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New syntheses of alkynes: a tale of serendipity and design

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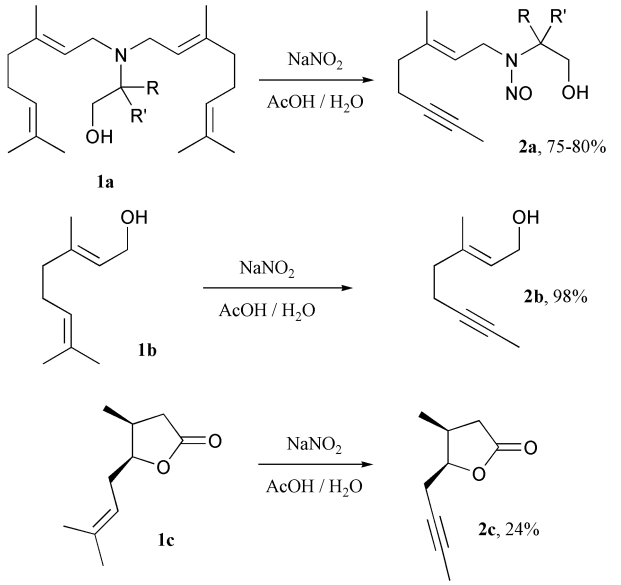
The story behind the development of several new syntheses of alkynes is presented.

Introduction

Of the functional groups most often manipulated by the organic chemist, alkynes occupy a truly unique position. The carbon–carbon triple bond may be usefully subjected to essentially all reaction types, from ionic and organometallic to radical and carbene processes, resulting in an incredibly rich and varied chemistry that has often been exploited in organic synthesis.[1] Nevertheless, despite the plethora of processes that have been developed over the past decades, finding a new way for creating a carbon–carbon triple bond still represents a worthwhile endeavour. Our incursion into this area started when we attempted to understand the mechanism of a strange transformation, accidentally discovered by S. L. Abidi in 1985.[2] This account candidly relates our undertaking, which ultimately culminated, we believe, in a practical and versatile synthesis of alkynes.

A very strange reaction

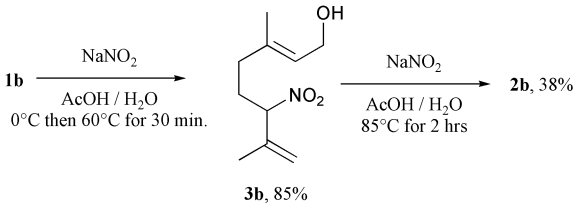
Abidi, working in the National Fishery Research Laboratory in the US, attempted a nitrosative dealkylation of tertiary terpenylethanolamines **1a** using an excess of sodium nitrite in acetic acid at 60 °C. The major compound from this reaction turned out to be, unexpectedly, *N*-nitrosoalkynylamines **2a**, as shown in Scheme 1.[2] The isopropylidene group in the geraniol chain was somehow converted into an alkyne group. This extraordinary transformation entails a very unusual, formal loss of the elements of methane by a mechanism that had yet to be determined. Simpler monoterpenes and related structures containing an isopropylidene group were also converted into the corresponding alkynes in yields ranging from 23–98%. Geraniol **1b**, for example, afforded alkyne **2b** nearly quantitatively. No mechanistic hypothesis was advanced by Abidi to rationalise these observations. Sometime later, the group of Corey disclosed the results of their extensive study of this strange reaction.[3] Although they could reproduce the transformation in the case of geraniol, the yield of alkyne remained low, ranging from 25 to 33%, quite at variance with the staggering 98% yield claimed by Abidi. The reason for the large difference in the yield is not yet clear. A poor yield of alkyne was also observed



Scheme 1 Some examples of the Abidi transformation.

more recently by Honda and his collaborators,[4] who applied the nitrosative cleavage to convert isopropylidene lactone **1c** into alkyne **2c**; catalytic hydrogenation of the triple bond then completed their synthesis of (−)-*cis*-whiskey lactone.

In one key experiment, the Harvard team treated geraniol with excess sodium nitrite in 60% aqueous acetic acid at 0 °C followed by a brief heating at 60 °C and obtained a good yield (85%) of allylic nitro derivative **3b** as shown in Scheme 2. The



Scheme 2 Allylic nitro intermediate in the Abidi reaction.

formation of this compound is not trivial and may involve further oxidation of a fleeting allylic nitroso intermediate. Exposure of **3b** to the harsher Abidi conditions gave the corresponding acetylene **2b** in 38% yield. With this crucial information in hand, the mechanism displayed in Scheme 3 could now be formulated.

According to this mechanistic view, further nitrosation of allylic nitro compound **3** leads to the dinitro intermediate **4**, in which the primary nitro group is then converted into aldehyde **5** by the action of the nitrosating reagent. Ring closure gives heterocycle **6**, which can tautomerise to **7** then to **8**. Finally, further nitrosation leads to an unstable nitrite **9**, which collapses with loss of nitric oxide and carbon dioxide into the observed

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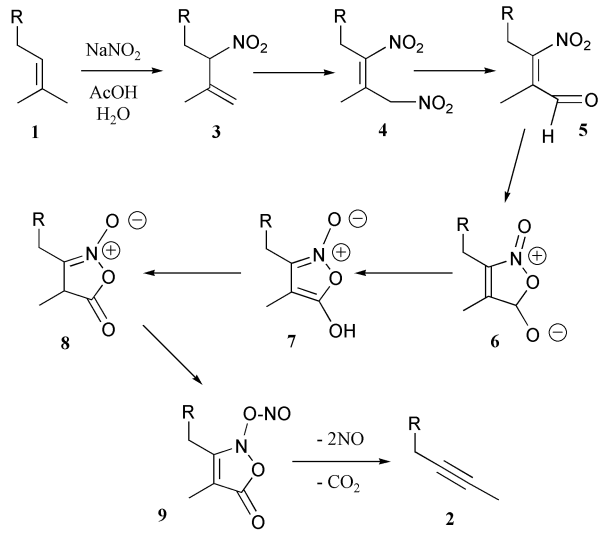
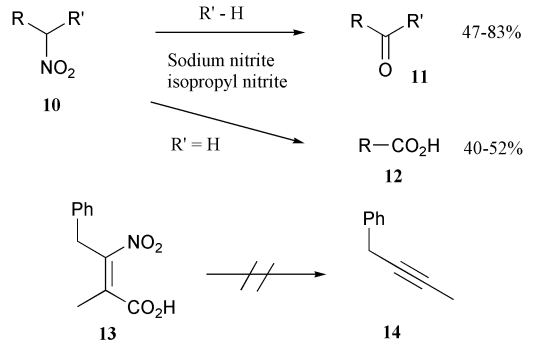


Scheme 3 First mechanistic hypothesis for the Abidi reaction.

alkyne. The feasibility of the sequence going from compound **8** to the alkyne **2** was tested with success on a model structure.[3] The only part of the proposed mechanism for which no experimental support could be provided concerned the conversion of the primary nitro group in **4** into aldehyde **5**.

The nitrosation of nitro compounds had been studied sporadically in the past,[5] and most notably by Kornblum and his students,[6] who found that nitrosation of secondary nitro derivatives **10** (R′ ≠ H) produced the corresponding ketones **11**, *whereas compounds with a primary nitro group* **10** (R′ = H) *gave the carboxylic acids* **12** *instead* (Scheme 4). It turns out

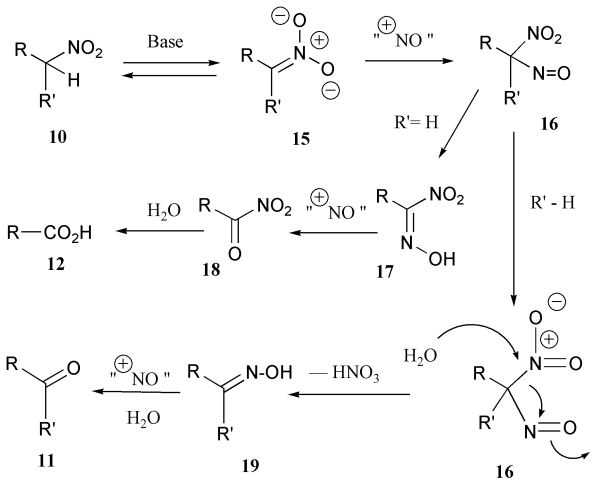


Scheme 4 The Kornblum reaction.

that the carboxylic acid analog **13** of the putative intermediate aldehyde **5** *does not proceed to alkyne* **14** *under the Abidi conditions*.[3] The section of the proposed mechanism connecting allylic nitro **3** with intermediate **8** remained therefore unsettled.

A new reaction of unsaturated oximes

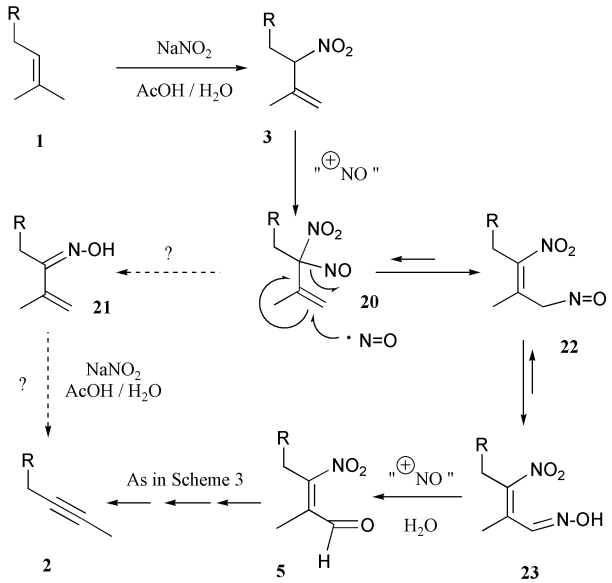
One important element of our own attempt at understanding the Abidi reaction came from a more careful look at the Kornblum process. Nitronates **15** are easily generated from aliphatic nitro compounds by the action of a weak base and these readily react with nitrosating agents to give pseudo nitroles **16** (Scheme 5).[5] Pseudo nitroles derived from primary nitro compounds tautomerise rapidly to the nitrolic acid isomer **17**, which undergoes cleavage by the nitrosating agent into nitroacyl compound **18** and ultimately hydrolysis to the carboxylic acid **12**. Pseudo nitroles derived from secondary nitro derivatives cannot tautomerise in the same way but can be attacked by a nucleophile in the medium (water, acetic acid) to give the corresponding oxime **19** and nitric acid, if the nucleophile is a



Scheme 5 Possible mechanism for the Kornblum reaction.

water molecule. The oxime thus formed is converted into ketone **11** by the combined action of nitrous acid and water (one of the lesser known Claisen reactions).[7]

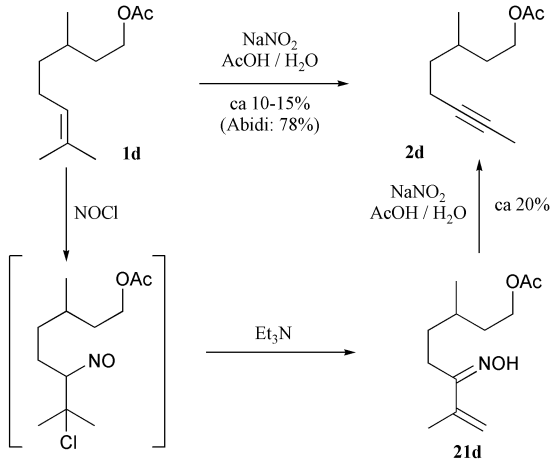
The formation and nitrosative cleavage of an oxime intermediate in the Kornblum reaction hinted at unsaturated oxime **21**, itself derived from pseudonitrole **20**, as a plausible intermediate on the route to the alkyne (Scheme 6). It is also



Scheme 6 Possible pathways for the Abidi reaction.

quite possible that pseudonitrole **20** undergoes a 1,3-shift of the nitroso group by a radical chain mechanism to give isomer **22**, which can now tautomerise to aldoxime **23** and thence to aldehyde **5** by the classical nitosative cleavage. This alternative path to aldehyde **5** circumvents the difficulty, raised in the discussion above, of generating it from the postulated dinitro intermediate **4** as outlined in Scheme 3. It was therefore reasonable from the outset to consider two broad mechanistic routes for the Abidi reaction: one involving oxime **21**, which had yet to be tested, and the other, *via* aldoxime **23**, representing a modified version of the mechanism proposed by Corey and his students.

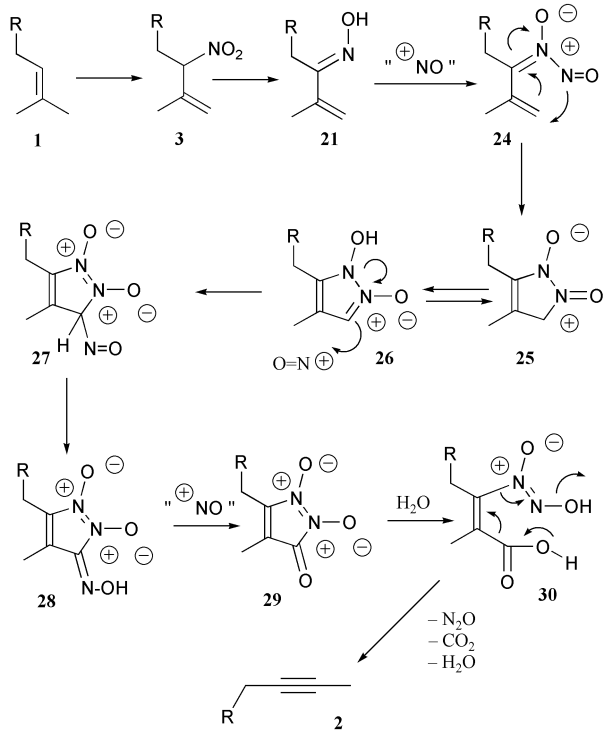
A simple way for generating unsaturated oximes possessing the substitution pattern similar to the putative intermediate **21** consists in treating an isopropylidene containing linear terpene first with nitrosyl chloride then with a weak base. This well known but nowadays little used transformation proceeds *via* a chloronitroso intermediate as illustrated by the conversion of citronellyl acetate **1d** into oxime **21d** (Scheme 7).[8] We were



Scheme 7 A new alkyne synthesis from unsaturated oximes.

delighted to find that exposure of this oxime to acetic acid and sodium nitrite indeed afforded the desired alkyne **2d**; unfortunately, the yield remained low (20% at best) in spite of all our exertions.[9] Furthermore, in our hands, the formation of the same alkyne **2d** directly from citronellyl acetate did not exceed 10–15%, much lower than the 78% yield reported by Abidi.[2] Other oximes, with a similar substitution pattern, also gave the corresponding alkynes under the same nitrosative conditions but the yield was disappointingly low in all cases. Despite the poor yield, our success in obtaining alkynes from unsaturated oximes of structural type **21** with an overall loss of one carbon supported our hypothesis that such oximes are *plausible*, even if by no means *certain*, intermediates in the Abidi reaction.

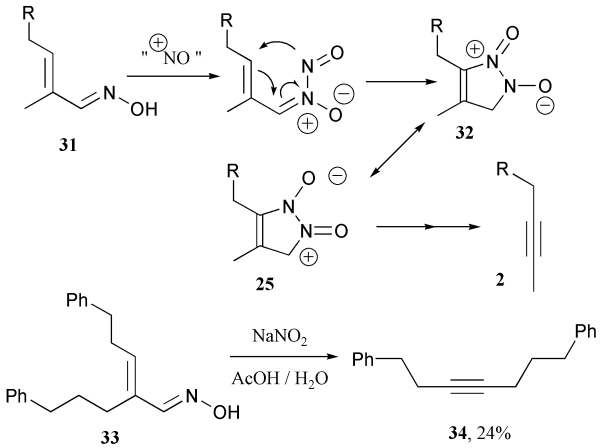
A mechanistic pathway rationalising the conversion of unsaturated oxime **21** into alkyne **2** is displayed in Scheme 8.



Scheme 8 An alternative mechanism for the Abidi reaction.

Thus, nitrosation leads to *N*-nitroso derivative **24** which can undergo an electrocyclisation into heterocycle **25**, by analogy with studies on unsaturated oximes carried out by Freeman and his co-workers some years ago.[10] This behaviour contrasts with ordinary, *saturated* oximes, where *N*-nitrosation is the prelude to their hydrolytic cleavage into ketones or aldehydes by the classical Claisen reaction mentioned above. Heterocycle **25** produced in this way then proceeds by a series of tautomerisations and nitrosations to a structure such as **30**, which can collapse into the alkyne with concomitant expulsion of nitrous oxide and carbon dioxide. The route outlined in Scheme 8 is one of several possible pathways linking heterocycle **25** with alkyne **2**. Ring opening for example may occur earlier or the order of the steps may be different.

We have not been able to perform model studies allowing us to clarify the latter part of the proposed mechanism. We could, however, adduce reasonably strong evidence for the electrocyclisation step by examining the behaviour of the isomeric oxime **31** upon nitrosation. As depicted in Scheme 9, *N-nitrosation and electrocyclisation lead to structure* **32***, which is simply another mesomeric form of heterocycle* **25**. An oxime of structure **31** should therefore also produce an alkyne under similar nitrosative conditions. This proved to be indeed the case: exposure of oxime **33** to the action of sodium nitrite and acetic acid gave rise to the corresponding alkyne **34** in 24% yield.[11] Starting oxime **33** was prepared by the condensation of nitromethane with 1,7-diphenyl-4-heptanone under catalysis by ethylenediamine,[12] followed by reduction of the resulting nitroalkene with carbon disulfide and triethylamine.[13]

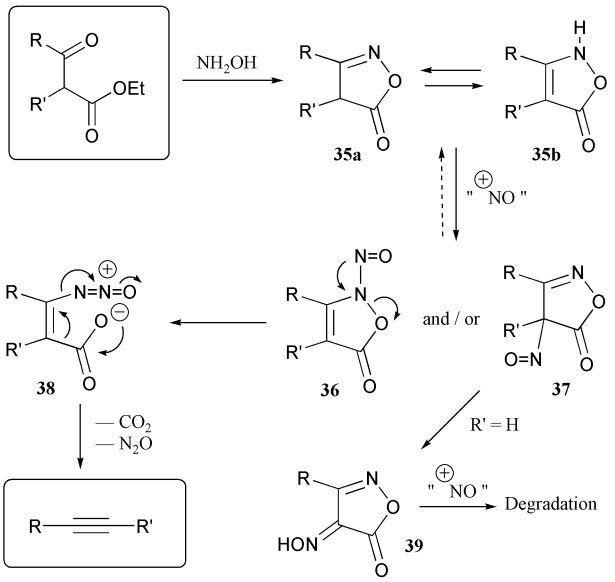


Scheme 9 Another synthesis of alkynes from unsaturated oximes.

A better synthesis of alkynes

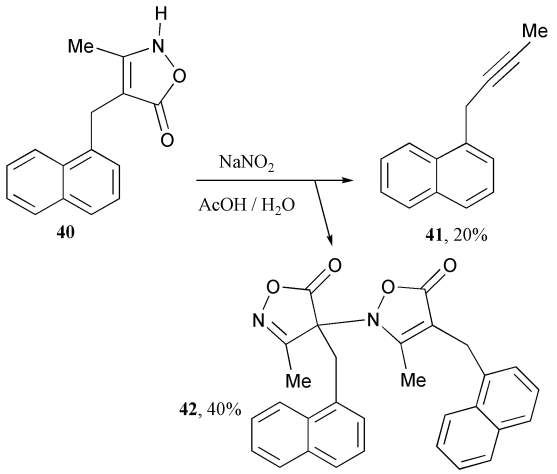
These new transformations of oximes are mechanistically complex and interesting, but rather disappointing from a synthetic standpoint: the precursors are not generally available and the yields are uniformly low. It seemed, however, that if it was possible to access rapidly and cleanly a late intermediate such as **30**, the numerous side reactions would be largely curtailed and maybe a more practical and useful synthesis of acetylenes could be implemented. We considered therefore the potential evolution of a 5-isoxazolinone **35** upon nitrosation (Scheme 10).

5-Isoxazolinones are well known heterocycles, easily made by condensing hydroxylamine with β-ketoesters.[14] They exist as an equilibrium between two main tautomers **35a** and **35b**, the predominance of one or the other depending on the nature of the substituents. Nitrosation could in principle give the *N*-nitroso and/or the *C*-nitroso isomers **36** and **37** respectively. Fragmentation of the former would lead to betaine **38**, with a structure very similar to that of **30** in Scheme 8, the penultimate intermediate we proposed for the Abidi reaction. In the same way, loss of nitrous oxide and carbon dioxide would furnish the desired alkyne. The *C*-nitroso isomer **37**, in contrast, cannot produce an alkyne but could undergo tautomerisation to oxime **39** if R′ = H, and this would certainly be followed by further



Scheme 10 Synthesis of alkynes from ketoesters.

unwanted degradation. If R′ ≠ H, however, then tautomerisation cannot take place and it seemed reasonable to assume that the *C*-nitroso isomer could be hydrolytically cleaved back to the starting isoxazolinone **35**. If this were the case, then the irreversible path to the alkyne through the *N*-nitroso intermediate **36** would completely drain the equilibrium in the desired manner. This conception looked mechanistically attractive and could be easily tested.

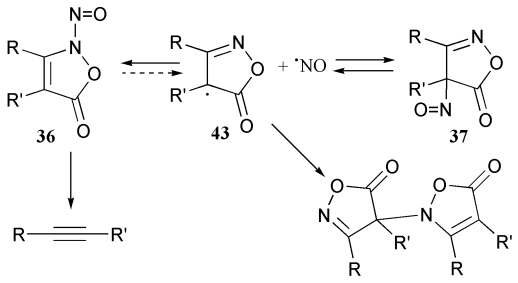


Scheme 11 First example and unexpected dimer formation.

In the event, treatment of oxazolinone **40** with acetic acid and sodium nitrite gave rise indeed to the expected alkyne **41**, but the yield was still a low 20%; however, the reaction was much cleaner now and another major product could be isolated and identified as the unsymmetrical dimer **42**.[15] Such dimers had earlier been reported by Marchesini *et al.* when an isoxazolinone was subjected to nitrous acid.[16] Curiously, these authors did not observe any alkyne in their reaction products. This unanticipated dimer was obviously the result of a radical–radical coupling and our mechanistic hypothesis had to be modified in the light of this observation.

Ferrous sulfate to the rescue

The nitrosation was presumably occurring mainly on the carbon site to give the *C*-nitroso derivative **37**, which was then undergoing homolysis instead of the initially imagined hydrolytic cleavage. This homolysis leads to nitric oxide, a persistent



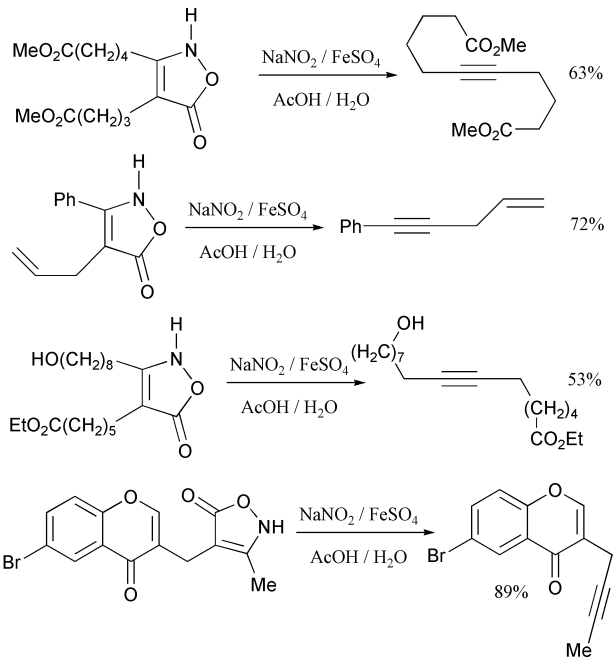
Scheme 12 Homolytic cleavage of *C*-nitroso isoxazolin-5-one.

radical, and to radical **43**, which is stabilised by conjugation and by a certain aromatic character. Nitric oxide, being a gas, eventually escapes from the medium, leaving radical **43** no choice but dimerisation. In order to eliminate the formation of dimer, nitric oxide had to be kept in the medium because its persistent character would ensure the complete domination of the cross-coupling between radical **43** and nitric oxide over self coupling leading to dimer. The persistent radical effect (also known as the Fischer-Ingold effect), which allows a high degree of control over the selectivity of fast radical-radical interactions, is an emerging concept in radical chemistry with important applications in controlled radical polymerisations.[17] In our case, the cross-coupling can of course furnish both the *N*- and *C*-nitroso regioisomers but since this is reversible, at least for the unwanted *C*-isomer, the irreversible fragmentation of the *N*-nitroso-isoxazolinone would drain all the material towards the alkyne.

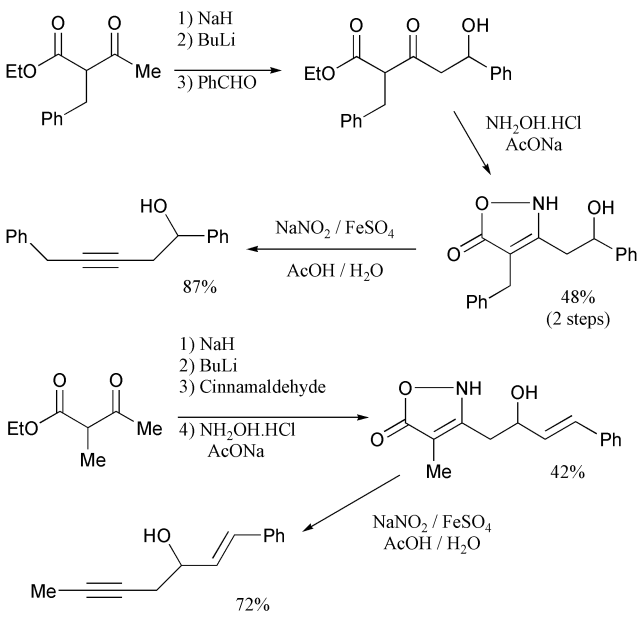
There are three ways to keep the nitric oxide in the medium: (a) close the system; (b) bubble nitric oxide from a commercial steel cylinder; and (c) generate nitric *in situ*. Options (a) and (b) are not practical for small scale work, and probably even dangerous in the case of the former, so we opted for the third solution. It turns out that nitric oxide is made by treating ferrous sulfate with sodium nitrite and acetic acid.[18] Since the last two reagents were in any case needed for our reaction, all we had to do was to add ferrous sulfate. Furthermore, having become aware of the presence of carbon radicals in the medium, we took the extra precaution of thoroughly deoxygenating the medium and the reagent solution beforehand.

With this modified procedure, the dimer formation was essentially completely suppressed and the yield of the somewhat fragile alkyne **41** increased threefold to 58%.[15] This modified procedure was applied successfully to various other substrates, as shown in Scheme 13. The last two examples are taken from more recent applications of this reaction by other groups.[19,20] It is worthy of note that skipped enynes, which are prone to rearrangements and are somewhat sensitive to aerial oxidation, can nevertheless be readily obtained. This new transformation of 5-isoxazolinones has allowed us to connect, through a functional group interconversion, a β-ketoesters with an alkyne: any synthesis of β-ketoesters is now potentially also a route to the corresponding alkynes. The rich chemistry of β-ketoesters[21] can thus be exploited to assemble acetylenes which otherwise might be accessible only with difficulty. The two examples in Scheme 14 show how the trapping of the dianion derived from β-ketoesters with benzaldehyde and cinnamaldehyde respectively can be used to construct highly functionalised alkynes.[22] Elimination of a water molecule from the products would in principle provide a route to conjugated enynes.

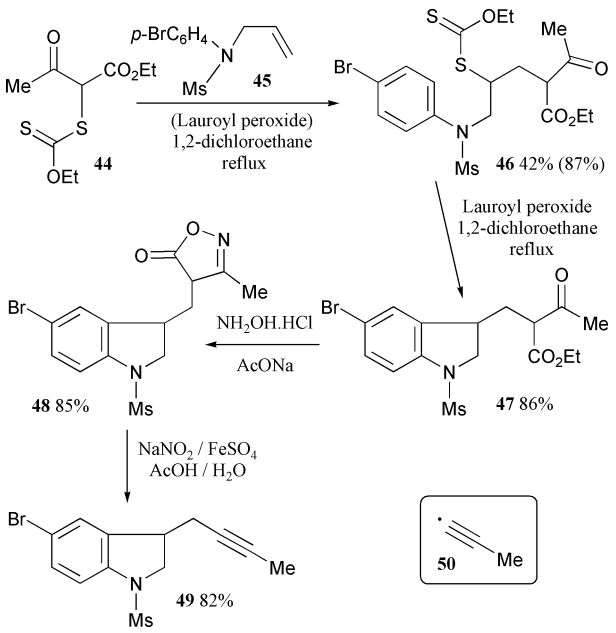
Generation of β-ketoesters is not limited to ionic chemistry. We have found over the past few years that the radical transfer of a xanthate group constitutes a very powerful tool for the tin-free creation of carbon–carbon bonds even across unactivated olefins.[23] In the present context, β-ketoester precursors for alkyne synthesis can be prepared simply by starting with a β-



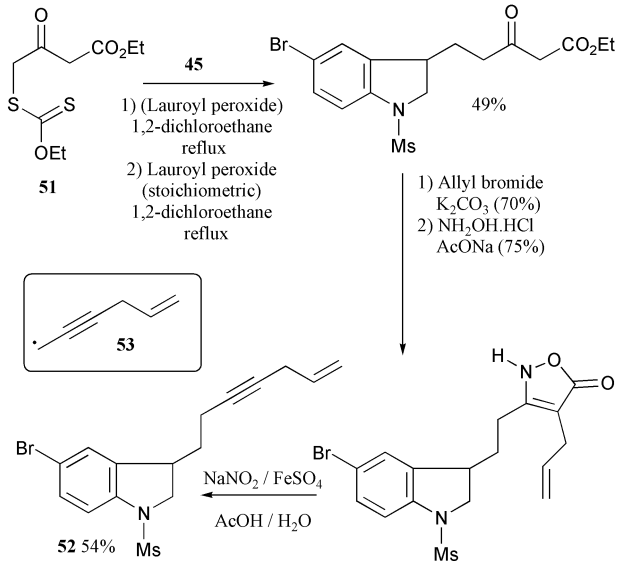
Scheme 13 Some examples of alkyne syntheses.



Scheme 14 Syntheses of enynes.



Scheme 15 Propynyl radical synthetic equivalent.



Scheme 16 Propargyl radical surrogate.

ketoester substituted by a xanthate group, such as **44** in Scheme 15.

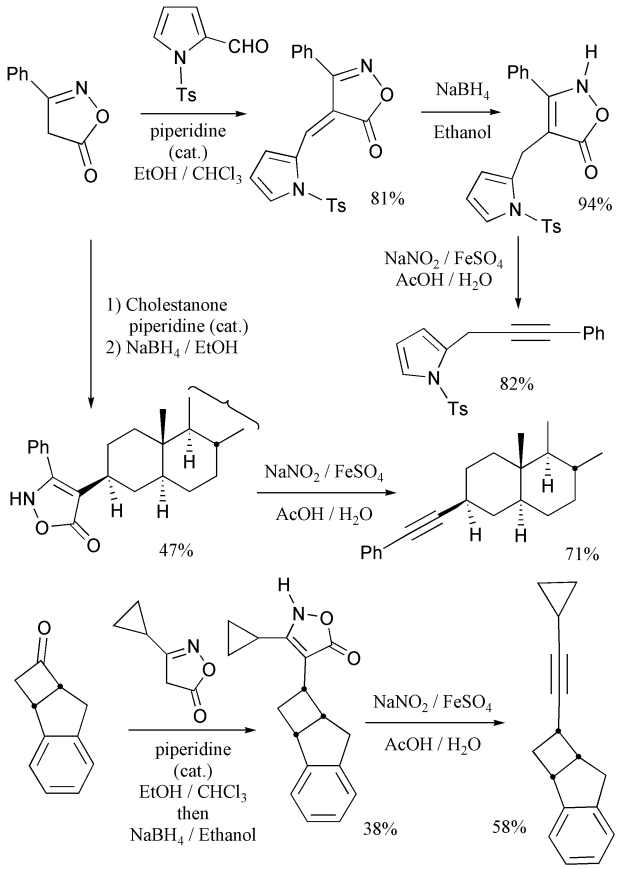
If the addition is performed as shown on a protected *N*-allyl aniline **45**, the first radical adduct **46** can then be forced to undergo a second radical reaction, namely closure onto the aromatic ring leading to indoline derivative **47**. Formation of the isoxazolidinone by treatment with hydroxylamine and subsequent nitrosative cleavage delivers alkyne **49** in good yield.[24]

This sequence is interesting because, overall, it corresponds formally to the addition, followed by cyclisation, of propynyl radical **50** to olefin **45**. Alkynyl radicals are highly reactive species that are extremely difficult to generate and capture in a synthetically useful manner.[25] In the present approach, β-ketoester xanthates such as **44** act as synthetic surrogates for the corresponding inaccessible and unruly alkynyl radicals.

By simply placing the xanthate group on the other side of the ketone as in **51** (Scheme 16), one obtains a synthetic equivalent of a propargyl radical.[24] Propargyl radicals, in contrast to alkynyls, are stabilised by resonance and are relatively easy to generate. However, their stability translates in practice into a certain lack of reactivity and intermolecular additions to unactivated olefins are not easily accomplished.[26] Xanthate **51**, however, readily undergoes addition to simple olefins and may thus be used as a propargylic radical synthetic equivalent. This is illustrated by the sequence in Scheme 16 starting with the same *N*-allyl-*p*-bromoaniline **45**.[24] The overall transformation leading to **52** corresponds to the addition and cyclisation of the hypothetical propargyl radical **53**. This example further highlights the ease with which a skipped enyne is elaborated using the isoxazolinone technology.

The isoxazolinones themselves also have a rich chemistry, even though little studied in comparison with that of β-ketoesters. For example, 5-isoxazolinones unsubstituted in position-4 readily undergo Knovenagel type condensations with aldehydes and ketones to give condensation products, much in the same way as other more common active methylene compounds.[15] These adducts contain a highly electrophilic

olefinic bond which can be reduced cleanly with borohydride.[27] This allows the synthesis of isoxazolinone precursors with interesting and sometimes complex substitution patterns, as demonstrated by the three examples in Scheme 17.[28] The



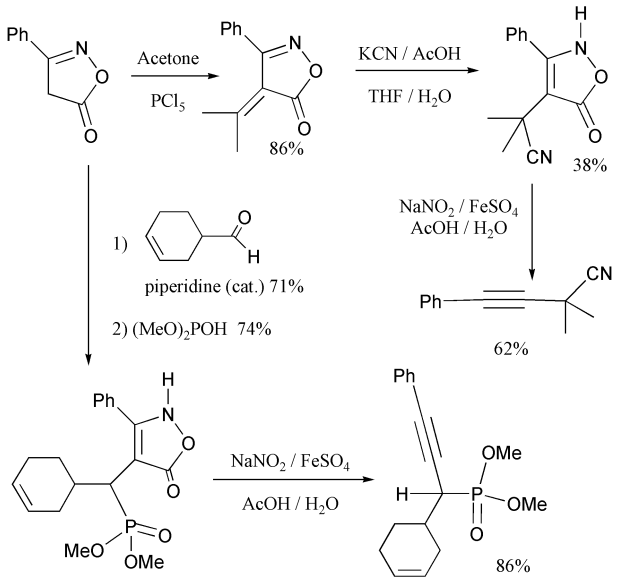
Scheme 17 Alkynes *via* reductive condensation of isoxazolin-5-ones with aldehydes and ketones.

stereochemistry in the last two alkynes is controlled at the reduction step by the shape of the substrate: attack of the hydride occurs from the least hindered α-side in the case of the cholestanone derivative and from the *exo* face of the cyclobutanone derived intermediate.

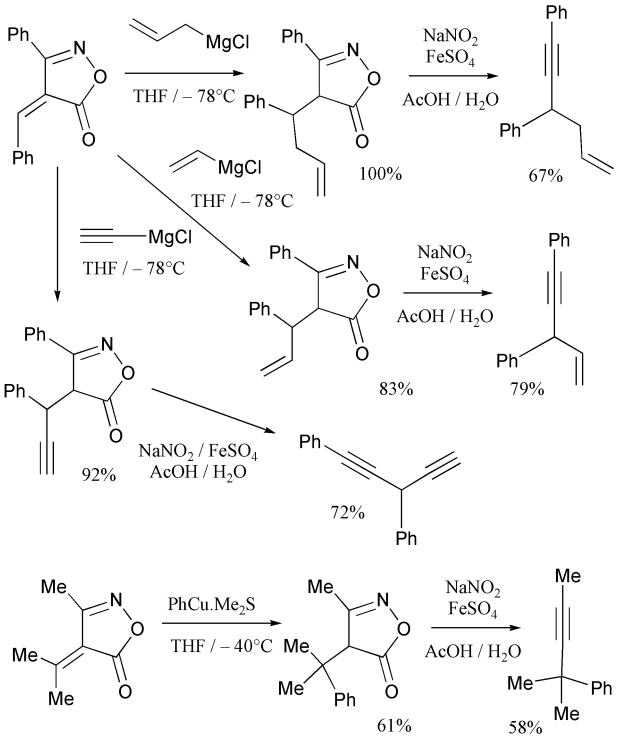
Various other nucleophiles are capable of undergoing similar conjugate additions and the adducts can then be converted into functionalised alkynes that would be difficult to obtain otherwise. The examples in Scheme 18 illustrate the synthesis of cyano and phosphonate containing acetylenes.[28] In the case of the phosphonates, mere heating of the alkylidene isoxazolinone with dimethyl phosphite was sufficient to bring about the Michael addition, without the need for added base.

It is perhaps the conjugate addition of organometallic derivatives that has the greatest synthetic potential since it opens access to an immense variety of branched alkynes obtained tediously by more conventional routes.[29] We have found that many types of organometallic species, including organolithium, Grignard reagents, organozinc, and organocuprates, add conjugatively to the activated olefin. A few examples are pictured in Scheme 19.[29] Quaternary centres can be created relatively easily by this approach as shown by the last example.

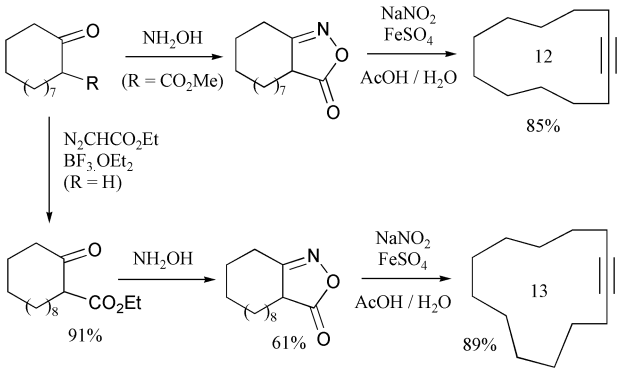
The ready synthesis of macrocyclic alkynes is another attractive feature of this route to alkynes. Cyclododecanone can be converted into the corresponding β-ketoester by the classical Claisen condensation and then to cyclododecyne (Scheme 20).[30] Because the nitrosative cleavage of the intermediate isoxazolinone occurs under very slightly acidic conditions, the cyclododecyne thus produced is free from the isomeric allene,



Scheme 18 Synthesis of functionalised alkynes.



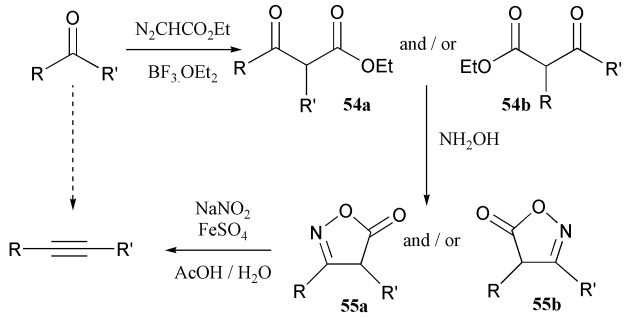
Scheme 19 Synthesis of branched alkynes.



Scheme 20 Synthesis of macrocyclic alkynes.

which is very difficult to remove in this case. The concomitant formation of the isomeric allene often plagues syntheses of alkynes relying on classical base induced eliminations.[31] One especially interesting reaction in the context of large ring acetylenes is the ring expansion of cycloalkanones using ethyl diazoacetate.[32] This provides directly the desired cyclic β-ketoester with one more carbon in the ring. In this way, cyclotridecyne can be rapidly obtained from cyclododecanone, as outlined in Scheme 20.[30]

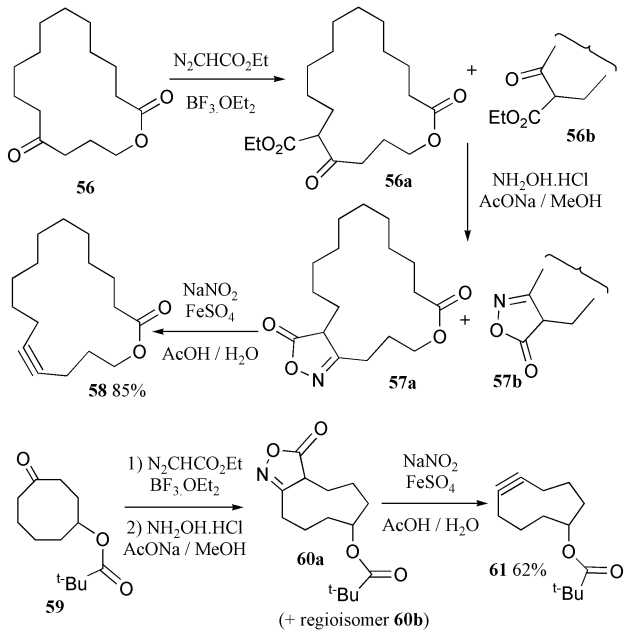
The ring enlargement is not generally regioselective and, in the case of unsymmetrical ketones, two regioisomeric β-ketoesters are normally produced.[32] We initially thought that this would be a serious limitation but, after a more careful examination, it turned out that this had no consequence at all: both regioisomers ultimately give the same alkyne! This is detailed in Scheme 21.



Scheme 21 Homologation of ketones with ethyl diazoacetate.

Starting with an unsymmetrical ketone (by the way, these considerations are not limited to cyclic ketones), homologation with diazoacetate leads to isomeric β-ketoesters **54a** and **54b**, which in turn furnish the isomeric isoxazolinones **55a** and **55b**. Nitrosative cleavage finally gives only one alkyne. The overall result is a formal excision of the carbonyl group and its replacement by a carbon–carbon triple bond.

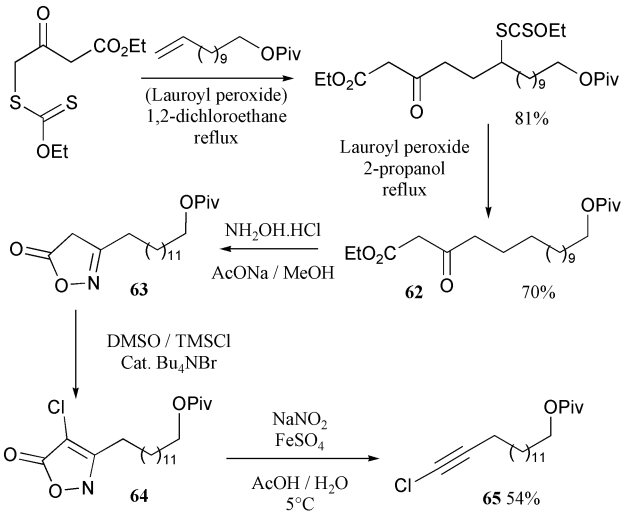
Two examples of macrocycloalkyne syntheses are shown in Scheme 22.[30] Ring expansion of 16-membered keto-lactone **56**,



Scheme 22 Synthesis of substituted macrocycloalkynes.

itself made in 4 steps from cyclododecanone according to the procedure of Hesse and co-workers, furnishes 17-membered ring β-ketoesters **56a** and **56b**, which in turn give the two regioisomeric isoxazolinones **57a** and **57b** upon treatment with hydroxylamine. Nitrosative cleavage without separation of the isomers finally provides only cycloalkyne **58** in 85% for the last step. In the same way, cyclononyne **61** was obtained from ketone **59** *via* the regioisomeric intermediate isoxazolinones **60a** and **60b**. This is the smallest aliphatic cycloalkyne we have prepared. The synthesis of smaller cycloalkynes may be hampered by the increasing diradical character of the strained triple bond and the presence of nitric oxide. We have briefly examined, but so far with only modest success, the possibility of generating and capturing benzyne by this method.[22]

Unfortunately, the isoxazoline method does not allow the direct synthesis of terminal alkynes. If the isoxazolin-5-one is not substituted in the 4-position, then the corresponding *C*-nitroso derivative **37** undergoes tautomerisation into oxime **39** (Scheme 10) and is subsequently degraded by the action of nitrous acid. Moreover, isoxazolinones unsubstituted at the 3-position (**35**, R = H) are not stable to fragmentation leading to the formation of a nitrile by cleavage of the N–O bond. One indirect solution we have devised to circumvent this limitation is to start with a 4-chloroisoxazolin-5-ones, which we found to be suitable progenitors of 1-chloroalkynes if the reaction temperature is lowered to 0–5 °C. One representative example is displayed in (Scheme 23) and concerns the synthesis of

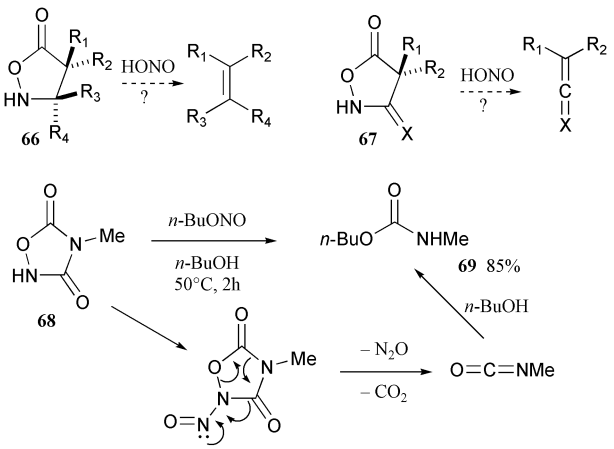


Scheme 23 Synthesis of 1-chloroalkynes.

1-chloroalkyne **65** from keto-ester **62** *via* intermediates **63** and **64**.[33] 1-chloroalkynes can be reduced to terminal alkynes but are also interesting in their own right, since they are substrates for a number of transition metal mediated coupling reactions. A more direct route to terminal alkynes has recently been reported by Fleming and Ramarao[34] based on the base induced fragmentation of enol triflates derived from ketoesters.

Some further perspectives

By seeking to better understand the strange reaction discovered by Abidi, we have uncovered a simple and practical yet powerful synthesis of alkynes. It usefully complements other methods involving the fragmentation of heterocyclic rings.[1,35] We have been able to determine to a certain extent its synthetic potential but we are far from having completely delineated its scope and compatibility with the various functional groups. Nor have we explored the possible exploitation of the radical component, which we have in the first instance suppressed by the addition of ferrous sulfate to the nitrosating mixture, but which may have interesting synthetic applications. The chemistry of isoxazolin-5-ones certainly deserves a more thorough



Scheme 24 Synthesis of methylisocyanate.

study: expanding variety of routes to this heterocyclic structure should open the way to hitherto inaccessible alkynes.

Many other aspects still need to be addressed. For instance, can this approach be extended, as indicated in Scheme 24, to the stereoselective synthesis of substituted alkenes by nitrosative cleavage of structures such as **66**? Could allenes, ketenes and related cumulenes be made by starting with heterocycles with a structure such as **67**? Access to these precursors presents us with a synthetic challenge we have not yet taken up, but the versatility of this approach for creating multiple bonds is perhaps highlighted by the easy formation of methyl isocyanate and its *in situ* capture as carbamate **69** by nitrosation of compound **68** with *n*-butyl nitrite in *n*-butanol.[36]

The Abidi reaction, the starting point of this adventure, still holds many unanswered mechanistic questions. Is more than one mechanism involved and can other intermediates be isolated? Perhaps further insight may be obtained by starting with hindered substrates, where the sequence of events may be halted at a point beyond the confirmed allylic nitro intermediate **3**. From a preparative view point, can experimental conditions be found allowing a clean obtention of the alkyne? The high yields initially reported by Abidi have not yet been reproduced in another laboratory.

We have proposed unsaturated oximes as possible intermediates but this so far remains confined to merely a plausible hypothesis. Can some of the later intermediates be isolated and can the experimental procedure be improved so as to make this transformation into alkynes synthetically useful?

These and many other questions remain unanswered at this stage. Nonetheless, our quest for understanding has taken us on a tortuous but exciting and eventful journey. We were fortunate to stumble upon the unexpected and to find that our toil and exertions in this fascinating area were ultimately richly rewarded.

Acknowledgements

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