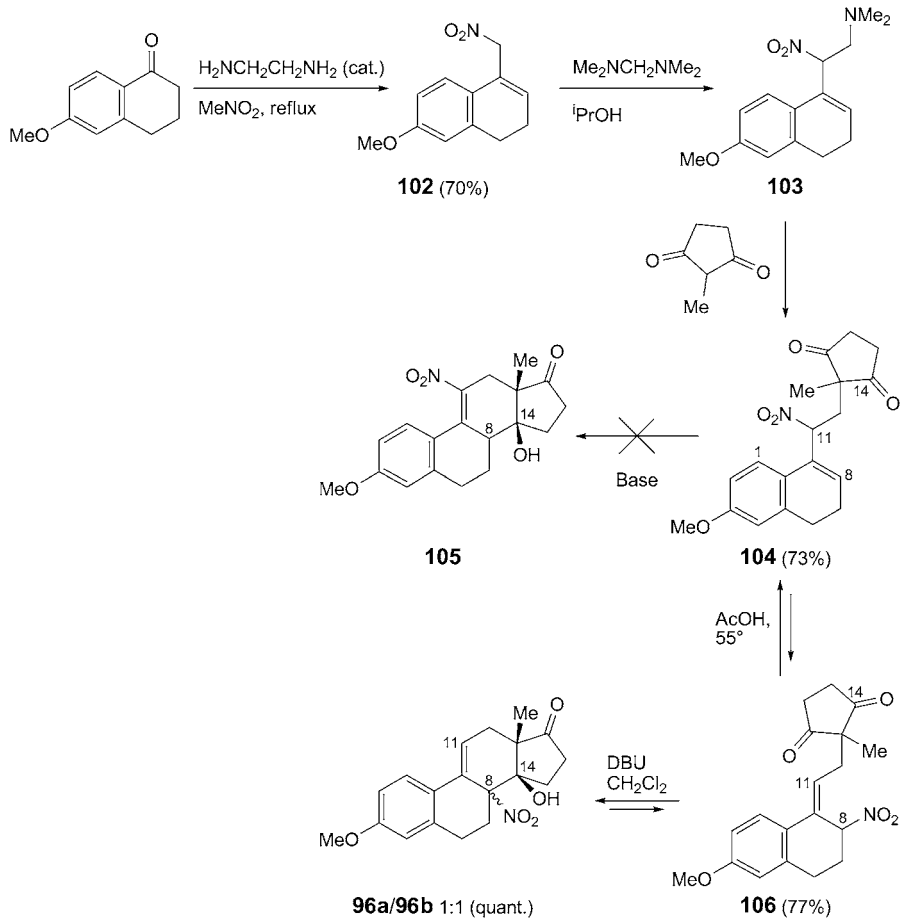


nitrites **99** and **101** in high yield from nitro alkenes **98** and **100**, respectively (*Scheme 20*), thus establishing definitively their intermediacy.

The synthesis of nitro steroids **96a** and **96b**, outlined in *Scheme 21*, is in itself quite interesting. It is short – only four steps – and involves an 'amusing' but also crucial serendipitous observation [21]. The first hurdle that had to be overcome was the condensation of $MeNO_2$ with 6-methoxytetralone, a notoriously unreactive aromatic ketone. The ethylenediamine-catalyzed condensation was indeed slow, but furnished nevertheless the desired nitro alkene **102** relatively efficiently. Stirring this compound with commercially available *N*,*N*,*N*′,*N*′-tetramethylmethanediamine afforded the *Mannich* adduct **103**, which was not isolated but simply treated with 2-methylcyclopentane-1,3-dione to give secosteroid **104** in good overall yield. This material contains all the C-atoms necessary for constructing the steroid skeleton. Our initial synthetic plan aimed at obtaining estrone derivative **105** by forming the key C(8)–C(14) bond through a vinylogous *Henry* reaction. Unfortunately, all the basic conditions we tried failed miserably. In most cases, a *retro-Michael* elimination of 2-methylcyclopentane-1,3-dione was observed, in essence reversing the previous step. However, gentle heating in AcOH caused an unexpected 1,3-migration of the NO_2 group to give isomeric nitro alkene **106** in good yield. Exposure of this isomer to DBU in CH_2Cl_2 induced the formation of the crucial C(8)–C(14) bond and provided the desired 8-nitro steroid **97a** and **97b** as a 1:1 mixture of epimers. Interestingly, running the reaction in MeOH afforded mostly 8β-epimer **97b**, which crystallized out of the medium. The *Henry* reaction is reversible and, in MeOH, this equilibrium is shifted by precipitation of the less soluble 8β-epimer.

This unprecedented acid-catalyzed 1,3-migration of the NO_2 group proceeds apparently through bridged cationic species **107** (*Scheme 22*). This intermediate is stabilized by the electron-donating aromatic ring. While the presence of the electron-donating MeO group is helpful, it is not necessary: the same, albeit slightly less efficient, transformation of the naked analog **108** to **110** was observed under the same

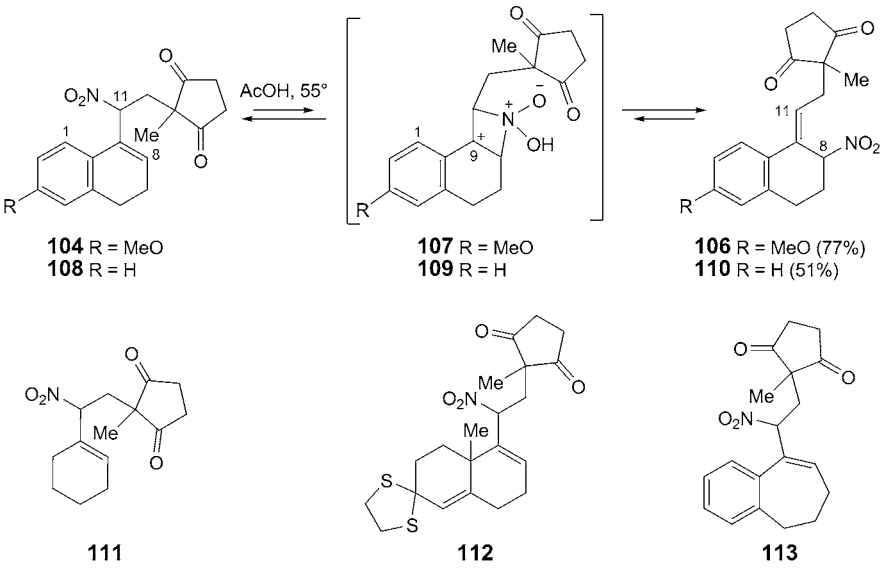
Scheme 21. *Synthesis of 8-Nitroestone Derivatives*



conditions [21b]. In contrast, no reaction was observed with non-aromatic derivatives **111** and **112** under otherwise identical experimental conditions. Acid, even as weak as silica, is necessary; indeed, addition of Et_3N inhibits the 1,3-shift of the NO_2 group. These observations are in accord with the proposed cationic mechanism. The reversible nature of this rearrangement is demonstrated by the partial isomerization of pure **106** back to the starting nitro alkene **104** under the same acidic conditions.

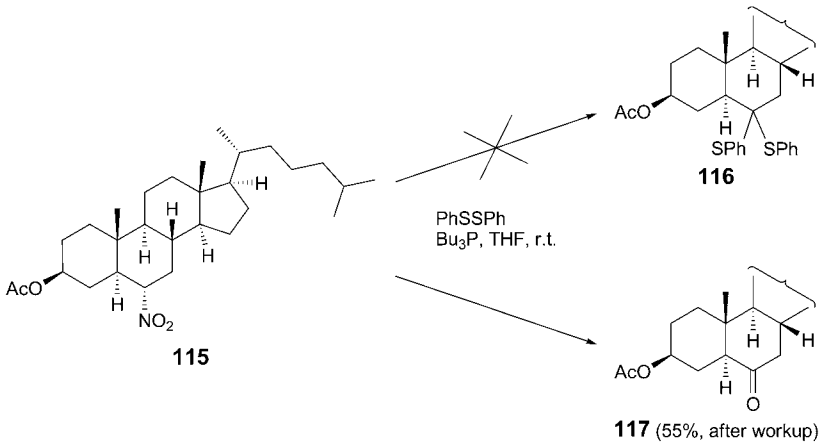
Presumably, this equilibrium is driven towards nitro alkene **106** by the relief of the *peri*-type repulsion between the NO_2 group at C(11) and the H-atom on the aromatic ring at C(1) (steroid numbering). This conjecture is supported by the fact that seven-membered ring homolog **113**, where the analogous *peri*-type repulsion is mostly absent, failed to undergo the 1,3-migration of the NO_2 group even though the corresponding cationic intermediate could have benefited from the same stabilization available to cation **109**. This process is, therefore, not general, being limited to tetralone-derived structures such as **104** and **108**, but it ultimately saved our nitro estrone synthesis.

Scheme 22. *Mechanism for the 1,3-Shift of the NO_2 group*



Serendipity Strikes Again. – The late Professor *Pierre Potier* once gave me what he termed the French – *macho* – definition of serendipity: to look for a needle in a haystack, and to find the farmer's daughter! Serendipity is a powerful ally of the chemist, and we have had perhaps more than our share of serendipitous findings. A few instances of serendipity have been mentioned above. Another such observation occurred when we exposed 6α-nitrocholestanyl acetate **115** to a mixture of Bu_3P and PhSSPh, in the naïve hope of converting the nitro steroid directly to dithioketal **116** (*Scheme 23*). This conjecture was based on what looked like a reasonable mechanistic

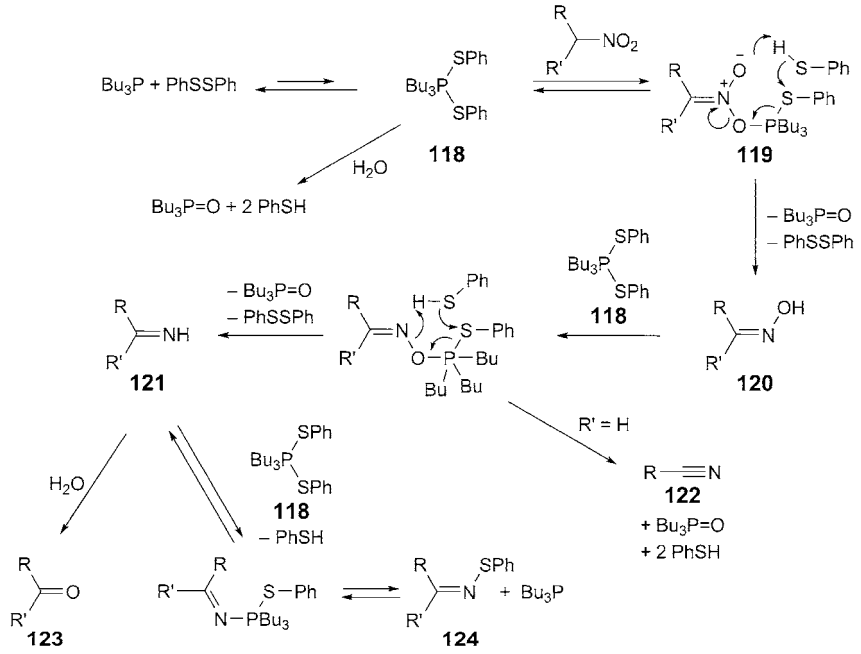
Scheme 23. *An Unusual Reductive* Nef *Reaction*



hypothesis. In the event, a smooth reaction took place, but the product isolated upon workup was 6-ketocholestanyl acetate **117** [23]. The outcome was immediately obvious, for we had earlier prepared this same ketone by an oxidative *Nef* reaction involving treatment of nitro steroid **115** with a combination of 3-iodoxybenzoic acid and a guanidine base, an oxidant system that was being developed by *Barton et al.* [24]. The reaction with Bu_3P and PhSSPh could be construed as a reductive *Nef* process, which indeed it is, but subsequent studies revealed unsuspected and fascinating mechanistic and synthetic aspects.

The mechanism that is most consistent with the experimental observations is outlined in *Scheme 24* [23c]. It involves reaction of the nitro compound *via* its nitronate with the reactive pentavalent P species **118** to give pentavalent P intermediate **119** and thiophenol. A counter-attack by the thiophenol on this intermediate produces oxime **120** and $Bu_3P{=}O$, and regenerates the PhSSPh. The oxime in turn reacts in the same manner with the pentavalent P species **118** to afford imine **121** in the case of ketoximes or nitrile **122** in the case of aldoximes ($R' = H$) derived from primary nitro compounds. Imine **121** is rapidly hydrolyzed into the corresponding ketone **123** upon workup.

Scheme 24. *Mechanism for the Reaction of Nitro Alkanes with PhSSPh/Bu_3P*

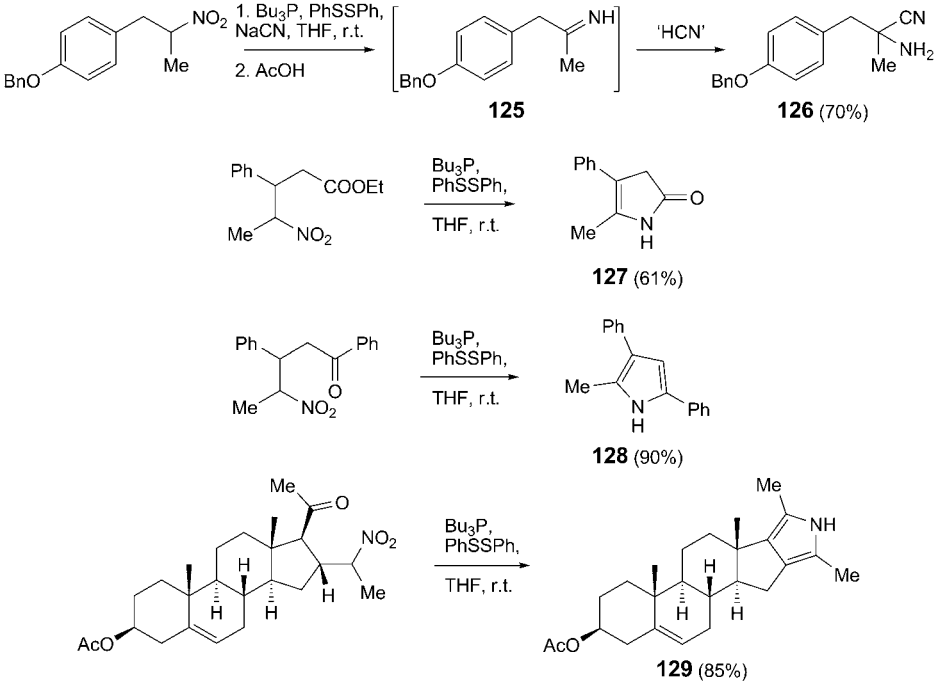


This mechanism implies that oximes **120** are intermediates in this process and undergo the transformations shown, which is indeed the case. Moreover, intermediate **118** reacts rapidly and irreversibly with H_2O and ensures a strictly anhydrous medium. It thus protects imine **121** against premature hydrolysis and allows its capture by a variety of reagents. If they are not sterically shielded, unsubstituted imines tend to be extremely sensitive to hydrolysis.

The conversion of secondary nitro derivatives cleanly to the corresponding unsubstituted imines **121** is a virtually unique property of the present method. In a further, unexpected twist in the mechanism, we found that, in the presence of excess PhSSPh, imine **121** was converted reversibly into *N*-phenylsulfenylimine **123**. *N*-Phenylsulfenylimines were later shown to be excellent precursors of iminyl radicals [25].

The formation of amino nitrile **126** is an illustration of the ability to intercept the hydrolytically labile intermediate imine **125** other than by simple hydrolysis (*Scheme 25*). The NaCN is placed in the medium at the outset and any adventitious H_2O it may contain is removed by the Bu_3P/PhSSPh reagent combination. Once the reduction is complete, AcOH is added to generate HCN *in situ*, which then adds to the imine.

Scheme 25. *Examples of Transformations of Nitro Alkanes with PhSSPh/Bu_3P*

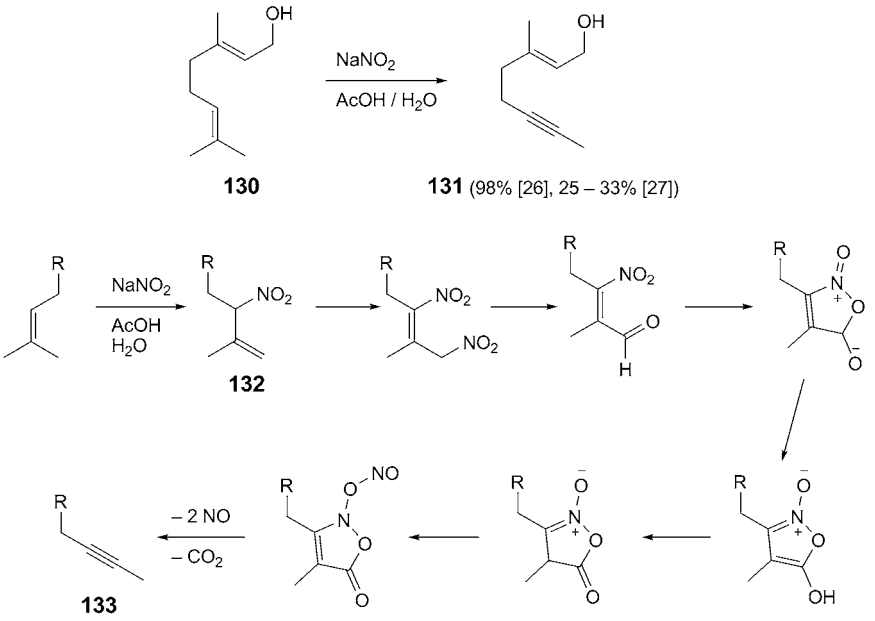


Internal capture of the imine is even easier and constitutes a very useful synthetic variant. γ-Nitro esters and nitro ketones, for example, are readily prepared by *Michael* addition of nitro alkanes to unsaturated esters and ketones, and their reduction by this unusual reducing system furnishes unsaturated γ-lactams and pyrroles respectively. This is exemplified by the synthesis of lactam **127** and pyrroles **128** and **129** depicted in *Scheme 25*.

A more impressive example of a serendipitous finding appeared in the literature in 1985 [26a]. While studying the nitrosating dealkylation of tertiary terpenylethanolamines, *S. L. Abidi*, a chemist at the National Fishery Research Laboratory in the US,

found that terpenes containing an isopropylidene group were converted to alkynes upon treatment with excess $NaNO_2$ in AcOH at 60° [26]. Geraniol **130** thus furnished alkyne **131** in a purported 98% yield (*Scheme 26*). This quite incredible transformation, which implies a formal loss of CH_4, was reproduced by several groups [26], but the yields were found to be vastly inferior to those reported by *Abidi* (25–33% instead of 98% in the case of geraniol [27a]).

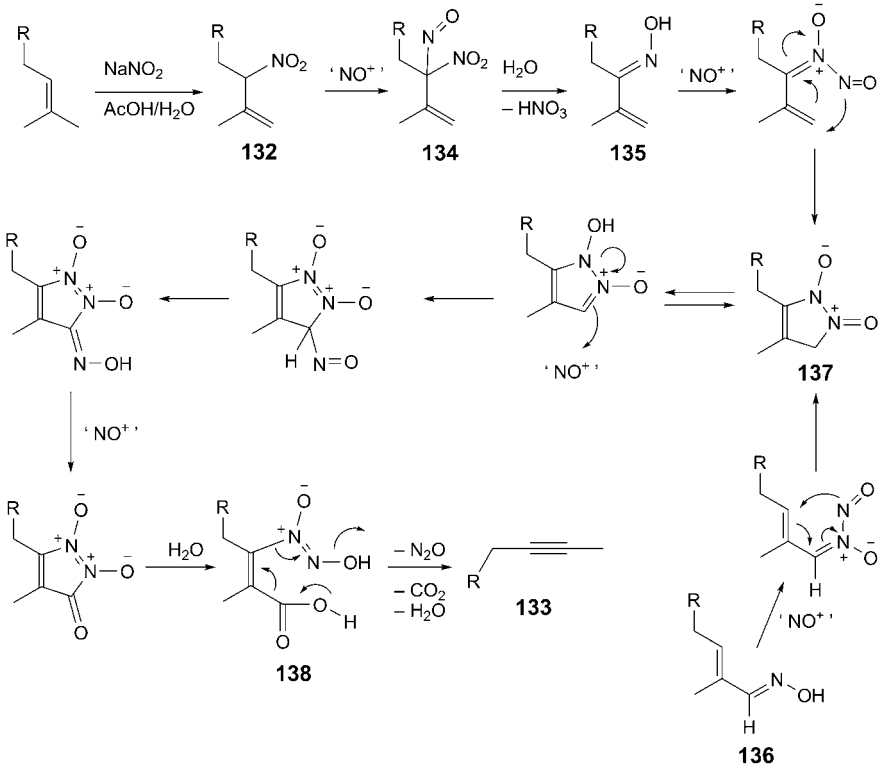
Scheme 26. *A Strange Synthesis of Alkynes from Isopropylidene Derivatives*



No mechanistic proposals were made in the original reports by *Abidi*, but, shortly afterwards, *Corey et al.* established that the first intermediate is allylic nitro derivative **132** (*Scheme 26*) [27a]. This intermediate could be isolated in 85% yield in the case of geraniol, by operating first at 0°, followed by a brief heating to 60°, and shown to be converted to alkyne **133** under the same nitrosating conditions. A plausible mechanism, displayed in *Scheme 26*, could now be formulated, the latter part of which was buttressed by model experiments.

The formation of allylic nitro derivative **132** early in the reaction pathway suggested to us an alternative route involving pseudo-nitrole **134** and unsaturated oxime **135** as the next intermediates (*Scheme 27*) [28]. Some support for this mechanism was obtained by demonstrating that unsaturated oxime of structure **135** could indeed be converted to alkyne **133** under the nitrosating conditions. The yields were low, but comparable to those we obtained in trying to reproduce the *Abidi* reaction itself. Further evidence for plausibility was adduced by showing that isomeric unsaturated oxime of structure **136** also proceeds to alkynes **133** under the same conditions. Both oximes of type **135** and **136** lead, upon nitrosation and electrocyclization, to the same

Scheme 27. *An Alternative Mechanism for the Formation of Alkynes*

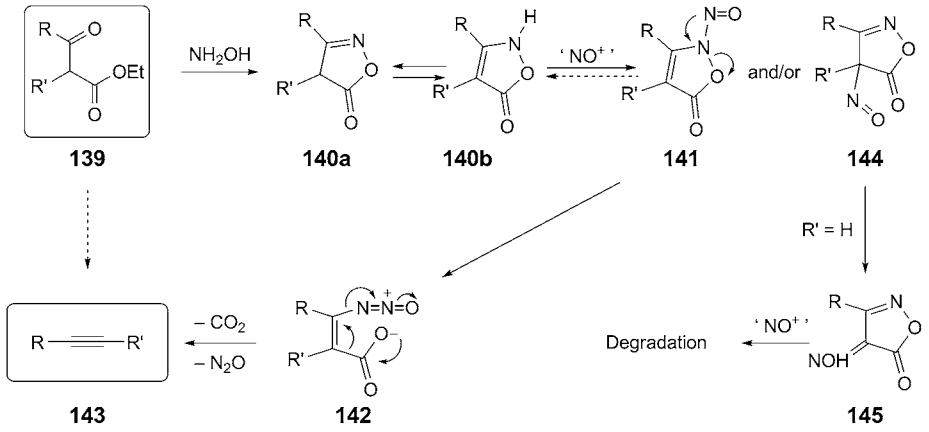


heterocyclic intermediate **137**; both can, therefore, enter the mechanistic manifold leading to alkyne **133**.

The remarkable transformation of allylic nitro intermediate **132** to alkyne **133** is clearly an exceedingly complex process that may well proceed by more than one pathway, for one mechanism does not exclude the other. Notwithstanding the striking mechanistic aspects, the fact that the actual yields are much lower than those initially reported by *Abidi* limits considerably the synthetic utility of this transformation. Nevertheless, examination of the later steps in the hypothetical mechanism in *Scheme 27* encouraged us to search for a simpler and faster way to access an unstable intermediate similar perhaps to structure **138** and thus eliminate most of the numerous possible side-reactions that afflict the *Abidi* reaction. One appealing and easily testable approach was the nitrosation of isoxazolinones.

Isoxazolinones having tautomeric structures **140a** and **140b** are well-known substances, trivially obtained from β-keto esters **139** and NH_2OH, and their *N*-nitrosation would lead to *N*-nitrosoisoxazolinone **141** (*Scheme 28*) where rupture of the weak N–O bond would furnish derivative **142**. This is a reasonable analog of the penultimate intermediate **138** in *Scheme 27* and should collapse in the same manner into alkyne **143**, with loss of CO_2 and N_2O [28b][29].

Scheme 28. *Synthesis of Alkynes from Keto Esters* via *Isoxazolinones*

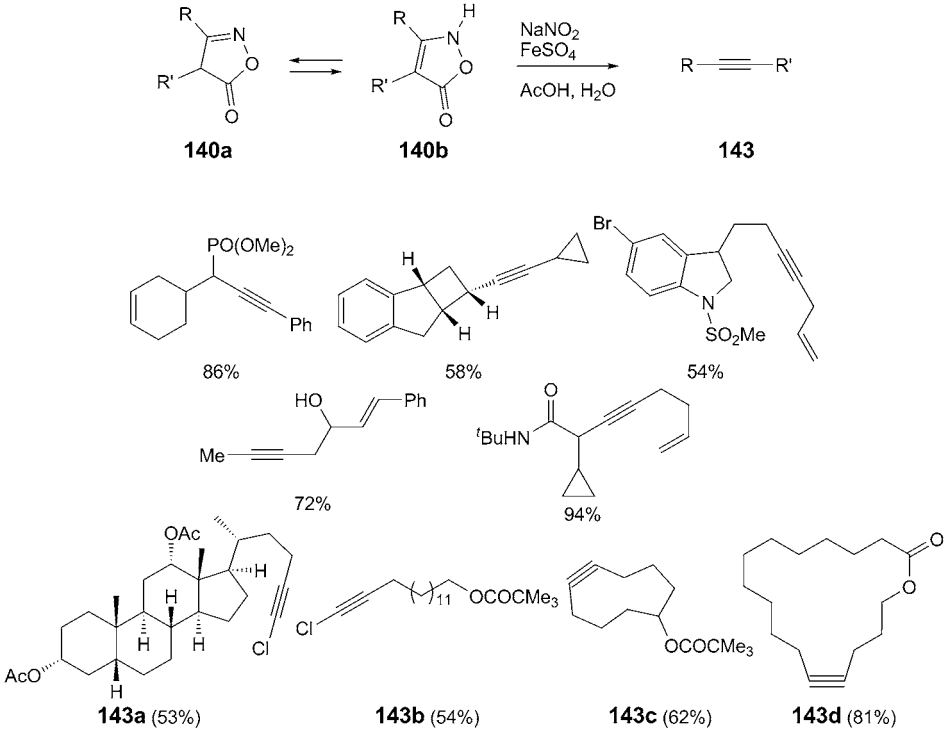


We indeed found that treatment of isoxazolinones with $NaNO_2$, AcOH, and $FeSO_4$ affords the desired alkynes in generally good yields. The inclusion of iron sulfate was dictated by the need to generate NO *in situ* to suppress an unexpected radical pathway arising from competing *C*-nitrosation of the isoxazolinone (the interested reader is directed to [28b] for a more detailed account). The main limitation is the need to have substituents R and R′ different from H. As shown in *Scheme 28*, the *C*-nitroso compound **144** readily isomerizes to oxime **145** when R′ = H and this leads to degradation products. When R = H, other problems arise. This method does not, therefore, allow the direct preparation of terminal alkynes.

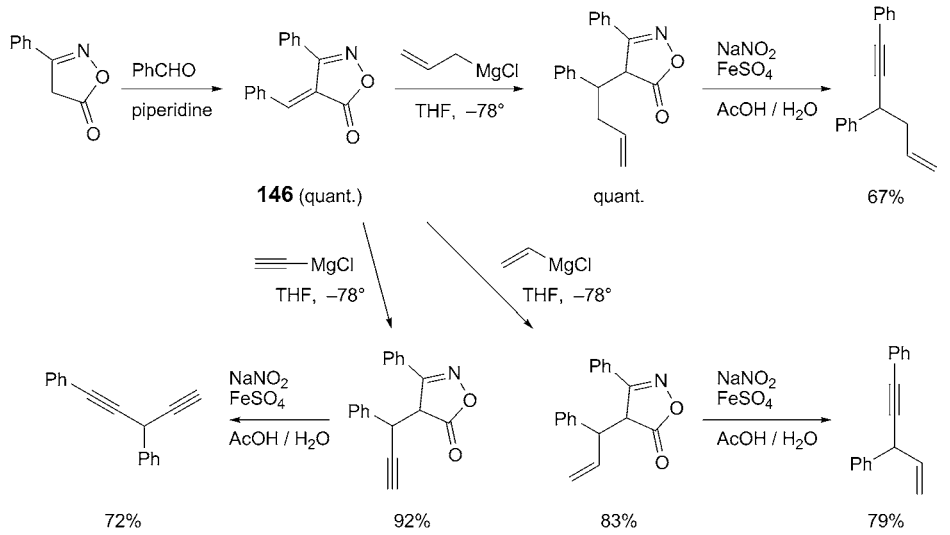
This new synthesis of alkynes, inspired by a curiosity-driven mechanistic study of the strange *Abidi* reaction, proved quite versatile and practical in view of the broad accessibility of the starting keto esters. Any route to β-keto esters **139** becomes potentially a route to the corresponding alkyne **133**. The nine assorted examples displayed in *Scheme 29* give an idea of the scope. Chloro alkynes (*e.g.*, **143a** and **143b**) can be prepared and, if needed, reduced to terminal alkynes [29e]. This compensates to a certain extent for the limitation mentioned above concerning the direct formation of terminal alkynes. Easy access to cycloalkynes, such as **143c** and **143d**, devoid of allene impurities, is another interesting feature of this method [29b]. Finally, the *Knoevenagel* condensation products of unsubstituted isoxazolinones with aldehydes and ketones (*e.g.*, **146**; *Scheme 30*) are highly electrophilic entities and react readily with numerous nucleophiles, including most organometallic reagents. This translates into convergent syntheses of various classes of alkynes, such as skipped enynes or diynes, as illustrated by the examples in *Scheme 30* [29c][29f][29g].

Some Concluding Remarks. – Professor *Seebach* titled his 1979 review in *Chimia: 'Nitroaliphatic Compounds – Ideal Intermediates in Synthesis?'* [30]. In view of the almost incredible number of possible transformations that the NO_2 group is capable of undergoing or mediating, the answer must be an emphatic *'yes!'*, even if the synthetic community has been rather slow in appreciating its huge potential. Our journey into the fascinating chemistry of the NO_2 group has spanned quite a few years. It started with

Scheme 29. *Examples of Alkynes from Isoxazolinones*



Scheme 30. *Further Examples of Alkynes from Isoxazolinones*



the struggle of a fumbling beginning graduate student trying to accomplish a simple condensation reaction of $MeNO_2$ on 17-keto steroids, then meandered into various transformations and rearrangements including a strange synthesis of acetylenes. Still, much more remains to be explored, and, hopefully, serendipity will strike again, and often.

I am deeply grateful to my students and collaborators, whose names appear in the references, and who made this chemistry possible through their skill and enthusiasm. I am especially indebted to Dr. *Béatrice Sire*, who has contributed decisively to many of the projects and was instrumental to their success. I also thank the following organizations and companies which have provided financial support over the years: Ecole Polytechnique, CNRS, DGA, MNRT, *Roussel-Uclaf* (now part of *Sanofi*), and *Glaxo-France*.

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