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The Oxime Portmanteau Motif: Released Heteroradicals Undergo Incisive EPR Interrogation and Deliver Diverse Heterocycles

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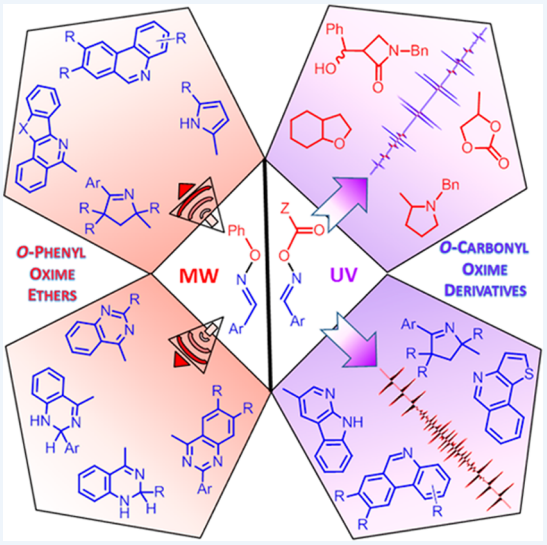
CONSPECTUS: Selective syntheses are now available for compounds of many classes, based on C-centered radicals, exploiting a diverse range of mechanisms. The prospect for chemistry based around N- and O-centered radicals is probably more favorable because of the importance of heterocycles as biologically active materials. Heteroradical chemistry is still comparatively underdeveloped due to the need for safe and easy ways of generating them. Oxime esters appeared promising candidates to meet this need because literature reports and our EPR spectroscopic examinations showed they readily dissociated on photolysis with production of a pair of N- and O-centered radicals. It soon became apparent that a whole suite of benign oxime-containing molecules could be pressed into service. The bimodality of the oxime motif meant that by suitable choice of functionality the reactions could be directed to yield selectively products from either the N-centered radicals or from the O-centered radicals.



We found that on one hand photolyses of acetophenone oxime esters of carboxylic acids yielded alicyclics. On the other hand, aromatic and heteroaromatic acyl oximes (as well as dioxime oxalates) afforded good yields of phenanthridines and related heterocycles. Easily prepared oxime oxalate amides released carbamoyl radicals, and pleasingly, β-lactams were thereby obtained. Oxime carbonates and oxime carbamates, available via our novel 1,1'-carbonyldiimidazole (CDI)-based preparations, were accessible alternatives for iminyl radicals and hence for phenanthridine preparations. In their second modes, these compounds proved their value as precursors for exotic alkoxycarbonyloxyl and carbamoyloxyl radicals.

Microwave-assistance was shown to be a particularly convenient procedure with *O*-phenyl oxime ethers. The iminyl radicals generated from such precursors with alkene, alkyne, and aromatic acceptor substituents furnished pyrrole, quinoline, phenanthridine, benzonaphthiridine, indolopyridine, and other systems. Microwave irradiations with 2-(aminoaryl)alkanone *O*-phenyl oximes enabled either dihydroquinazolines or quinazolines to be obtained in very good yields.

The fine quality of the EPR spectra, acquired during photolyses of all the *O*-carbonyl oxime types, marked this as an important complement to existing ways of obtaining such spectra in solution. Quantifications enabled SARs to be obtained for key reaction types of N- and O-centered radicals, thus putting mechanistic chemistry in this area on a much firmer footing. Surprises included the inverse *gem*-dimethyl effect in 5-*exo*-cyclizations of iminyls and the interplay of *spiro*- with *ortho*-cyclization onto aromatics. Insights into unusual 4-*exo*-cyclizations of carbamoyl radicals showed the process to be more viable than pent-4-enyl 4-*exo*-ring closure. Another surprise was the magnitude of the difference in CO_2 loss rate from alkoxycarbonyloxyl radicals as compared with acyloxyl radicals. Their rapid 5-*exo*-cyclization was charted, as was their preferred *spiro*-cyclization onto aromatics. The first evidence that N-monosubstituted carbamoyloxyls had finite lifetimes was also forthcoming.

It is evident that oxime derivatives have excellent credentials as reagents for radical generation and that there is ample room to extend their applications to additional radical types and for further heterocycle syntheses. There is also clear scope for the development of preparative procedures based around the alkoxyl and aminyl radicals that emerge downstream from oxime carbonate and oxime carbamate dissociations.

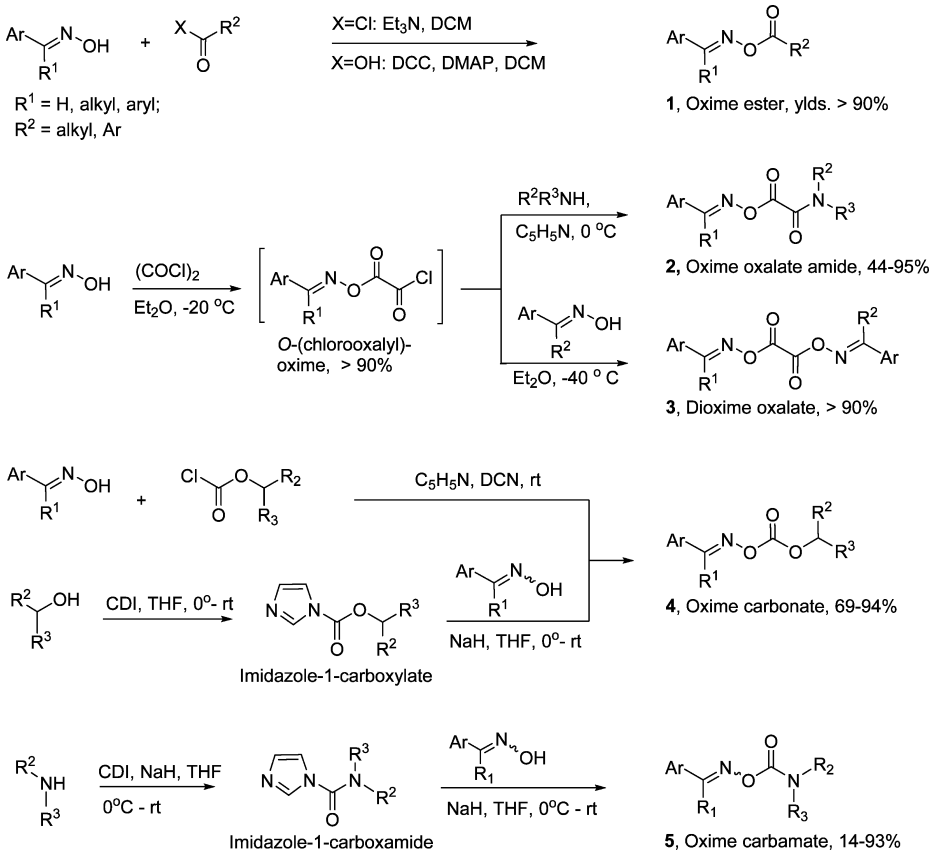
1. INTRODUCTION

Oxime is a portmanteau term[1] because it combines two words, oxygen and imine, into one, neatly representing the idea of oxygen bonded to sp^2-hybridized nitrogen. Oxime N−O bonds are weak enough[2,3] to imply that they should selectively cleave to generate N- and O-centered radicals. The assimilation of radical-mediated synthetic methods into the mainstream of preparative organic chemistry is hindered by the need to rely on unattractive reagents such as peroxides, azo-compounds, or organotin hydrides. Many oxime derivatives are easily prepared, are nontoxic and nonexplosive, and have long shelf lives. Accordingly, the prospect beckoned us of (a) evolving oximes for greener radical chemistry and (b) of developing precursors

Received: January 14, 2014
Published: March 21, 2014

   dx.doi.org/10.1021/ar500017f | Acc. Chem. Res. 2014, 47, 1406−1416

Scheme 1. Types of Oxime Carbonyls Investigated with Preparative Methods



for meagerly studied N- and O-centered species thereby giving entry to diverse heterocycle systems.

Sporadic reports have appeared since the 1970s of UV photolyses of oxime esters of aliphatic carboxylic acids yielding iminyl and carbon-centered radicals.[4] The group of Hasebe had developed arylations and chlorinations from benzophenone oxime esters.[5] Zard had generated iminyl radicals from cyclobutanone and other oxime esters in several ingenious ways.[6] We recognized that a whole suite of oxime-containing molecules could be employed, extending the field well beyond oxime carboxylate esters. Specific oxime-containing structures were discovered that deliver a sizable corpus of useful and esoteric radicals spanning C-, N- and O-centered types. Our investigation covered two classes: first, oxime carbonyls, containing the C═N−OCH(═O)−Z unit, and second, oxime ethers, containing the C═N−OAr unit. Scheme 1 shows the five distinct types of oxime carbonyls (**1**−**5**) that we have investigated with their main synthetic routes.

The outstanding property of oxime derivatives is their bimodality, which enables them to cleave to two species centered on different atoms. Varieties designed with small Z (Me, OEt, OPh) are effective sources of preparatively useful iminyl radicals because the byproducts are small, volatile, or otherwise easily removed (MeH, HOEt, HOPh). In the second mode, R^1 and Ar are chosen such that the resulting byproducts [R^1ArC═NH, R^1ArC═O] are small or volatile and easily separated, thus facilitating preparations mediated by O-centered radicals.

The X-ray crystal structures for particular examples of **2**, **3**, and **4** revealed that in each case extended all-*trans* structures were adopted with the ArC═N−OCH(═O)−Z units close to planar (Figure 1).[7] This assisted $\pi-\pi$ stacking between the aromatic rings of the oxime and the 4-methoxyacetophenone (MAP) used as photosensitizer and thereby promoted energy transfer. The N−O bond lengths were somewhat longer than in oximes themselves, and this was certainly consistent with their ready scission.

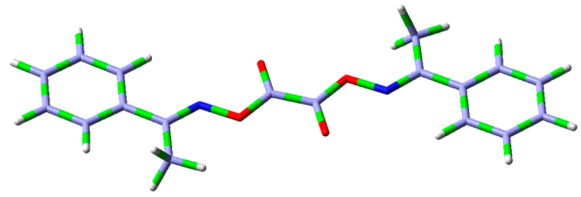


Figure 1. Extended structure adopted by PhMeC═NOC(O)(O)-CON═CMePh dioxime oxalate.

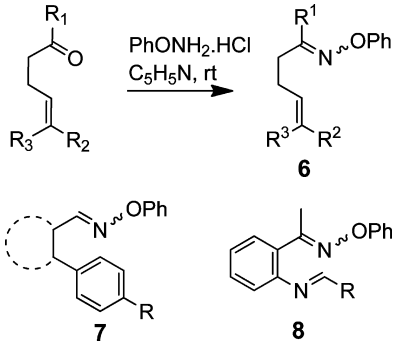
Theoretical calculations (CASPT2/6-31G*//CASSCF/6-31G* level) on model acyl oximes pointed to photoexitation populating a singlet state. Relaxation then led directly to N−O bond breaking, due to the coupling between the imine π^* and the N−O σ^* orbitals.[8]

The second main class that we investigated was oxime ethers, and Scheme 2 shows types **6**−**8** containing alkenyl, aromatic, and iminyl substituents.

Concurrently with our study, Narasaka and co-workers showed that ring closure of γ,δ-unsaturated or β-aryl oximes was induced by a single electron transfer with Cu or phenolic reagents to give various pyrroles, quinolines, and carbolines. Dihydropyrroles were also prepared by photolytic reactions of similar oxime ester types.[9] Remarkable parallels and counterparts to this radical chemistry can also be found in palladium and copper catalyzed reactions of specific oxime esters.[10]

dx.doi.org/10.1021/ar500017f | *Acc. Chem. Res.* 2014, 47, 1406−1416

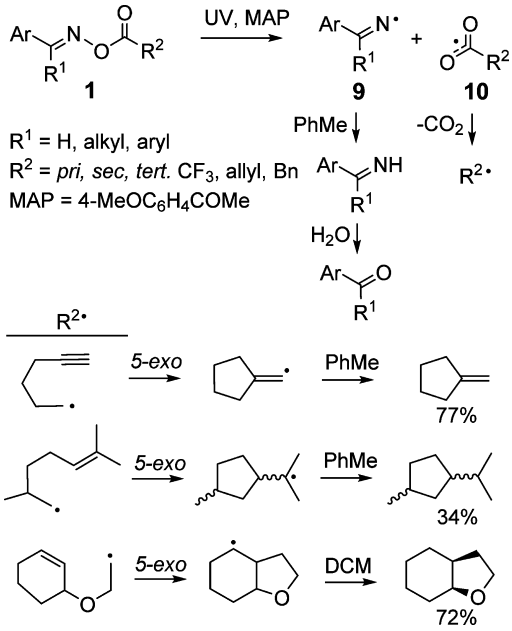
Scheme 2. Types of Oxime Ethers Investigated with the Main Synthetic Route



2. THE BIMODALITY OF OXIME ESTERS AND DIOXIME OXALATES: ALICYCLIC AND HETEROCYCLIC PREPARATIONS

For preparative purposes, thermal reactions would be convenient and desirable, but in practice all oxime carbonyls **1**−**5** resisted thermal methods, and clean radical generation was not achievable either by conventional heating or by MW irradiation[11] or even on flash vacuum pyrolysis.[12] On the other hand, UV photolyses led to selective N−O scission with generation of iminyls **9** and acyloxyl radicals **10.** The iminyls primarily ended up as imines (or their ketone hydrolysis products) after H atom abstraction from solvent (Scheme 3).

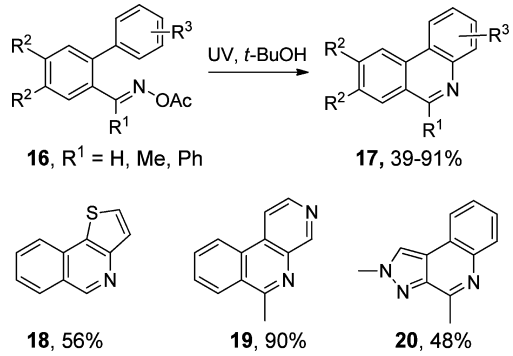
Scheme 3. Preparations of Alicyclics by UV Photolyses of Oxime Esters



The acyloxyls **10** lost CO_2 extremely rapidly releasing C-centered radicals, $R^{2\bullet}$, for further transformations.[13] An aromatic ring adjacent to the imine in **1** and **3** was found to be necessary for efficient UV harvesting. Furthermore, electron-releasing 2- or 4-MeO-substituents further improved efficiency, as did the inclusion of MAP photosensitizer. *pri*-Alkyl, *sec*-alkyl, and *tert*-alkyl radicals, as well as resonance-stabilized allyl or benzyl radicals and even σ-radicals such as CF_3 and cyclopropyl, were readily generated. Radicals having hex-5-enyl type acceptors underwent rapid 5-*exo* ring closures affording alicyclics in useful yields on H-abstraction from solvent (Scheme 3). Overall the process amounted to a clean decarboxylative route from carboxylic acids to alicyclics.

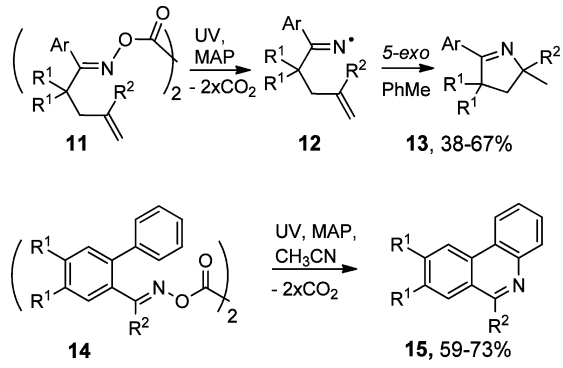
Alonso et al. tapped into the alternative iminyl generating mode with acyl oximes **16**[14] and described syntheses of phenanthridines **17**, including natural products trisphaeridine and vasconine, as well as heterocyclic systems **18**, **19**, and **20** (Scheme 4). The CO_2 and methane, derived from the accompanying $MeCO_2^{\bullet}$ radicals, volatilized away.

Scheme 4. Preparations of Heterocycles from Acyl Oximes[14]



Symmetrical and unsymmetrical dioxime oxalates **3**,[15] easily made from the corresponding ketones, hydrolyzed or degraded comparatively readily but nevertheless functioned as atom-efficient sources of iminyl radicals because the only byproduct was CO_2.[16] Photolyses of dioxime oxalates **11** containing butenyl acceptors released iminyl radicals **12** that underwent 5-*exo* cyclizations to afford 3,4-dihydropyrroles **13** in good yields (Scheme 5). Ar groups adjacent to the imine unit were again

Scheme 5. Preparations of Dihydropyrroles and Phenanthridines from Dioxime Oxalates



necessary, but access to dihydropyrroles without 2-aryl substituents was also gained by means of unsymmetrical dioxime oxalates in which just one lobe contained an acetophenone (or benzaldehyde) oxime to harvest light. Phenanthridines **15** were obtained via the dioxime oxalates **14** derived from biphenyl ketones (Scheme 5).

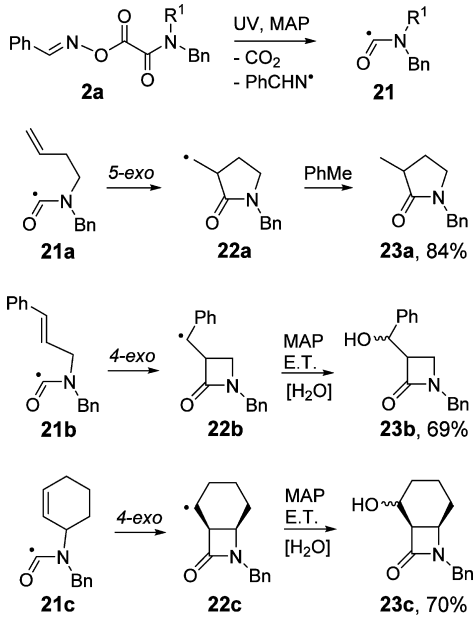
3. OXIME OXALATE AMIDES: ENTRY TO β- AND γ-LACTAM MANIFOLDS

Photolyses of toluene solutions of individual oxime oxalate amides **2a** (Scheme 1) with MAP delivered, after rapid CO_2 loss, carbamoyl (aminoacyl) radicals **21a**−**c**. The *N*-butenyl example

dx.doi.org/10.1021/ar500017f | Acc. Chem. Res. 2014, 47, 1406−1416

21a readily cyclized producing 2-oxopyrrolidinylmethyl radical **22a** and hence 1-benzyl-3-methylpyrrolidin-2-one **23a** in high yield.[17] Radical cyclizations in the 4-*exo* mode producing strained four-member rings are not usually viable because the reverse ring-opening dominates.[18] The equilibrium can be biased in favor of the ring-closed product by rapid trapping of the cyclized radical or by other means.[19] The four-membered azetidinone ring system occurs in several families of powerful β-lactam antibiotics. Remarkably, no less than four radical-based disconnections for this system have been investigated.[19] We found that the allyl-type carbamoyl radicals **21b** and **21c** cyclized readily enabling good yields of the corresponding azetidin-2-ones **23b** and **23c** to be obtained as mixtures of stereoisomers (Scheme 6).

Scheme 6. Preparations of β- and γ-Lactams from Oxime Oxalate Amides



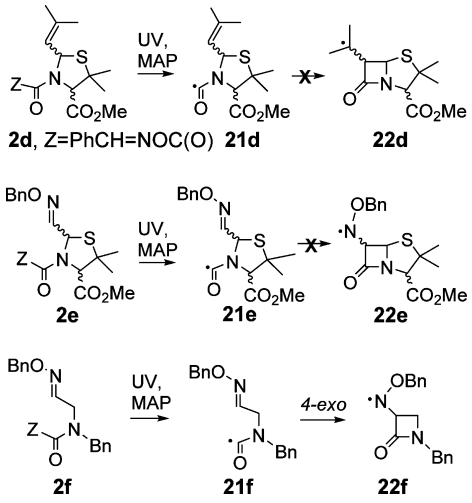
The hydroxyl substituents in **23b,c** were a welcome infusion of useful functionality that was likely due to electron transfer from the ring-closed radicals **22b,c** to MAP, with the production of the corresponding carbocations, which then reacted with moisture.

That radical **21d** was produced upon UV irradiation of 2-alkenyl functionalized thiazolidine oxalate amide **2d** (Scheme 7) was confirmed by EPR spectroscopy, but cyclization failed and none of 3-isopropyl-penicillin **22d** could be isolated. Cyclizations onto oxime ether acceptors were known to be faster than onto alkenes, but again, although carbamoyl radical **21e** was spectroscopically observed on UV irradiation of **2e**, none of the penicillin derivative **22e** could be obtained.[20] Evidently 4-*exo*-cyclization is rendered more difficult by the adjacent five-membered thiazolidine ring. On UV irradiation of noncyclic precursor **2f**, both carbamoyl intermediate **21f** and its ring-closed azetidinylmethyl radical counterpart **22f** were duly observed, showing the viability of this route to β-lactams (Scheme 7).[20,21]

4. THE DUAL ROLE OF OXIME CARBONATES AS IMINYL AND O-CENTERED RADICAL PRECURSORS

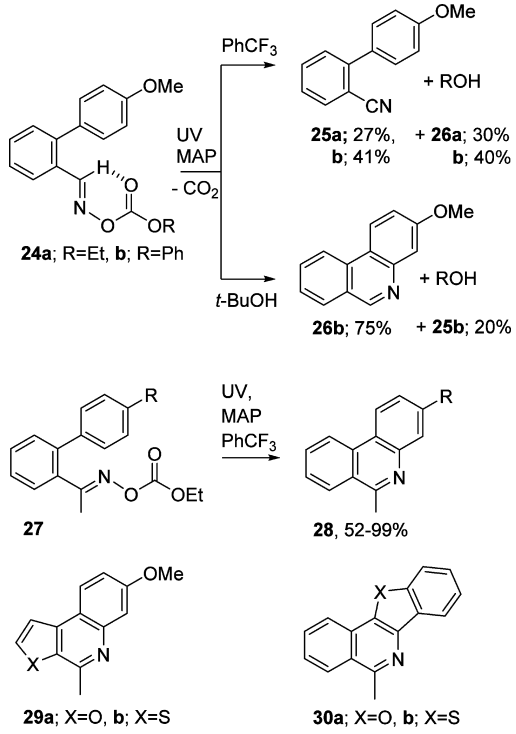
The bimodal character of oxime carbonates **4** enabled them to be deployed either for the production of iminyl radical derived products or for O-centered radical processes.[22,23] In the first

Scheme 7. Towards Penicillin and β-Lactam Antibiotics



mode, phenanthridine derivatives **26a,b** were isolated from UV photolyses with biphenyl-2-carbaldehyde *O*-ethoxycarbonyl or *O*-phenoxycarbonyl oximes **24a,b** (Scheme 8), although significant amounts of biphenyl-2-carbonitrile **25** accompanied the phenanthridines.

Scheme 8. Nitriles and Heterocycles from Photolyses of *O*-Ethyl- and *O*-Phenyl-oxime Carbonates



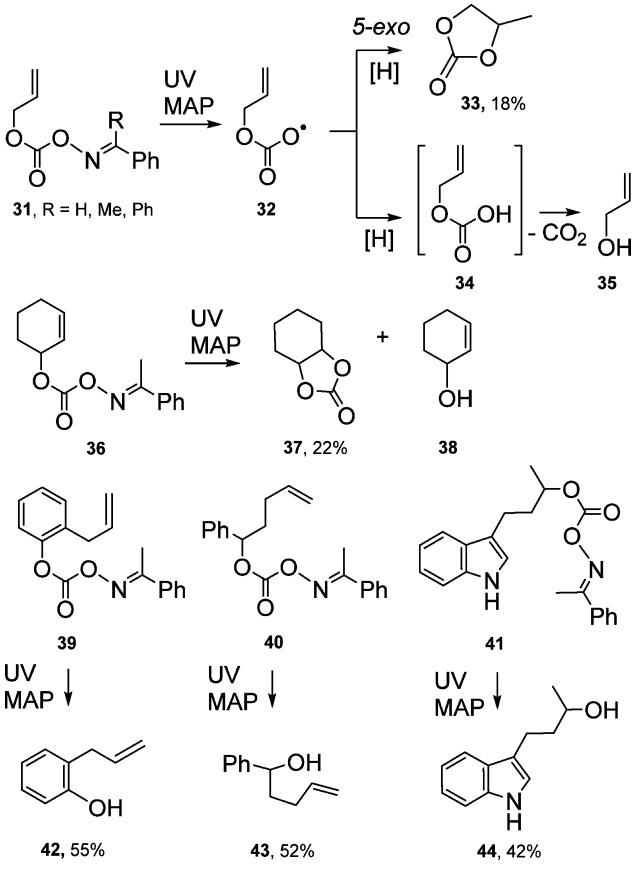
The nitrile **25** was probably produced by a competing pericyclic mechanism (Scheme 8), and in order to disrupt the intramolecular H-bonding in **24**, *t*-butanol was employed as solvent. Pleasingly, this resulted in a greater yield of phenanthridine **26**, but some nitrile **3** still interfered. To avert this, a methyl group was introduced as in **27**, thus blocking the electrocyclic pathway. Good to excellent yields of phenanthridines **28**, 4-methylfuro- and thieno-quinolines **29a,b**, and 5-

dx.doi.org/10.1021/ar500017f | Acc. Chem. Res. 2014, 47, 1406−1416

methylbenzofuro- and thieno-isoquinolines **30a,b** were derived from **27** and analogous oxime carbonates (Scheme 8).

Benzaldehyde and acetophenone oxime carbonates were deployed in mode 2 as sources of the rarely studied O-centered alkoxycarbonyloxyl radicals •OC(O)OR. Previous EPR and LFP observations with fragile dialkyl peroxydicarbonates[24,25] and *N*-hydroxypyridine-2-thione carbonate precursors[26] had shown that they added rapidly to alkenes and aromatics and that decarboxylation was relatively slow. We found that UV photolyses of *O*-allyl type oxime carbonates **31** and **36** delivered 1,5-dioxolan-2-ones **33** and **37** in low yields accompanied by allyl alcohols **35** and **38**. Precursors **39**−**41** were designed to yield pent-4-enyloxyl type radicals, after CO_2 loss from the initial alkoxycarbonyloxyls. Pent-4-enyloxyls were known to undergo 5-*exo*-cyclizations very rapidly,[27] and hence, had they been produced, tetrahydrofuranyl derivatives should have been formed. In each case, however, only alcohols **42**−**44** were obtained (Scheme 9), so we concluded that the alkoxycarbonyloxyl radicals rapidly abstracted H atoms producing unstable alkyl carbonic acids such as **34**, which speedily decomposed with formation of CO_2 and alcohols.

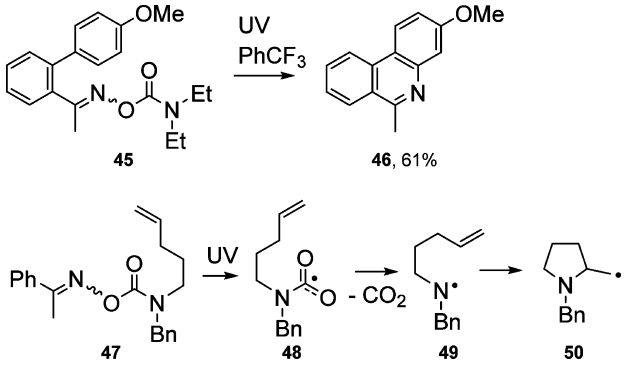
Scheme 9. Products from Alkoxycarbonyloxyl Radicals Released from Oxime Carbonates



5. OXIME CARBAMATES RELEASE A TRIAD OF IMINYL, CARBAMOYLOXYL, AND AMINYL RADICALS

Oxime carbamates **5** (Scheme 1) prepared from secondary amines by our novel phosgene free method were stable and readily handled, but those from primary amines were difficult to purify and degraded comparatively quickly. Photodissociations of their N−O bonds released iminyl radicals and fragile carbamoyloxyl radicals **48**.[28] Phenanthridines **46** were prepared via iminyl radicals generated from diethylcarbamoyl oximes **45** in much the same way as with oxime esters (Scheme 10).

Scheme 10. Reactions of Iminyl and Aminyl Radicals Derived from Oxime Carbamates



Only aminyls ($R^1R^2N^•$) had been detected in previous approaches to carbamoyloxyl radicals.[25,29] Our spectroscopic investigations with oxime carbamates indicated that, above room temperature, both *N*-alkyl and *N*,*N*-dialkylcarbamoyloxyls cleanly lost CO_2 and produced aminyl radicals such as **49** (Scheme 10).

6. MICROWAVE MANIPULATIONS WITH *O*-PHENYL OXIME ETHERS

Oxime ethers, in contrast to oxime esters, did not dissociate on UV irradiation.[30] On heating at 150 °C, however, *O*-benzyl ketoximes ($R^1R^2C{=}N{-}O{-}CH_2Ph$) furnished products from both O−C and N−O bond scission.[31] Promisingly, aryl and alkyl *O*-phenyl oxime ethers ($R^1R^2C{=}N{-}OPh$) underwent clean N−O bond homolyses at moderate temperatures yielding iminyl and phenoxyl radicals.[2b] The resonance stabilization of the released phenoxyl radical ensured this selective bond scission.

$$R^1R^2C{=}N{-}OPh \rightarrow R^1R^2C{=}N^• + PhO^•$$

Synthetic methodology with conventional heating was unsuccessful because of the long reaction times and complications from side processes. Microwave (MW) methods often promote more efficient reactions,[32] and a good number of MW assisted organic syntheses (MAOS) involving radicals have been described.[33] Thermolyses of *O*-phenyl oxime ethers were dramatically improved by MAOS techniques leading to superior preparations of several types of heterocycles. MW irradiation at 160 °C of precursors **6** in toluene solution containing 1-ethyl-3-methylimidazolium hexafluorophosphate (emimPF_6) as ionic liquid (IL), promoted efficient dissociations to iminyl and phenoxyl radicals. The phenoxyl radicals abstracted H atoms from the toluene solvent, and the resulting phenol was easily separated.

This MAOS tactic with alkenone *O*-phenyl oxime ethers **51** produced dihydropyrroles **52** in very good yields,[34] and alkynyl acceptor **53** furnished pyrrole **54** (Scheme 11). Iminyl radical ring closures onto aromatic acceptors, for example, **55**, were also easily accomplished under MAOS conditions leading to quinoline derivatives, phenanthridines **56**, benzonaphthiridines **57**, benzothienoquinoline **58**, indolopyridine derivative **59**, and tetrahydroindoloquinoline **60** (Scheme 11).

Diaza-heterocycles were made by an extension of this strategy employing imine-functionalized *O*-phenyl oxime ethers.[35] The

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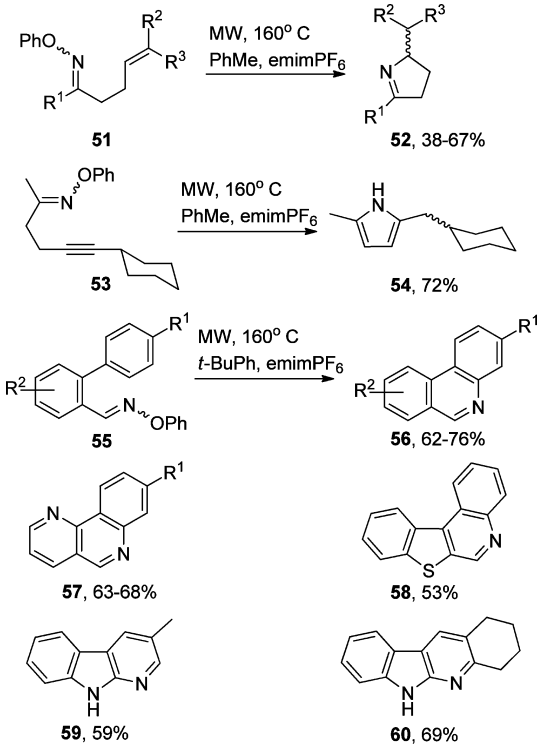
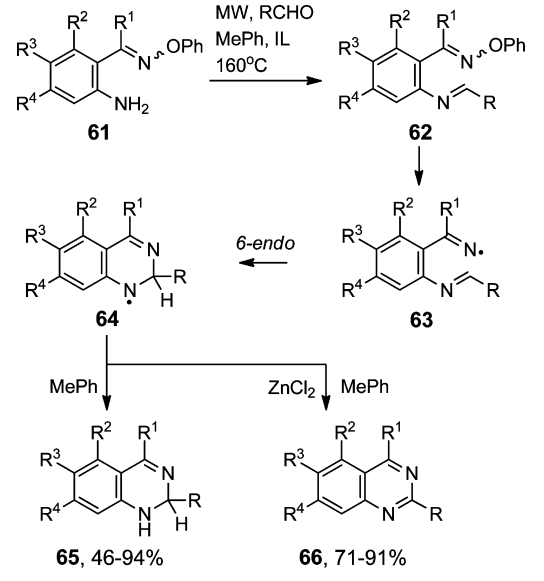
Scheme 11. Heterocyclic Systems Accessible by MAOS with *O*-Phenyl Oxime Ethers



architecture of iminyl-oxime ethers **62** was potentially suitable for iminyl ring closure to either indazole or quinazoline structures. MW irradiation was known to assist the formation of imines;[36] therefore the step yielding imines **62** was integrated with MW generation of iminyl radicals **63** so as to combine the whole sequence in one pot (Scheme 12). This protocol with oxime ethers **61** and aldehydes delivered dihydroquinazolines **65** in good to excellent yields (Scheme 12). Iminyl radicals **63** ring closed onto the C═N bond with exclusive production of

Scheme 12. Preparation of Dihydroquinazolines and Quinazolines from MW Assisted Reactions of 2-Aminoarylalkanone *O*-Phenyl Oximes



quinazolin-1-yl radicals **64**; indazoles were never detected. This is likely because aminyl radicals **64** are more resonance stabilized and because of a polarity mismatch in the 5-*exo* approach of the nucleophilic iminyl radical to the nitrogen atom of the imine. Reactions with aliphatic aldehydes were very efficient; somewhat lower dihydroquinazoline yields were obtained with aromatic and heterocyclic aldehydes, but most ketones failed to react.

There were indications that imine formation was incomplete, so since $ZnCl_2$ was known to promote this,[37] submolar equivalents were included, and forthwith excellent product yields were obtained with aliphatic, aromatic, and heterocyclic aldehydes. The surprising outcome, however, was that quinazolines **66** were formed directly, rather than dihydroquinazolines (Scheme 12). This was attributed to a lowering of the pK_a of the proton at the 2-position by coordination of Zn(II) to the iminyl N-atom of radical **64**, hence facilitating deprotonation and aromatization to **66**.

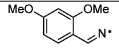
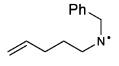
This protocol also worked well for oxime ethers with a variety of substituents in their anilinic units. With ketone reaction partners, the dihydroquinazoline products were usually contaminated with byproducts, and yields were poor.

7. INTERROGATION OF RADICAL MOTIONS AND MECHANISMS BY EPR SPECTROSCOPY

All members of the carbonyl oxime suite on UV irradiation in solution with MAP, in the resonant cavity of a 9 GHz EPR spectrometer, gave rise to EPR spectra of transient radicals. Oxime esters **1** supplied signals from both iminyl $ArR^1C{=}N^\bullet$ and C-centered radicals $R^{2\bullet}$. In this way, primary, secondary, and tertiary alkyl, allyl, and benzyl type radicals, and even product species from σ-radicals such as cyclopropyl, could be conveniently observed.[13] C-Centered radicals had already been intensively studied by EPR, so we focused in on more exotic carbamoyl, N-centered, and O-centered radicals.

EPR spectra for an eclectic selection of iminyl radicals were obtained from photolyses of all the carbonyl oxime precursors **1**−**5**.[38] The spectra from $ArCR{=}N^\bullet$ were insensitive to the type of Ar ring or to the substituents in this ring and generally consisted of a simple 1:1:1 triplet with ∼10 G splitting (see Table 1). Spectra from iminyls with β-H atoms, $ArCH{=}N^\bullet$, such as the one shown in Figure 2a for radical **67** (Table 1), were particularly valuable because the large a(H) of about 80 G left an uncluttered central window where spectra from other species could be

Table 1. EPR Parameters of C-, N-, and O-Centered Radicals Generated from Oxime Derivatives

Radical	Structure	*g*-factor	hfs/G
iminyl **67**		2.0034	a(N) = 10.0, a(1H) = 81.2, a(2H) = 0.4 G
iminyl **68**		2.0033	a(N) = 9.8, a(2H) = 1.4, a(3H) = 1.2 G.
carbamoyl **21a**		2.0017	a(N) = 21.8, a(4H) = 0.7 G
aminyl **82**		2.0048	a(N) = 14.6, a(4H) = 36.0 G
aminyl **82**		2.0048	a(N) = 14.2, a(2H) = 35.4, a(2H) = 36.9 G
phenoxyl		2.0049	a(1H) = 9.9, a(2H) = 6.9, a(2H) = 2.0 G

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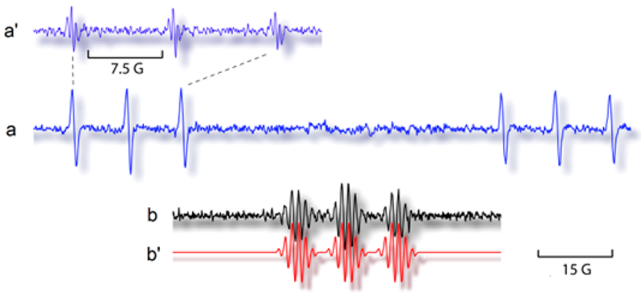


Figure 2. EPR spectra of iminyl radicals in *t*-BuPh solution. (a) Iminyl **67**. (a′) Scale expansion of spectrum a showing resolved aryl-H hfs. (b) Spectrum of iminyl **68** in black. (b′) Computer simulation of **68** in red.

observed, unobscured by iminyl peaks, as illustrated in Figure 2a. Small hyperfine splittings (hfs) from H atoms in the Ar rings could occasionally be observed under high resolution (Figure 2a′ and Table 1). The spectra from dialkyliminyls often displayed additional fine structure from γ-H atoms, as in the spectrum from radical **68** (Figure 2b and Table 1). UV irradiations of carbonyl oximes **1**, **2**, **4**, and **5** generated equal proportions of an iminyl radical and a second species, and therefore the iminyl spectra were extremely valuable as reference markers for assessing and monitoring the concentrations of other radicals.

The EPR parameters of iminyls implied that they were σ-type radicals with their unpaired electrons in orbitals centered on the N-atoms *in the nodal plane* of the C═N π-system. The DFT computed SOMO [B3LYP/6-311+G(2d,p)] for model radical **69** (R^1 = Ph, R^2 = Me) supports this conclusion (Figure 3). Delocalization of the unpaired electron into the ring π-system of aryliminyls is minor, and consequently ring substituents only exert weak effects on the reactivity of aryliminyls.

Although preparative chemistry based around iminyl radicals is well developed,[6b,39] quantitative data on the dynamics of individual processes is sparse. In the absence of reaction partners,

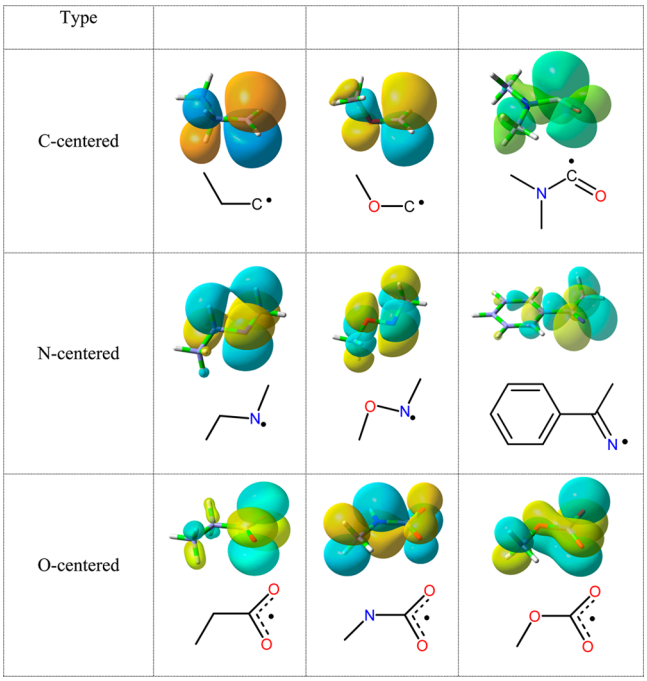
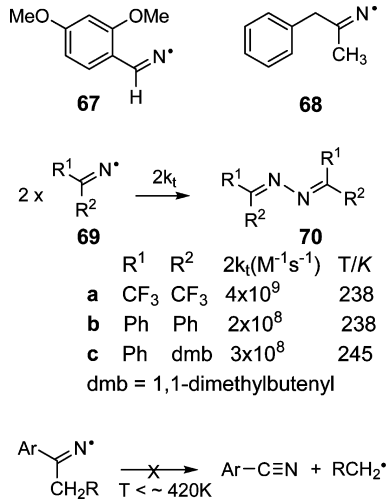


Figure 3. Comparison of SOMOs [B3LYP/6-311+G(2d,p)] of model C- and heteroatom-centered radicals.

iminyl radicals terminate rapidly by N to N coupling to give azines **70** (Scheme 13).[38] The termination rate constants ($2k_t$)

Scheme 13. Iminyl Radicals and Termination Rate Constants[38,41]



for iminyls were measured from the decay curves of their EPR signals and found to be very large (Scheme 13). These king size $2k_t$ values signify that iminyl couplings of small to moderately sized species are diffusion controlled, just as are the terminations of small C-centered radicals.

Iminyls do undergo β-scissions to nitriles and alkyl radicals (Scheme 13); however, these dissociations are not important for aryliminyls or for iminyls with primary alkyl substituents at $T \lesssim 420$ K. The only known rate constant for H-abstraction by an iminyl (6,6-diphenylhex-5-en-2-iminyl) was about a factor of 16 slower than for its C-centered analogue.[40] This slow H-abstraction is crucial for the success of many N-heterocycle syntheses because ring closure is often in competition with H-abstraction.

Structure−activity relationships (SARs) for iminyl 5-*exo*-cyclizations provide a valuable resource for planning N-heterocycle syntheses. Extending from the one previously available data point,[40] our EPR data provided such a SAR (Scheme 14). We generated a modest set of functionalized butenyl-iminyls **71a−f** from oxime ester and dioxime oxalate precursors (Scheme 14).[41] The EPR spectrum of iminyl **71a** appeared as a triplet at 205 K (Figure 4, Im). As temperature was increased, its concentration decreased and that of the ring closed dihydropyrrolomethyl radical **72a** increased (Figure 4, 260 K). Similarly, all the iminyls **71a−f** selectively ring closed in the 5-*exo*-mode, irrespective of the substitution pattern around the C═C double bond. Rate constants (k_c) for the ring closures were determined from spectra like these by the usual steady-state kinetic EPR method (Scheme 14).

The k_c for phenylpentenyliminyl **71a** was a factor of 25 less than k_c for archetype C-centered hex-5-enyl radical cyclization. The main surprise in the SAR trend, as compared with hex-5-enyls, was that the 2,2-dimethyl-1-phenylpent-4-enyliminyl radical **71e** ring closed more slowly than **71a** showing a substantial *inverse gem*-dimethyl effect. DFT computations suggested steric interaction of the Ph with the CMe_2 group pushed the aromatic ring out of conjugation with the plane of the imine moiety. To check on this, pentenyliminyls lacking this Ph substituent were needed. We were not able to study the simplest,

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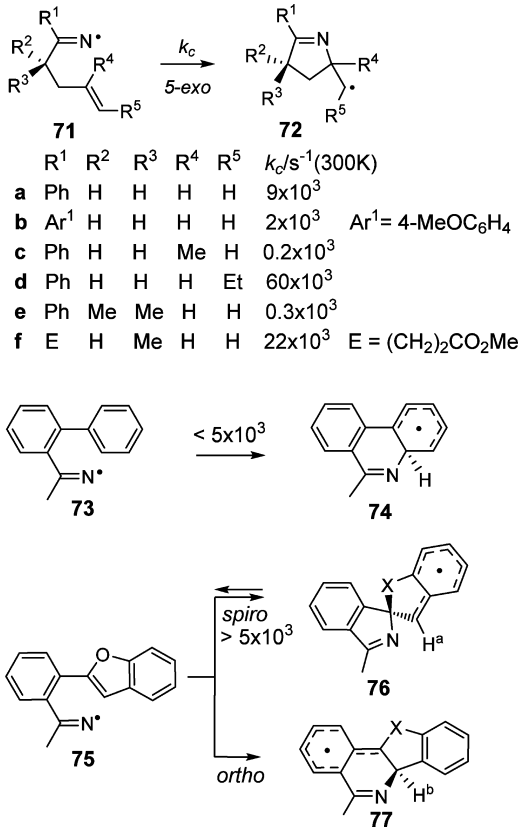
Scheme 14. Dynamics of Ring Closures of Iminyl Radicals



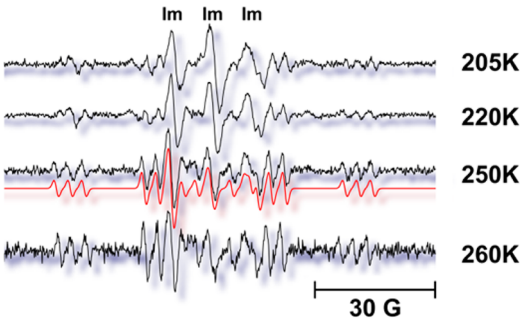


Figure 4. EPR spectra showing ring closure of iminyl **71a** (Im) to dihydropyrrolomethyl **72a**. Experimental spectra in black. The spectrum at 250 K is matched by a computer simulation (red) including both species.

2,2-dimethylpentenyliminyl, due to a competing process, but the radical containing a single Me substituent in the pentenyl chain, **71f**, was successfully generated from an unsymmetrical dioxime oxalate. The k_c for this species was a factor of 2.5 larger than k_c for **71a** suggesting that the normal positive *gem*-dimethyl effect does operate for pentenyliminyls lacking the aromatic substituent at the C═N bond. This is an intriguing example of a *gem*-dimethyl effect, which can be inverted by changing the substituent on the C atom adjacent to the CMe_2 group from alkyl to aryl. Caution is obviously needed before making broad generalizations about CMe_2 groups accelerating ring closure reactions!

Product analyses (see Schemes 4 and 5) implied that phenanthridinyl **74** was the main intermediate from iminyl radical ring closures onto aromatic acceptors. In an interesting contrast, EPR spectra obtained during photolyses of a benzofuran-containing oxime carbonate precursor showed that iminyl **75** selectively underwent the uncommon *spiro*-cyclization giving benzyl type radical **76**.[42] The rate constants shown in Scheme 14 were estimated from the EPR data and show the iminyl *spiro* process to be about an order of magnitude slower than for archetype C-centered radicals. Curiously, the product from **75** was benzofuroisoquinoline derivative **30a** (Scheme 8), which implied *ortho*-radicals 77 as intermediates and appeared to conflict with the EPR result! The most likely explanation, which was supported by DFT computations, was that at the temperature of the preparative experiments (~100 K higher than the EPR study) the *spiro*-cyclization became reversible whereas the 6-*ortho*-process did not. *Ortho*-product **30a** therefore accumulated because of thermodynamic control.

Photolyses of oxime oxalate amides yielded EPR spectra of carbamoyl radicals (A) along with iminyl radicals (I). Carbamoyl **21a** ring closed in 5-*exo* mode even at 220 K to produce the *N*-benzylpyrrolidin-2-onylmethyl radical **22a** (C), and Figure 5 is a remarkably clear "snapshot" of all three species at 220 K.

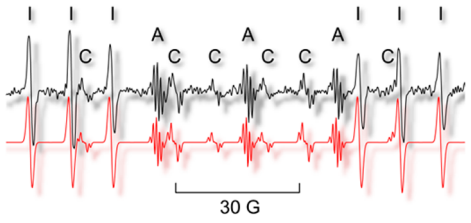
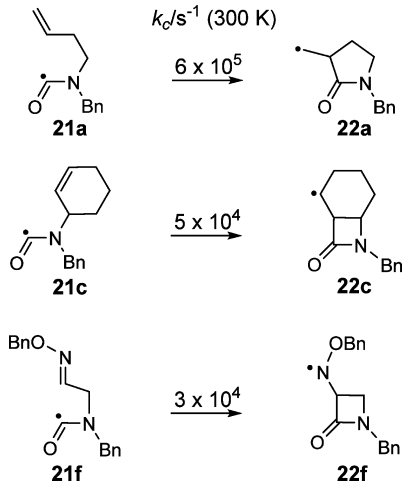


Figure 5. EPR spectra of PhCH═N• (I), carbamoyl **21a** (A), and *N*-benzylpyrrolidin-2-onylmethyl radical **22a** (C) at 220 K in *t*-BuPh solution. Black, experimental; red, computer simulation.

The EPR parameters of **21a** and other carbamoyls indicate that they have considerable σ-character and are structurally akin to formyl and vinyl radicals (Table 1). The DFT computed SOMO for the model $Me_2NC^{\bullet}(=O)$ (Figure 3) illustrates the sizable σ-orbital associated with the carbonyl C atom.

The k_c for the 5-*exo* cyclization of **21a**, obtained by the steady state kinetic EPR method (Scheme 15), was slightly greater than the k_c for hex-5-enyl radical, as anticipated for a σ-radical and in view of the stabilizing amide group in the cyclized radical **22a**. Carbamoyls **21c** and **21f** presented a unique opportunity to study the dynamics of β-lactam ring formation.[21] The rate

Scheme 15. Rate Constants for Carbamoyl Radical Cyclizations



dx.doi.org/10.1021/ar500017f | Acc. Chem. Res. 2014, 47, 1406−1416

constants for their 4-*exo* ring closures onto C═C and C═NO bonds, respectively, exceeded that for 4-*exo* closure of pent-4-enyl type radicals but, of course, were smaller than those for 5-*exo* ring closures.

Oxime carbonates **4** and oxime carbamates **5** enabled the exotic and rarely encountered alkoxycarbonyloxyl **78** and carbamoyloxyl radicals **79** to be investigated.[23,28] The former species lose CO_2 with release of alkoxyl radicals $R^1O^{\bullet}$,[43] whereas the latter extrude CO_2 with formation of aminyl radicals **82**. DFT computations predicted that CO_2 extrusion would become slower across the series $MeCH_2CO_2^{\bullet}$ to $EtNHCO_2^{\bullet}$ to $EtOCO_2^{\bullet}$. Furthermore, CO_2 loss was computed to be slower for $RNHCO_2^{\bullet}$ than for $R_2NCO_2^{\bullet}$ such that the former might have sufficient structural integrity for detection by EPR. The computed SOMOs demonstrate a dramatic contrast between $MeCH_2CO_2^{\bullet}$, which is confined mainly to the CO_2 unit, and $EtNHCO_2^{\bullet}$ or $EtOCO_2^{\bullet}$, with SOMOs delocalized to the adjacent heteroatoms and alkyl substituents (Figure 3). This was a further hint that monoalkyl $RNHCO_2^{\bullet}$ radicals might behave like $EtOCO_2^{\bullet}$ radicals in losing CO_2 comparatively slowly.

O-Allyloxycarbonyloxyls **78** (R^1 = allyl) cyclized in 5-*exo*-mode to dioxolan-2-onylmethyls **80**, and kinetic EPR showed the rate to be nearly an order of magnitude faster than the archetype hex-5-enyl (Scheme 16). *O*-Benzyloxycarbonyloxyl radicals **78** (R^1 = Bn) selectively cyclized in the unusual *spiro*-mode to radicals **79**, which were observable by EPR spectroscopy at temperatures below 270 K. Rate data for CO_2 loss was obtained by kinetic EPR and showed this to be a remarkable 7 orders of magnitude slower than the analogous CO_2 loss from $EtCO_2^{\bullet}$ radicals (Scheme 16)!

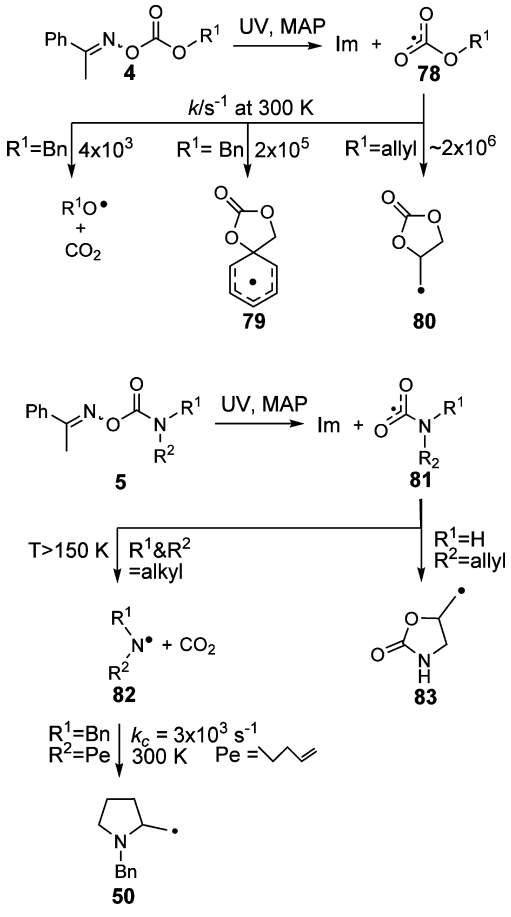
Rate and Arrhenius parameters were also obtained for benzyloxycarbonyloxyl *spiro*-cyclizations.[44] In conformity with the known high rates of alkoxycarbonyloxyl addition and abstraction reactions, k_c^{spiro} for **78** (R^1 = Bn) to **79** was greater than that of 4-phenylbutyl, the analogous C-centered radical.

The first evidence that N-monosubstituted carbamoyloxyl radicals **81** (R^1 = H) had finite lifetimes was provided by the spectroscopic detection of the ring closed oxazolidin-2-onylmethyl radical **83** at low temperatures.[28] However, decarboxylation was rapid at room temperature for both N-mono- and N,N-disubstituted **81** such that they functioned as clean sources of aminyl radicals **82** (Scheme 16). The EPR spectral data (Table 1) and DFT computations (Figure 3) showed these aminyls to be π-type radicals reminiscent of secondary alkyl radicals. The 5-*exo*-ring closure of *N*-benzylpent-4-en-1-aminyl radical **82** to *N*-benzylpyrrolidin-2-ylmethyl **84** was also monitored by EPR spectroscopy and found to be comparatively slow (Scheme 16).

An assemblage of rate constants for 5-*exo* cyclizations [$k_c^{5\text{-}exo}$ (300 K)] of model N-, C-, and O-centered alkenyl type radicals demonstrates how this ring closure depends strongly on the nature of the radical-bearing atom (Figure 6). The rate constants span 5 orders of magnitude and fall neatly into three areas. N-Centered, including aminyl and iminyl, cyclize the slowest. C-Centered, including alkyl and acyl, cyclize at intermediate rates, and O-centered are fastest. Of course, k_c values outside the indicated ranges are possible for radicals containing dissimilar substituents. The rates are clearly not directly related to the electronegativities of the initial radical centers but probably reflect the reaction exothermicities.

Figure 6 neatly illustrates why C-radical chemistry has developed so much more fully. Rates of N-radical additions to C═C acceptors are slow, so room temperature preparative procedures are troublesome, C-radical rates are just right for rt protocols, and O-radical rates are suitably high, but competition from β-scission (CO_2 loss or ketone formation) fiercely competes.

Scheme 16. Reaction Pathways and Rate Constants for Alkoxycarbonyloxyl and Carbamoyloxyl Radicals



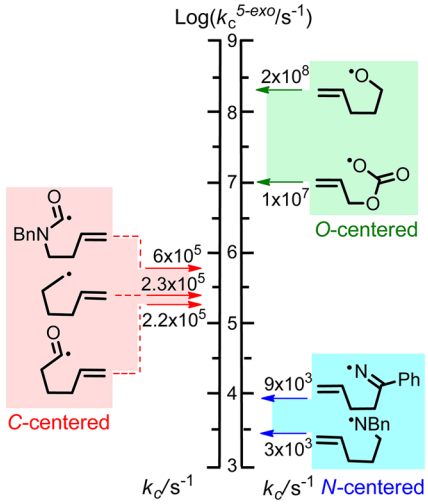


Figure 6. Comparison of 5-*exo*-cyclization rate constants for radicals centered on N-, C-, and O-atoms.

dx.doi.org/10.1021/ar500017f | Acc. Chem. Res. 2014, 47, 1406−1416

8. CONCLUSION

Safe, easily handled precursors with long shelf-lives can be chosen from the above oxime derivative suite for a huge range of C-, N-, and O-centered radicals. The scope is obviously greatly extendable. These precursors lend themselves to green radical-mediated preparations of a great variety of alicycles and heterocycles. Both β- and γ-lactams can be conveniently obtained from suitably unsaturated amines via oxime oxalate amides. Currently methods for stereocontrol of the cyclization steps have not been investigated. The multiplicity of iminyl production methods from carbonyl compounds offers exceptional flexibility in the choice of either photochemical or MW-assisted routes for pyrrole, quinoline, and isoquinoline containing heterocyclic systems. *O*-Phenyl oxime ether scaffolds offer effective methodology for diaza-containing quinazoline production. The elegance of the EPR spectra pinpointed oxime derivatives as prime choices for structural and dynamic studies. By this means, mechanistic information even on the rapidly evolving alkoxycarbonyloxyl and carbamoyloxyl radicals was obtained. There is obvious scope for the development of synthetic protocols based around the alkoxyl and aminyl radicals that they produce at organic laboratory temperatures.

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Notes

The author declares no competing financial interest.

Biography

John C. Walton is Research Professor of Chemistry at the University of St. Andrews. He was born in St. Albans and was educated at Watford Grammar School and Sheffield University (B.Sc., D.Sc.), England. He joined the faculty of Dundee University in 1967 and moved to St. Andrews University (Ph.D.) in 1970, rising to full professor of chemistry in 1997 and becoming Research Professor of Chemistry in 2007. His early work was on structure–activity relationships for radical addition reactions and expanded to encompass applications of physical organic methods to organic mechanisms. He is known for EPR spectroscopic studies of delocalized radicals, for the discovery of an EPR method for conformational analysis of cyclic radicals, and for the first observations of strained cage radicals including cubyl. Recently he has developed "clean" radical-mediated synthetic protocols including (i) methods based on "pro-aromatic" cyclohexadienyl reagents, (ii) development of a suite of oxime derivatives for heterocycle syntheses, and (iii) photoredox methods employing titanium dioxide and carboxylic acids.

ACKNOWLEDGMENTS

J.C.W. thanks all the talented co-workers named in the references. Financial support from GSK, EPSRC (Grant EP/I003479/1), and EaStCHEM is gratefully acknowledged.

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