Chemical adventures with oximes

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Affectionately dedicated to the memory of Sir Derek H. R. Barton

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Abstract

This account is a collection of vignettes describing new reactions discovered in the author’s group revolving around the chemistry of oximes. They range from ionic transformations, including reduction to unsubstituted imines and the formation of α-electrophiles, to the generation and capture of iminyl radicals, to a general synthesis of alkynes. The mechanistic reasonings and occasional serendipitous observations underlying these discoveries are discussed briefly.

Keywords: Oximes, imines, enamides, iminyls, α-electrophiles, alkynes
1. Introduction. An Early Encounter with Oximes

My interest in the chemistry of oximes started early. The main project of my PhD thesis under Sir Derek Barton, funded by the now defunct Roussel-Uclaf, was the construction of the corticosteroid side chain starting from 17-ketosteroids. The latter had become readily available raw materials on an industrial scale by the microbiological degradation of abundant sterols such as cholesterol and, especially, β-sitosterol and related plant sterols obtained from the waste material of the soya bean and tall oil industries.¹ The first method we devised was based on earlier observations made in a collaborative study by Professor Barton, then still at Imperial College, conducted with the team of Professor McGhie at Birkbeck College.² In this work, it was found that prolonged heating of 20-ketoxime 1 in a mixture of acetic anhydride and pyridine produces first enimide 3 which, upon contact with basic alumina, gives enamide 4 (Scheme 1). This strange reaction entails reduction of intermediate oxime acetate 2 by unknown species produced in situ by oligomerization of acetic anhydride. The reaction mixture turns completely black, but the yield of ene-imide 3 is surprisingly good. Furthermore, there is strong evidence that iminyl radicals are involved.³ Treatment of enamide 4 with anhydrous lead tetraacetate results in a clean acetoxylation of the 17α-position to give acetylimine 5, which is readily isomerized into enamide 6 by exposure to anhydrous acetic acid. A second acetoxylation under slightly harsher conditions then introduces an acetoxy group at C-21. Finally, mild hydrolysis of acetylimide 7 furnishes the desired corticosteroid 8.

This ingenious sequence is however not suitable for the large-scale production of corticosteroids. We therefore conceived of a different route based on the formation of novel dihydro-oxazole 10 via sensitive epoxide 9.⁴,⁵ The m-chlorobenzoic acid co-produced in the epoxidation step is sufficient to induce the rearrangement into key-intermediate 10. This compound is readily converted into bromo-derivative 11, which undergoes mild acid hydrolysis to give bromo-ketone 12. Finally, displacement with acetate provides corticosteroid acetate 8. Interestingly, brief heating of dihydro-oxazole 10 in neat pyridinium hydrochloride at high temperature (150-160 °C) induces ring opening, and addition of water and workup causes spontaneous hydrolysis to give enone 13. Δ¹⁶, 20-Ketosteroids are important starting materials for accessing 16-substituted corticosteroids such as dexamethasone and betamethasone.
Scheme 1. Syntheses of the corticosteroid side-chain.

Enamide 4 derives from pregnanone oxime 1 and not from a 17-ketosteroid. To access an analogous enamide from the latter, we used the Horner-Wadsworth-Emmons (HWE) condensation of isocyanophosphonate 15 with ketone 14 to form unsaturated isonitrile 16 (Scheme 2). Exposure to formic acid in ethyl acetate then furnishes ene-formamide 17 with concomitant unmasking of the enone in ring A. This enamide could then be converted into corticosteroid 18 using similar chemistry as above. In this case, the corresponding intermediate dihydro-oxazole 19 is somewhat fragile; it was therefore not isolated but brominated and hydrolysed in situ.
Another route to corticosteroids from 17-ketosteroids proceeding through an enamide relied on an improved and interesting reduction of oximes. This strategy, outlined in Scheme 3, started from known alkene 20 derived from the corresponding 17-ketosteroid through a Wittig olefination. Exposure to in situ generated nitrosyl chloride in ice-cold dichloromethane furnished nitrososteroid 21, which was not isolated. The dichloromethane was simply evaporated and replaced with wet THF and triethylamine. This induced the elimination of HCl and formation of unsaturated oxime 22. This compound was not purified but heated to 100 °C in acetic anhydride with addition of iron powder resulting in the smooth formation of dieneimide 23 in 85% overall yield. Adsorption on basic alumina and elution gave the corresponding acetenamide 24 quantitatively. Hydrolysis of this substance would furnish enone 25, whereas prior bromination would give bromoketone 26 and substitution of the bromine with acetate would provide acetoxyketone 27, all of which are useful precursors to 16-substituted corticosteroids as stated above.

The application of the acetic anhydride / iron powder combination arose from discussions with the late Dr Jean Buendia of Roussel-Uclaf, who funded this work. It was conceived in order to replace the acetic anhydride/pyridine used above to convert oxime 1 into acetamide 4, which is not practical for large scale work. The rationale underlying this new reduction of oximes is displayed in the lower part of Scheme 3. The acetic anhydride first converts generic ketoxime 28 into acetate 29, which then is able to accept an electron from the iron to give radical anion. This extra electron goes into the σ* orbital of the N—O bond resulting in its rupture, with the formation of iminyl radical 31 and an acetate anion. A second electron transfer leads to iminyl anion 32 that is rapidly protonated. The protonation step may in fact precede, and indeed facilitate, the electron transfer. In any case, the resulting imine 33 is finally acetylated by the excess acetic anhydride to give N-acetylimine 34, which can tautomerize into the corresponding acetenamide and further acetylated (cf., 22 → 23).
Scheme 3. An alternative route to corticosteroids from 17-ketosteroids.

2. An Unusual Reduction of Nitroalkanes and Ketoximes

In parallel to the isocyanide and enamide routes described above, another route to corticosteroids was explored involving the condensation of nitromethane with 17-ketosteroid as the key-step.\textsuperscript{7,8} This is a non-trivial transformation that we accomplished by using ethylenediamine and certain congeners as efficient catalysts to overcome the poor reactivity of the sterically hindered 17-ketone. I have always been fascinated by the incredibly rich chemistry of nitro compounds and, over the years, we uncovered, by accident or by design, several new reactions.\textsuperscript{9} One such discovery arose when, in a misconceived attempt to convert a secondary nitro compound directly into a dithioketal, 6α-nitrocholestanyl acetate 35 was treated with a combination of tri-n-butylphosphine and diphenyl disulfide (Scheme 4). The reaction resulted in the clean formation of 6-ketosteroid 36 after an aqueous workup.\textsuperscript{10,11}
Scheme 4. A reduction of nitroalkanes and ketoximes.

The mechanism that ultimately accounted for our experimental observations is displayed in Scheme 4. The phosphine and the disulfide react reversibly to give pentavalent phosphorus species 37 which can reduce the nitroalkane into the corresponding oxime 28 with recovery of the disulfide, as shown (Path A). In turn, the oxime is reduced into imine 33 which is hydrolysed to ketone 41 upon workup. The driving force is the formation of a strong P—O bond and, while the disulfide is regenerated and its action is catalytic, it is in practice best used in stoichiometric amounts, especially in small scale work, to avoid slow kinetics and because a portion of it is destroyed by any adventitious water present (path B). The oxime is reduced faster than the starting nitro compound and, not unexpectedly, primary nitro compounds and aldoximes (R' = H) are converted into nitriles 42. One unexpected transformation was observed when an excess diphenyl disulfide was used. The reaction furnished phenylsulfonylimine 44, a rare family of compounds, through an equilibrium involving intermediate 43.

This reagent combination proved to be an excellent reductant for oximes. Vilarrasa and co-workers later reported that, in some cases, the tri-n-butylphosphine can be advantageously replaced by the more reactive trimethylphosphine. Since water is removed irreversibly through path A, the medium is strictly anhydrous and the hydrolytically labile imines 33 are protected against premature hydrolysis. They can therefore be captured by various reagents allowing many synthetically useful transformations, in addition to simple hydrolysis to the corresponding ketone 41. A few examples are deployed in Scheme 5.
Steroid oxime 45 can thus be converted into ketone 47 by hydrolysis of intermediate imine 46, whereas reduction and acetylation furnish 17-β-acetamide 48 and interception by in situ generated hydrogen cyanide produces aminonitrile 49. Performing the reaction in the presence of excess disulfide generates phenylsulphenimine 50 in modest yield. More impressive examples of this last transformation were later disclosed by Jung and co-workers at Syngenta\textsuperscript{15} and by Lukin and Narayanan at Abbott\textsuperscript{16} and later by Vilarrasa.\textsuperscript{13} The first group reported the synthesis of avermectin B1 (mixture of B1a and B1b) derivatives 51\textsubscript{a,b} in high yield from the corresponding oximes, whereas the last two studied erythromycin analogues. Another interesting transformation is the capture of the intermediate imine with S-phenyl thioacetate, as illustrated by the efficient conversion of cyclopentanone oxime into acetamide 52.\textsuperscript{11} S-phenyl thioacetate is compatible with the reducing combination and can be added at the start of the reaction. It captures the imine as it is formed and avoids the unwanted trimerization often observed with simple unhindered N-unsubstituted imines.

3. Multiple Routes to Iminyls and Other Nitrogen Radicals

The unexpected formation of sulphenylimines 44, as exemplified by compound 50, raised the question of the possibility of using such derivatives as precursors for the little studied iminyl radicals. The affinity of stannyl radicals for sulfur and the relative weakness of the N—S bond seemed like a good driving force. Indeed, slow addition of tri-n-butylstannane and AIBN to a solution of 17-sulphenylimine 50 in refluxing benzene afforded 13-epi-17-iminyl-steroid 56 in high yield through the formation and ring-opening of iminyl radical 53 followed by
closure of tertiary radical 54 to give the more stable epimeric iminyl radical 55 with the less strained cis-CD ring junction.\textsuperscript{17} This is a rare case where the hydrolytically labile unsubstituted imine 56 is sterically protected and can be isolated in good yield. Acid hydrolysis furnishes the corresponding ketone 57 with concomitant cleavage of the acetate at position 3.

\chemfig{N~\text{Ph}^{\text{N-OAc}}^{\text{CMe_3}}} \xrightarrow{\text{Ni / AcOH, isopropanol reflux}} \chemfig{N^{\text{Ph}}^{\text{Me}}} \xrightarrow{\text{Ni / AcOH, isopropanol reflux}} \chemfig{N^{\text{Ph}}^{\text{Me}}} \xrightarrow{\text{Ni / AcOH, isopropanol reflux}} \chemfig{N^{\text{Ph}}^{\text{Me}}} \xrightarrow{\text{Ni / AcOH, isopropanol reflux}} \chemfig{N^{\text{Ph}}^{\text{Me}}}

Scheme 6. Generation and capture of iminyl radicals.

Sulphenylimines proved to be excellent precursors for the generation and capture of iminyl radicals; however, their preparation is not generally straightforward, which limits the synthetic utility of this method. We therefore devised another route based on the observation pictured in Scheme 3, namely that the dissolving metal reduction of oxime acetate 29 proceeds via iminyl radical intermediate 31. The problem that had to be addressed was the need for a reducing system where the electron transfer leading to iminyl anion 32 is sufficiently slow to allow a synthetically useful interception of iminyl radical 31. We used the epimerisation of 17-steroid iminyl radical 53 as a convenient radical clock to gauge its lifetime and thus rapidly screen various metal/acid combinations.\textsuperscript{18} Ultimately, we found that crude nickel powder and acetic acid in an organic solvent such as octane allowed the clean formation of 13-epi-steroid 59, starting from 17-oxime acetate 58. In the absence of the organic solvent or replacement of nickel by more reducing metals (such as iron) results in simple conversion of oxime acetate 58 back to the natural 17-ketone (not shown) with little, if any of the 13-epimer 59. Under these latter conditions, the intermediate iminyl radical 53 does not live long enough to allow installation of the equilibrium leading to the more stable epimer 55.
The iminyl radical can be captured by a suitably located alkene in a more generally useful synthetic transformation. This is illustrated by the formation of pyrrolenines 61 and 64. The oxime pivalate precursor 63 of the latter is derived from thevinone, the Diels-Alder adduct of thebaine with methyl vinyl ketone. In these cyclisations, isopropanol serves as the final hydrogen atom donor to quench the cyclised radical (e.g. 62). The use of the oxime pivalates instead of the acetates is to limit unwanted hydrolysis back to the oxime, which we occasionally observed.

We were surprised to find that in the case of oxime acetate 66, the reaction did not furnish the expected pyrrolenine but gave instead alkene 67 as the major product in addition to a small amount of tertiary acetate 68 (Scheme 7). In the case of the methyl analogue 69, it is tertiary acetate 71 that dominated, with little or no alkene 70. Initially, with our mind fixated on radical chemistry, we assumed that the tertiary radical arising from the cyclisation of the iminyl was not abstracting a hydrogen atom from the isopropanol rapidly enough and was finally either reacting with adventitious oxygen or being oxidized to the corresponding cation by electron transfer, perhaps to the starting oxime acetate. Nevertheless, we later returned to this reaction and performed a blank experiment on compound 66 in the absence of the nickel powder. Pyrrolenines 67 and 68 were indeed produced, albeit in different ratios. Obviously, in the case of electron rich internal alkene traps, an ionic substitution involving nucleophilic attack on the oxime nitrogen, as shown in structure 72, overtakes the radical process.

Scheme 7. Unusual ionic reactions of oxime esters.
Two other experiments we performed were replacing the isopropanol with t-butanol, a solvent that lacks easily abstractable hydrogen atoms, and using cupric acetate (conditions A) or ferric chloride (conditions B) in place of the nickel powder. Under the former conditions, oxime acetates 66 and 69 furnished alkenes 68 and 70 respectively in good yield. Under the latter, oxime acetate 66 was converted mostly into tertiary alcohol 73. We later also found that with ferric chloride, and in the absence of acetic acid, even substrates with unsubstituted terminal alkenes reacted to give chlorine-substituted pyrrolenines. Thus, oxime acetate 60, which under the Ni/AcOH/isopropanol conditions produces reduced pyrrolene 61 (Scheme 6), now reacts with ferric chloride to give chloride 74. The reaction of this compound with methyllithium leads to bicyclic aziridine 75 in quantitative yield (by NMR). Pyrrolenes 77-82 are further examples of this ferric chloride mediated transformation.

Scheme 8. Iminyl radicals from oxime benzoates.
In parallel, we developed a more traditional route to iminyl radicals, based this time on oxime benzoates 87. A few years before the publication of the famous Barton-McCombie deoxygenation,21 Khoo and Lee reported a deoxygenation process for alcohols based on reacting the corresponding benzoates 83 with tri-n-butyltin hydride (Scheme 8).22 This older method did not attract much attention because it is limited to cases where the carbon-centered radical 85 generated is particularly stabilized (e. g., benzylic or allylic). The attack of a benzoate by stannyl radicals is relatively slow and strongly reversible. If the subsequent fragmentation of adduct 84 is also slow because the carbon radical 85 produced is unstabilized, then the whole sequence becomes inefficient. In contrast, the Barton-McCombie deoxygenation employs xanthates 86 and other related thiocarbonyl derivatives. The reaction of stannyl radicals with a thiocarbonyl group, while still reversible, is much faster as compared to a carbonyl and compensates for the relative sluggishness of the subsequent irreversible rupture of the C—O bond. This gives the Barton-McCombie deoxygenation a much broader scope and raises it to a genuine landmark in radical chemistry.

In view of these considerations, we surmised that, in the case of oxime benzoates 87, the first reversible but sluggish addition of the stannyl radicals to the carbonyl of the benzoate will now be compensated by a fast irreversible scission of the relatively weak N—O bond to give iminyl radicals 31. Indeed, this simple approach proved effective for generating not only iminyls but most other synthetically useful nitrogen centered radicals such as amidyls, carbamyls, ureidyl, and amidinyls.23-26 Three examples are presented in the lower part of Scheme 8 illustrating generation and capture of iminyls. In the case of deoxyglucose derived oxime 90, the resulting pyrroline 91 did not survive chromatographic purification on silica and underwent elimination into pyrrole 92. Cyclobutyliminyl radical 94 cleaves regioselectively to give ultimately nitrile 95 in high yield.

The logical question that next arose was how would oxime xanthates behave? Both the radical addition to the thiocarbonyl and the subsequent fragmentation steps are now so fast and efficient that radical chains can be initiated and propagated under organotin-free conditions by simple heating and/or irradiation with visible light (Scheme 9).27

Scheme 9. Iminyl radicals from oxime xanthates.
We found that oxime xanthates such as 97 can be prepared in the usual way, by treating the anion of the oxime with carbon disulfide and methyl iodide in one pot. These substances proved to be relatively fragile, being sensitive to heat and light, but could be quickly purified by chromatography on silica and used directly in the desired radical transformation. Thus, irradiation of xanthate 97 with visible light at room temperature generates iminyl radical 98 which rapidly cyclizes, and the resulting tertiary carbon radical 99 reacts with starting xanthate 97 to give dithiocarbonate 100 and iminyl 98 that propagates the chain. The intermediate carbon radical 99 can be captured by an electrophilic alkene, such as phenyl vinylsulfone, to give more complex pyrrolenine 101. It is also possible to accomplish a bromine atom transfer to give bromide 102 by irradiating in bromotrichloromethane as the solvent.

4. An Alliance with Xanthates

Much of our research efforts have revolved around the chemistry of xanthates. Nearly 40 years ago, we uncovered an unusually powerful process whereby, under appropriate conditions, a xanthate can be made to add to an alkene by a radical chain mechanism. A new carbon-carbon bond and a new carbon-sulfur bond are formed in the process and the method exhibits numerous interesting aspects that will not be discussed here. With respect to oximes, this xanthate chemistry can be applied in many ways to rapidly construct various interesting oxime derived structures. In the example displayed at the top of Scheme 10, pyruvate xanthate 103 adds to allyl acetate to give adduct 105, where the new bonds formed are colored in red. The reaction proceeds via radical 104 and is initiated by substoichiometric amounts of DLP (di-lauroyl peroxide, also sold under lauroyl peroxide). Many other alkenes can be used and the oxime benzoate can in principle be subjected to a variety of transformations, including reduction into the corresponding amine, thus opening a simple access to numerous novel amino acids.

Alternatively, the oxime motif can be placed on the alkene partner, as shown in the second example where p-fluoroacetophenyl xanthate 106 smoothly adds to the terminal alkene of xanthate 107 to give adduct 108. Because of the presence of the secondary butyl group on the xanthate, this compound undergoes a Chugaev elimination upon heating to 200 °C in diphenyl ether to form thiol 109 which, under these rather harsh thermal conditions, reacts further through intermediate 110 to produce dihydrothiazine 111 in a useful yield. Dihydrothiazines were a virtually unknown class of heterocycles before the present route was developed.
Scheme 10. The xanthate route to pyruvyloximes and dihydrothiazines.

The xanthate group in the addition products of phenacyl xanthates can be further exploited to mediate a second carbon-carbon formation through ring-closure onto the aromatic ring. This constitutes a practical, convergent route to α-tetralones.\(^{33}\) It can be accomplished by treating the adduct with stoichiometric amounts of peroxide, as shown by the conversion of adduct 113 derived from xanthate 112 and allylbenzene into oxime 114, obtained by treatment of the intermediate tetralone (not shown) with hydroxylamine under the usual conditions (Scheme 11). The initial purpose of this synthesis was to establish a general approach to naphthylamines by application of the little used Schreeter reaction. This is an extension of the earlier Semmler-Wolff reaction and allows the conversion of oximes of α-tetralones into \(N\)-acetyl-naphthylamines. Thus, oxime 114 was first acetylated into acetate 115 by heating gently in neat acetic anhydride followed by addition of acetic and methanesulfonic acids and a more vigorous heating to 130 °C.\(^{34}\) The expected \(N\)-acetyl-naphthylamine 116 was indeed isolated; it was, however, the minor component. The major product turned out to be tetracyclic ketone 117, produced after a hydrolytic workup. We had in fact unwittingly captured an intermediate in the Schreeter reaction and diverted it from its normal pathway.
Scheme 11. Oximes as α-electrophiles.

The normal Schroeter sequence leading to the naphthylamide 116 starts by acetylation of oxime acetate 115 to give intermediate 118 which, under the strongly acidic medium, is in equilibrium with protonated species 119. Loss of a proton and cleavage of the relatively weak N—O bond (path a) gives naphthylamide 116 after tautomerization of the intermediate N-acetylimine (not shown). Because of the presence of a suitably located pendant phenyl ring, a competing intramolecular Friedel-Crafts reaction can take place leading to N-acetylenimide 120, according to path b. This compound cannot tautomerize to the corresponding N-acetylenamide and is simply hydrolyzed into ketone 117 upon aqueous basic workup. This serendipitous finding opens a simple, flexible, and modular pathway to rare tetracyclic bridged ketones such as 117. Furthermore, the intermediate acetylimides (e.g. 120) can be isolated by modifying the workup procedure and serve, in principle as a springboard to access a variety of nitrogen derivatives (amines, aminonitriles, amino acids, etc.).

5. Syntheses of Alkynes

Serendipity is a wonderful ally in chemical research and in science, more generally. One remarkable accidental discovery was made many years ago by Sharon L. Abidi, a chemist working at the National Fishery Research Laboratory in the US. She was interested in the effects of nitrite on the environment and, in one study, reacted...
tertiary terpeneethanolamines 121 with an excess of sodium nitrite in acetic acid at 60°C. The major products from these reactions turned out to be, unexpectedly, N-nitrosoalkynylamines 122 (Scheme 12). In this incredible transformation, the isopropylidene group in the geraniol chain is somehow converted into an alkyne by the formal loss of the elements of methane. These observations were first described in 1985 and then in two subsequent papers in 1986, but no mechanism was provided. Shortly thereafter, Corey and co-workers reported the results of their mechanistic study. While they could reproduce the reaction, they could not reproduce the yields (nor could we). For instance, Abidi claimed a nearly quantitative yield for acetylene 124 from geraniol 123, but the Harvard group could only secure 25-33%, certainly after much hard work. However, they made a key finding, namely that allylic nitro derivative 125 is an intermediate that can be isolated in good yield by working under somewhat gentler conditions and a shorter reaction time.

**Scheme 12.** A remarkable synthesis of alkynes.

This key information allowed us to formulate an alternative mechanism where we postulated that unsaturated oxime 129 could be a later intermediate, as shown in the generic sequence outlined at the top of in Scheme 13. This substance would derive from pseudo nitrole 128, formed by nitrosation of Corey’s allylic nitro intermediate 127. Pseudo nitroles are well-known derivatives, even if they have attracted little attention in recent times. So now the question is whether an unsaturated oxime such as 129 could indeed furnish alkyne 130 under the Abidi conditions.
Scheme 13. Unsaturated oxime as a possible intermediate.

To test the plausibility of this mechanistic hypothesis, we prepared oxime 134 from citronellyl acetate 131 by treatment with nitrosyl chloride and elimination of HCl with mild base in a manner similar to the one we used earlier to obtain steroid oxime 22 (Scheme 3). In the event, exposure to sodium nitrite in hot aqueous acetic acid indeed gave rise to the expected alkyne 132 in around 20% yield. In our hands, the direct conversion of citronellyl acetate 131 into alkyne 132 proceeded in only 10-15%, in stark variance with Abidi’s claim of a 78% yield for this transformation. Thus, despite the poor yield, unsaturated oxime 134 could nevertheless be an intermediate in the Abidi reaction.

Saturated oximes react with nitrous acid to give back the parent aldehyde or ketone. This reaction is one of the lesser known Claisen reactions. In contrast, work by the late Jeremiah Freeman showed that α,β-unsaturated oximes give unusual heterocyclic structures when exposed to nitrous acid. However, α,β-unsaturated oximes where the alkene moiety is terminal and unsubstituted, as in generic structure 129, were not examined in these studies. Nevertheless, in strict analogy with Freeman’s findings, we postulated that oxime 129 reacts with nitrous acid to give N-nitroso intermediate 135, which then undergoes an electrocyclic ring closure into heterocycle 136, as pictured in Scheme 14; but, unlike the more substituted examples studied by Freeman, heterocycle 136 can proceed further by a series of tautomerizations and nitrosations to furnish ultimately intermediate 141 which finally collapses into the desired alkyne 130. The driving force is the loss of carbon dioxide, nitrous oxide, and water.
Scheme 14. A plausible mechanism for alkyne formation.

While this mechanism is mostly speculative, we did obtain some evidence for the first steps. If heterocycle 136 is indeed a possible intermediate, then isomeric oxime 142 should also produce acetylene 130 under the same nitrosative conditions. This is because its nitrosation would give derivative 143 and electrocyclic ring closure would lead to the same postulated heterocyclic intermediate 136. Indeed, when we subjected oxime 145 to the action of sodium nitrite in aqueous acetic acid, we were pleased to find that the expected alkyne 146 was formed in a yield comparable to the one observed for the conversion of citronellol derived oxime 134 into alkyne 132.

In attempting to understand the mechanism of the remarkable reaction discovered by Abidi, we thus discovered a hitherto unknown transformation of α,β-unsaturated oximes of type 129 and 142 into alkynes 130. However, even if the poor yields could be improved, this finding would remain of modest synthetic utility because of the quite limited availability of such oxime substrates. Nevertheless, this study guided us to another possibility, which ultimately proved vastly more interesting. By reflecting upon the structure of late intermediate 141, it occurred to us that an analogous unstable species 151 could in fact be obtained directly by nitrosating an isoxazolinone 148 (Scheme 15). This nitrosation could occur at positions 2 and/or 4 of the isoxazolone to give N-nitroso- and/or C-nitroso isoxazolones 149 and/or 150 respectively. Only the former can collapse into unstable species 151, which would then lose carbon dioxide and nitrous oxide to furnish the desired alkyne 152. We surmised that the unreacted C-nitroso isomer 150 could in principle revert back to starting material 148a,b by an ionic “retro-nitrosation” through attack by water on the nitroso group, and this
would hence ensure that all the substrate would eventually be transformed into alkyne 152. We also realized from the outset that C-4 had to be substituted (i.e., \( R' \neq H \)); for otherwise the nitroso group will rapidly tautomerize into the more stable oxime 153 which would then lead to decomposition products upon nitrosation. At any rate, this hypothesis was easily tested, since isoxazolones 148, which can be viewed superficially as cyclic oxime esters, were well-known and accessible in one step from readily available \( \beta \)-ketoesters 147.

![Scheme 15. An alternative route to alkyynes.](image)

Our first experiment was only partially successful. The reaction was quite clean but the expected alkyne was formed as the minor component in modest yield. The major product turned out to be an unsymmetrical dimer of structure 155. Clearly, such a compound almost certainly arose from the nitrogen to carbon coupling of radical 154. This key observation indicated that nitroso intermediates 149 and (especially) 150 were undergoing a spontaneous reversible homolysis at room temperature. The gaseous nitric oxide released escapes from the medium leaving radicals 154 behind which ultimately couple to give dimer 155. To curtail the formation of this unwanted side-product, we modified our experimental procedure. First, now that we knew that radicals were involved, we operated under an inert atmosphere and thoroughly degassed the solutions, in contrast to the preliminary experiments performed in an open flask. Second, we added ferrous sulfate and allowed it to react with part of the sodium nitrite and acetic acid (used in excess) before the addition of the substrate and the remainder of the reagents. The combination of ferrous sulfate with sodium nitrite and acetic
acid generates nitric oxide in situ and, since this is a persistent radical, its presence prevents the formation of unwanted dimers 155 by selectively capturing radical 154 through what is called the persistent radical effect (PRE). PRE, also known as the Fischer-Ingold effect, is an extremely important principle that is unfortunately not widely appreciated.\textsuperscript{44,45} Thus, in our system, isomeric nitroso intermediates 149 and 150 were not interconverting by an ionic “retro-nitrosation” as we initially anticipated, but rather via homolysis to radical 154 which reversibly recombines with nitric oxide.

With this key experimental modification in place, the transformation of isoxazolinones 148 into alkynes 152 becomes a quite powerful synthetic tool. Five examples are displayed in Scheme 16. Only one tautomer for the isoxazolinone precursors is shown for clarity. Diyne 157 is taken from a very recent study by Tavakoli and Dudley and represents a valuable precursor for the synthesis of polycyclic compounds.\textsuperscript{46} The skipped arrangement between the alkyne and the ester is quite sensitive to base induced isomerization to the allene but survives under the mildly acidic experimental conditions of our procedure. The skipped enyne in example 161 is also a rather fragile arrangement vis-à-vis base and oxidation.\textsuperscript{47}

\begin{Scheme}
\begin{center}
\includegraphics[width=\textwidth]{Scheme_16.png}
\end{center}
\end{Scheme}

\textbf{Scheme 16.} Examples of alkynes.

As stated above, oxazolidinones 148 with \( R' = \text{H} \) are not suitable for the synthesis of terminal alkynes because the corresponding C-nitroso intermediate 150 rapidly isomerizes into oxime 153. It is however
possible to prepare terminal chloroalkynes such as 164 by starting with 4-chloro-oxazolidinone precursor 163. Chloroalkynes can be reduced to the parent terminal alkynes or used in a number of transition metal catalyzed transformations. The β-ketoesters used to prepare oxazolidinones 158, 160, and 162 were all three obtained using the xanthate radical addition briefly described above, applied twice for the first two. The carbon-carbon bonds created through this procedure are colored in red. A further example of this alliance is outlined in Scheme 17.

This transformation connects β-ketoesters with alkynes. Any method that furnishes β-ketoesters can be used in principle to obtain the corresponding alkynes via the intermediate isoxazolinone. For instance, the generation and capture of the dianions of β-ketoesters, and especially acetoacetates, is a powerful, well-established synthetic tool. Thus, the dianion of ethyl 2-methyl-acetoacetate 165 reacts with cinnamaldehyde at the least acidic terminus and condensation with hydroxylamine provides isoxazolinone 166. Nitrosative cleavage then furnishes the expected corresponding alkyne 167.

Scheme 17. Further examples of alkynes.

An alternative approach to produce more complex β-ketoesters starts with di-xanthate 168. This substance undergoes regioselective radical addition to allyl p-chlorobenzoate to give adduct 169. The high regioselectivity is the result of the greater radical stabilization of the radical in-between the ester and the ketone. Again, the difference in radical stabilities allows a second regioselective radical addition of adduct 169 to allylbenzene to produce compound 170, from which both xanthate groups can be reduced off with tris(trimethylsilyl)silane. Condensation of the resulting ketoester 171 with hydroxylamine and nitrosative cleavage affords alkyne 173. Numerous other alkene partners could in principle be used in this sequence to...
provide a broad variety of alkynes. In a sense, di-xanthate 168 is the synthetic equivalent of hypothetical diradical 174.

A further important route to β-ketoesters consists in the Lewis acid promoted reaction of ketones with diazoacetates.\(^\text{52}\) In the case of 4-pivaloxy-cyclooctanone 175, this leads to two regioisomeric ketoesters 176a and 176b containing one extra carbon in the ring (Scheme 18).\(^\text{53}\) Interestingly, the corresponding isoxazolinones 177a and 177b produce the same alkyne 178 upon nitrosative cleavage. Overall, this transformation can be viewed as the insertion of a two-carbon acetylene motif in place of the ketone, with a corresponding increase in the size of the ring by one carbon atom. An analogous sequence was used to prepare cycloalkynes 179-183. Indeed, the association of the ring expansion of cyclokanones with diazoacetates with the nitrosative cleavage of the derived isoxazolinones represents a particularly convenient route to cycloalkynes. It tolerates a variety of substituents and does not suffer from the formation of the difficult to remove allene isomers often observed with methods relying on base-induced eliminations.

Scheme 18. Examples of cycloalkynes.

Finally, further alkyne diversity can be secured by exploiting the specific reactivity of the isoxazolinone moiety itself. For example, 4-unsubstituted isoxazolinones 184 participate readily in Knoevenagel-type condensations with aldehydes and ketones to give strongly electrophilic alkylidene derivatives 185. These can be reduced with borohydride or subjected to conjugate additions by numerous nucleophiles (Scheme 19),\(^\text{54-58}\) leading to functional isoxazolinones 186 and then to alkynes 187.

The examples assembled in Scheme 19 illustrate some of the possibilities. Alkynes 188, 189, and 190 were obtained through reduction of the 4-alkylidene isoxazolidinone precursors with sodium borohydride.\(^\text{54}\) In the first two, the hydride attacks stereoselectively from the least hindered face of the molecules. Alkynes 191 and 192, both reported by Jurberg and co-workers,\(^\text{55,56}\) were derived by a chiral amine mediated addition of monoprotected 1,4-cyclohexanedione, for the first, and a Lewis acid catalyzed Mukaiyama-type addition of an enol silyl ether, for the second. The high levels of diastereo- and enantio-selectivities in the case of alkyne 191
are impressive. In examples 193 and 194, the nucleophiles are dimethyl phosphite and hydrogen cyanide, respectively, whereas for alkynes 195 and 196, a Reformatsky reagent and t-butyl isocyanide were used as the nucleophilic partners. Alkynes 197, 198, 199, and 200 all arise from reaction of the same 4-benzylidene isoxazolinone with an allenylzinc derivative for the first and with three different Grignard reagents for the others. Alkyne 197 was obtained as one diastereoisomer, but its configuration was not determined. The last example, 201, results from the conjugate addition of phenylcopper to 3-methyl-4-isopropylideneisoxazolinone.

Scheme 19. Alkynes from further modifications of isoxazolinones.

Conclusions

Working with oximes over the years has been a constant source of wonder and pleasant surprises. That a moiety as small as an oxime could have such a rich and varied chemistry is indeed something to behold. Our adventures in this area have been a mix of conceptions and serendipitous observations. They have nevertheless resulted in a number of synthetically useful findings. Perhaps the most general and enduring in the long run are the reduction to unsubstituted imines, the various methods for the generation of iminyls and
their extension to other nitrogen centered radicals, and, finally, the powerful synthesis of alkynes, which provides a concise access to numerous structures not readily available by other routes. Hopefully, the present brief account will inspire younger chemists to carry the torch and expand further the chemistry of this remarkable functional group.

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