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Thermal Decomposition of *N*-Acyloxy-*N*-alkoxyamides – a New HERON Reaction

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The HERON reaction has been observed in the thermal decompositions of *N*-acyloxy-*N*-alkoxyamides **1b**, members of the class of anomeric amides. The *N*,*N*-bisoxo-substitution results in reduced amide resonance and this, combined with an n_O–σ^*_{NOAcyl} anomeric destabilization of the N–OAcyl bond, results in their intramolecular rearrangement to anhydrides **42** and alkoxynitrenes **43** in competition with homolysis of the N–OAcyl bond to alkoxyamidyls **51**. The primary HERON product alkoxynitrenes are scavenged by oxygen, giving a nitrate ester, in competition with a rearrangement to nitriles and dimerization to hyponitrites, leading, under the conditions, to alcohols and aldehydes. Persistent alkoxyamidyls most likely form a 1,3-diradical in a solvent-cage reaction, which cyclizes to 3,5-disubstituted-(5*H*)-1,4,2-dioxazoles **47**. Substituent effects support this competition reaction.

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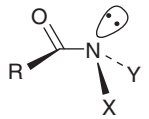
Anomeric amides **1** (Chart 1) are defined as amides that bear two heteroatoms at the amide nitrogen.[1,2] In all of these structures, the amide nitrogen responds to the collective electronegativity of the substituents in rehybridizing from sp^2 to sp^3. This facilitates an electron density distribution that better satisfies the electron demand of the nitrogen substituents, *X* and *Y*. The configurational change results in smaller angles at nitrogen and reduced p-character of the lone-pair orbital with attendant disconnection from the amide carbonyl, as evidenced by spectroscopic properties, radically reduced amide isomerization barriers, reactivity patterns, and theoretical attributes. The properties of various congeners of this class of amides have been reviewed,[1,2] as have the structural, theoretical, spectroscopic properties, the reactivity patterns and biological activities of *N*-acyloxy-*N*-alkoxyamides **1b**.[3] There is ample evidence of pyramidality in *N*-alkoxy-*N*-chloroamides (**1a**, X = Cl), *N*-acyloxy-*N*-alkoxyamides **1b**, *N*,*N*-dialkoxyamides **1c**, *N*-alkoxy-*N*-aminoamides **1d**, and *N*,*N*-dihaloamides **1f**.[1–7]



1a X = Cl, Br, I, Y = OR
1b X = OAcyl, Y = OR
1c X = Y = OR
1d X = NR_2, Y = OR
1e X = SR, Y = OR
1f X = Y = halogen

Chart 1.

In effect, in all these amides, resonance is to a large degree diminished (Fig. 2a) and the contribution of structure II (Fig. 1) to the resonance hybrid I ↔ II ↔ III is reduced. The combined electronegativity of the triad of heteroatoms (*X*N*Y*) also destabilizes resonance form III (Fig. 1), and the best representation of an anomeric amide is I.

Anomeric amides have different properties to those displayed by primary amides and secondary *N*-alkyl- or tertiary *N*,*N*-dialkylamides in two respects. On the one hand, bisheteroatom substitution at nitrogen impacts strongly on the nitrogen hybridization and the degree of amide resonance. On the other hand, the lone-pair synergy, as a consequence of anomeric effects operating through the nitrogen, influences both conformational preferences and the reactivity of various congeners.[1–3]

Fig. 2b illustrates that in *X*N*Y* systems, as with anomeric carbon centres,[8–10] two anomeric interactions are possible and these involve either an n_Y–σ^*_{NX} or an n_X–σ^*_{NY} overlap where n_X and n_Y represent the p-type lone pairs on *X* and *Y* and σ^*_{NX} and σ^*_{NY} represent the N–*X* and N–*Y* antibonding orbitals. In either case, the result is a net stabilization of the lone pair of electrons. Except where the nitrogen is symmetrically substituted, one of these interactions will be stronger.

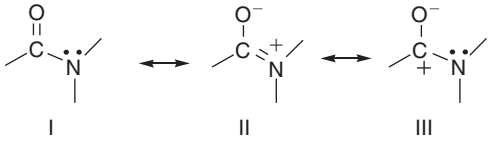


Fig. 1. Resonance in a conventional amide.

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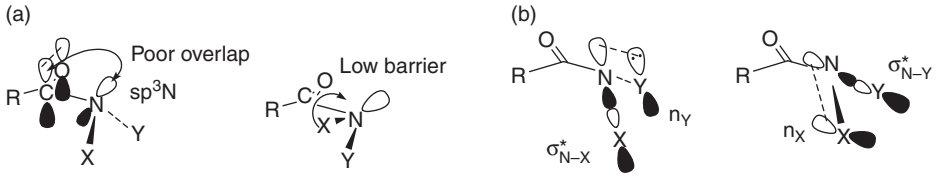


Fig. 2. (a) Loss of resonance and (b) anomeric interactions in bisheteroatom-substituted amides.

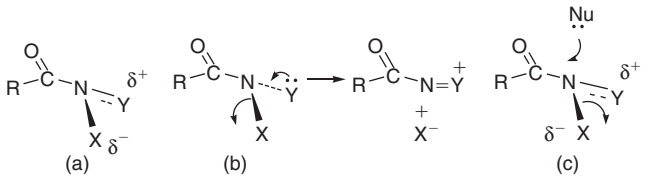


Fig. 3. (a) Polarized structure; (b) anomerically induced elimination; (c) S_N2 reaction at nitrogen.

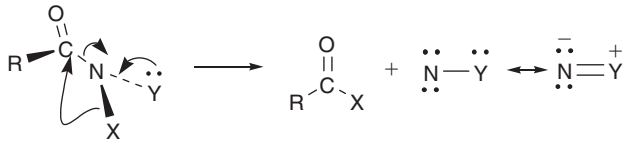
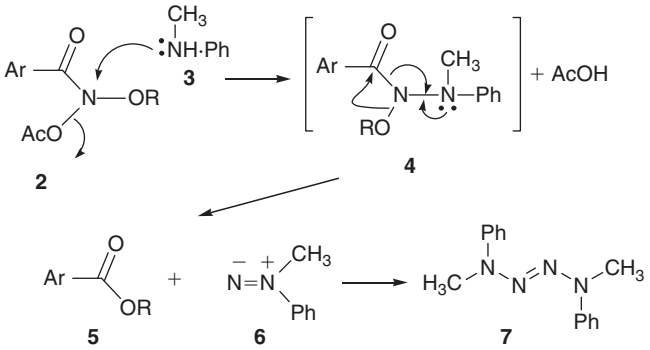


Fig. 4. The HERON reaction of an anomeric amide.



Scheme 1.

Where one of the anomeric interactions at nitrogen, say the n_Y–σ^*_{NX}, is significantly stronger, the ground-state structures should facilitate overlap between a lone-pair orbital on heteroatom *Y* with a σ^*_{NX} orbital (Fig. 2b), resulting in shorter than normal N–*Y* bonds, longer than normal N–*X* bonds and significant barriers to rotation about the N–*Y* bond.

In an *XNY* system, another consequence of a strong n_Y–σ^*_{NX} anomeric interaction should be polarization, as shown in Fig. 3a. Where *Y* is a good electron-pair donor and *X* a strongly electronaffinic atom or group, elimination might be expected, yielding a stabilized nitrenium ion (Fig. 3b). Work in the authors' laboratories and elsewhere has established that nitrenium ions are strongly stabilized by neighbouring heteroatoms including oxygen.[11–17] Such a process would be promoted by polar solvents, as well as acid or Lewis-acid complexation with *X*. Thus, unimolecular decomposition would be expected to be more significant in strongly anomeric amides.

In systems with moderate anomeric overlap, this together with negative hyperconjugation and anchimeric-assisted weakening of the N–*X* bond should promote S_N2 reactions at nitrogen leading to loss of X^- (Fig. 3c). S_N2 reactivity of several anomeric amides has been reported.[1–3,18–22]

Where *X* is a poor leaving group, anomeric destabilization of the N–*X* bond can lead to a novel rearrangement. The HERON (from *He*teroatom *r*earrangements *o*n *n*itrogen) reaction[A] of anomeric amides was discovered in the mid-1990s and involves a concerted migration of the *X* atom or group from the amide nitrogen to the carbonyl carbon with expulsion of a *Y*-stabilized nitrene (Fig. 4).[23] To date, numerous examples of HERON reactivity have been observed in the reactions of both ONO and NNO anomeric systems[1,4,21,22,24–26] and it has recently been reviewed.[23]

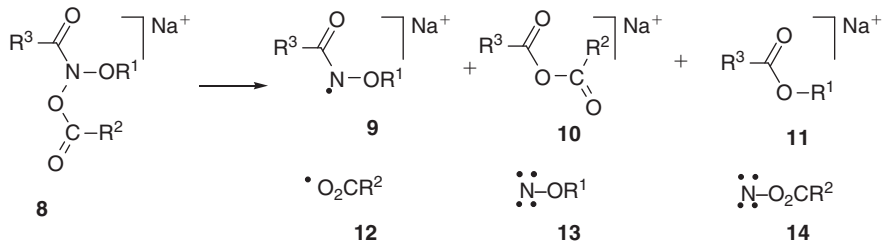
N-Acyloxy-*N*-alkoxyamides **1b** constitute a class of direct-acting mutagens whose biological activity, structure, and reactivity have been widely studied.[3,18,20,21,27–36] With acid catalysis, they undergo S_N1 reactions at nitrogen,[28,29] and they have been shown to react bimolecularly with a variety of nucleophiles such as aromatic amines,[3,18,21,22,36] thiols,[3] azide,[19,37] and hydroxide.[32] Reaction with aromatic amines such *N*-methylaniline **3** in methanol generates intermediate *N*-alkoxy-*N*-(*N*′-methylanilino) amides **4** that themselves are anomeric and undergo the HERON reaction (Scheme 1).[2–4,19,22–26,37,38] In this, the first HERON reaction, the loosely bound lone pair on nitrogen drives migration of the alkoxyl group from nitrogen to the carbonyl carbon. The N–C bond breaks in concert with the migration, yielding esters **5** and the 1,1-diazene **6** in what is, in effect, an S_N2 reaction at the acyl carbon. Under these conditions, the diazene **6** dimerizes to the tetrazene **7**. The reaction has been modelled theoretically and proceeds with moderate activation energies of 84–105 kJ mol^{-1}.[4,39]

We recently reported that *N*-acyloxy-*N*-alkoxyamides undergo HERON reactions in the gas phase under electrospray ionization mass spectrometry (ESI-MS) conditions.[23] The sodiated molecular ion **8** was observed to undergo collision-induced decomposition to sodiated alkoxyamidyl radical **9**, sodiated anhydride **10**, and to a limited extent, sodiated ester **11** (Scheme 2). Concurrent undetectable products should be the acyloxyl radical **12**, the alkoxynitrene **13**, and the acyloxynitrene **14**.

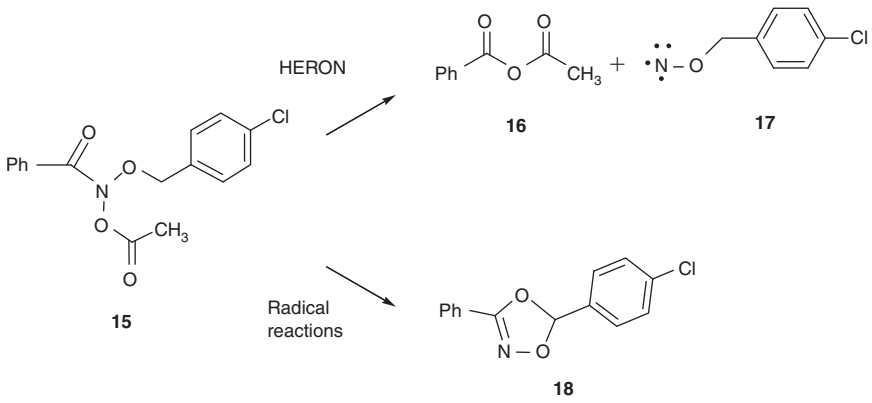
B3LYP/6–31G(d) calculations on the model *N*-formyloxy-*N*-methoxyformamide **8** (R^1 = Me, $R^2 = R^3$ = H) predict that HERON rearrangement of both methoxyl and formyloxyl are possible but with high activation energy (E_A). Migration of methoxyl (162 kJ mol^{-1}) is more favourable by some 18 kJ mol^{-1}.[23]

In this paper, we report that *N*-acyloxy-*N*-alkoxyamides themselves undergo HERON reactions in non-polar solvents, at high temperature, in competition with homolytic processes.

[A]First presented to the 2nd Heron Island Conference on Reactive Intermediates and Unusual Molecules, Heron Island, Australia, 1994.



Scheme 2.



Scheme 3.

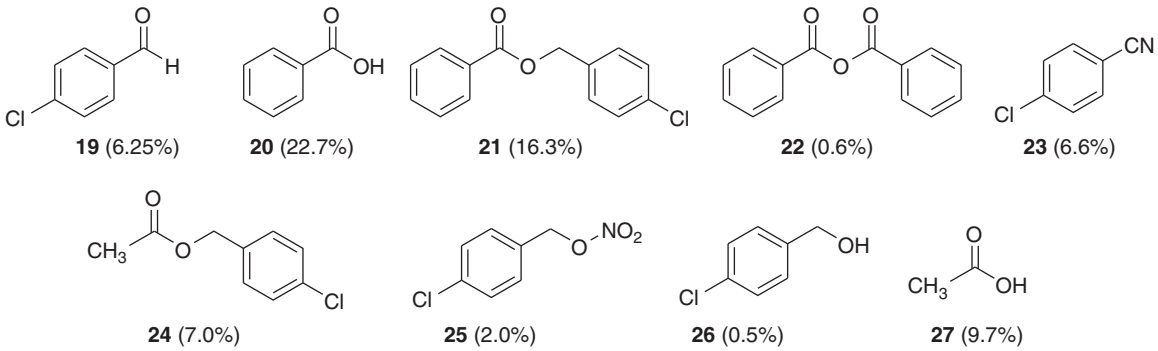


Fig. 5. Products from HERON decomposition of *N*-acetoxy-*N*-(4-chlorobenzyloxy)benzamide **15**. Average mass percentages for each product, calculated from eight decompositions under identical conditions, are displayed in parentheses.

Results and Discussion

In polar solvents at room temperature, *N*-acyloxy-*N*-alkoxyamides undergo both S_N1 and S_N2 reactions at nitrogen. However, thermolysis of *N*-acyloxy-*N*-alkoxyamides in non-polar solvents at elevated temperatures results in a mixture of products that we attribute to both an intramolecular HERON reaction and homolytic decomposition.

N-Acetoxy-*N*-(4-chlorobenzyloxy)benzamide **15** is susceptible to decomposition at temperatures approaching 90°C in toluene. Initial decomposition (Scheme 3) occurs through two competing reaction pathways, the foremost of which is a HERON reaction, producing acetic benzoic anhydride **16** and 4-chlorobenzyloxynitrene **17**. The minor pathway appears to involve a radical decomposition leading ultimately to formation of 5-(4-chlorophenyl)-3-phenyl-(5*H*)-1,4,2-dioxazole **18**.

Primary products acetic benzoic anhydride **16** and the reactive intermediate 4-chlorobenzyloxynitrene **17** from the HERON mode of decomposition react further, leading to a complex range of stable secondary products (Fig. 5), which in this case are all detectable by ^{1}H NMR spectroscopy (Fig. 6) as well as GC-MS. These were 4-chlorobenzaldehyde **19**, benzoic acid **20**, 4-chlorobenzyl benzoate **21**, benzoic anhydride **22**, 4-chlorobenzonitrile **23**, 4-chlorobenzyl acetate **24**, 4-chlorobenzyl nitrate **25**, 4-chlorobenzyl alcohol **26**, and acetic acid **27**. The dioxazole **18** was also evident from characteristic resonances for the methine at δ 6.3 ppm and the *ortho* proton doublet of the 3-phenyl ring, which appears at δ 7.75 ppm.[40]

Evidence for the HERON Reaction Pathway

4-Chlorobenzyloxynitrene Formation

Acetic benzoic anhydride was a minor product but critical evidence for the operation of the HERON reaction was the observation of characteristic products from alkoxynitrene **17**. Although alkoxynitrenes have received little attention in the

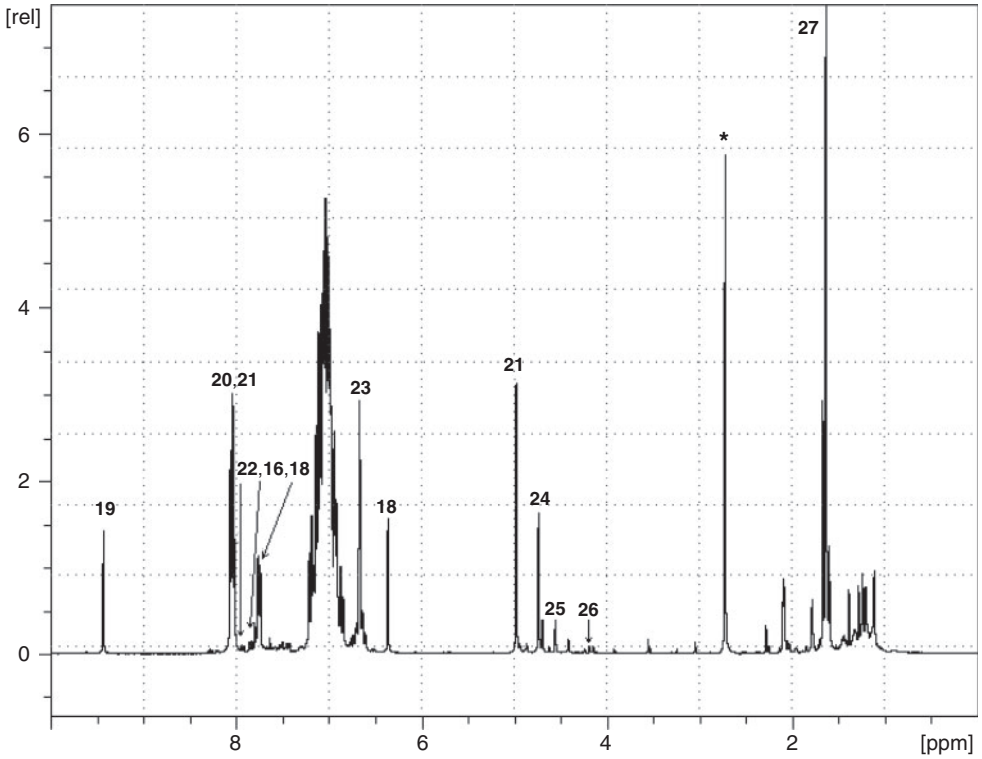
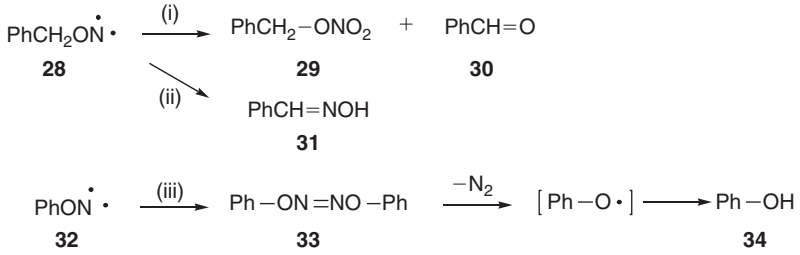


Fig. 6. ^{1}H NMR spectrum of a fully decomposed sample of *N*-acetoxy-*N*-(4-chlorobenzyloxy)benzamide **15** in [D8]toluene. Numbers correspond to products **18**–**27** and * denotes the internal standard, diphenylethane.



Scheme 4.

literature to date, they are believed to be stabilized nitrenes that exist as triplet ground states.[41] Toscano and coworkers recently showed that benzyloxynitrene **28** is efficiently scavenged by molecular oxygen, giving nitrate ester **29** and benzaldehyde **30** (Scheme 4i) in competition with rearrangement to benzaldoxime **31** (Scheme 4ii).[42,43] Furthermore, they suggest that phenoxynitrene **32** can dimerize to the hyponitrite **33** that decomposes thermally to phenoxyl radicals, leading to phenol **34** (Scheme 4iii).

4-Chlorobenzyl nitrate **25** was identified as a product of the decomposition by ^{1}H NMR spectroscopy and GC-MS by comparison with a standard, which was synthesized from silver nitrate and 4-chlorobenzyl bromide. In support of this, decompositions of two identical mixtures, one purged with nitrogen and the second purged with oxygen, were performed and the reaction mixtures were analyzed by GC-MS. Although it was a minor component of the mixtures, the yield of nitrate was shown to increase with increasing concentration of oxygen (Fig. 7). A similar observation could be made in the ^{1}H NMR spectrum of the two reaction mixtures (see Accessory Publication).

4-Chlorobenzonitrile **23** has been identified and confirmed as a product of decomposition by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, and GC-MS with the aid of a standard. All four protons resonate together in the ^{1}H NMR spectrum in [D8] toluene at δ 6.65, well apart from the other aromatic protons (Fig. 6). In the ^{13}C NMR spectrum in [D8]toluene, three resonances at δ 146, 120, and 114 were characteristic and clear of other aromatic signals (see Accessory Publication).

As benzyloxynitrene is known to rearrange to benzaldoxime,[42,43] we propose that 4-chlorobenzyloxynitrene **35** rearranges to **36** and then 4-chlorobenzaldoxime **37**, either in a concerted fashion through the singlet state, which must form from the initial HERON reaction, or in a stepwise fashion as proposed by Toscano, after relaxation to the more stable triplet state. In the presence of anhydride, the oxime can dehydrate via the ester **38** to 4-chlorobenzonitrile (Scheme 5).

4-Chlorobenzaldoxime **37** was synthesized and monitored by ^{1}H NMR spectroscopy under standard reaction conditions in [D8]toluene, with and without acetic anhydride. Whereas no reaction occurred in the absence of acetic anhydride, as expected

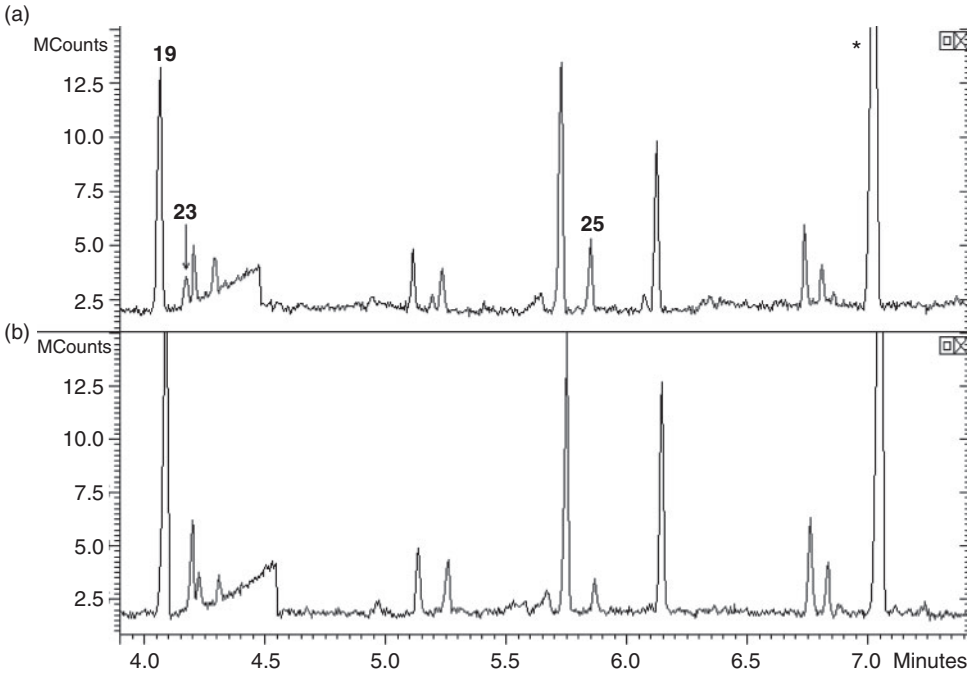
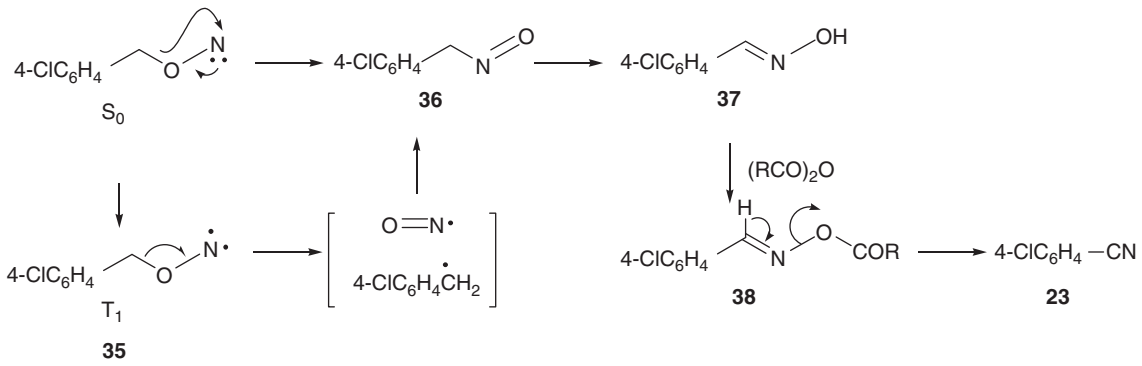


Fig. 7. Decrease in concentrations of 4-chlorobenzyl nitrate **25** and increase in 4-chlorobenzaldehyde **19** and 4-chlorobenzonitrile **23** as the concentration of oxygen decreases from (a) mixture purged with oxygen, to (b) purged with nitrogen, as monitored by GC-MS. The internal standard, diphenylethane, is labelled with *.



Scheme 5.

the reaction containing both 4-chlorobenzaldoxime and acetic anhydride reacted smoothly to form 4-chlorobenzonitrile (Fig. 8). The unstable intermediate that is generated is presumably the acetate ester of the oxime (**38**, R = Me).

4-Chlorobenzaldehyde **19** was identified by both ^{1}H NMR spectroscopy and GC-MS as a prominent product in the decomposition mixtures, along with small amounts of 4-chlorobenzyl alcohol **26**. Alkoxynitrene could also be expected to dimerize to form a hyponitrite **39**, which would be likely to decompose to N_2 and two 4-chlorobenzyloxyl radicals **40**, the source of both 4-chlorobenzyl alcohol and 4-chlorobenzaldehyde (Scheme 6).[44,45]

The corresponding hyponitrite was synthesized from 4-chlorobenzyl bromide and silver hyponitrite and decomposed in [D8]toluene at 90°C, giving both 4-chlorobenzyl alcohol **26** (major) and 4-chlorobenzaldehyde **19** (minor) (Fig. 9), confirming that **39** can be the source of both products. Interestingly, in the thermal decomposition mixtures of *N*-acetoxy-*N*-(4-chlorobenzyloxy)benzamide, there is always a large excess of 4-chlorobenzaldehyde relative to 4-chlorobenzyl alcohol. However, under the reaction conditions, alcohol would be expected to be consumed by reaction with anhydride, providing a source of both 4-chlorobenzyl benzoate **21** as well as 4-chlorobenzyl acetate **24**, significant products from the reaction (see below).

Finally, careful analysis of the GC-MS traces of the reaction mixtures with different degrees of oxygen saturation indicates that the 4-chlorobenzonitrile **23**, which was present in the reaction purged with nitrogen (Fig. 7b), was reduced in concentration where oxygen was present (Fig. 7a). In addition, there was a significant reduction in the amount of 4-chlorobenzaldehyde **19**. These factors confirm that rearrangement to oxime and dimerization to hyponitrite are competitive pathways with nitrate ester formation. The presence of some benzaldehyde where nitrile is largely eliminated may suggest that it is also formed from the nitrate ester, as suggested by Toscano and coworkers.[42,43]

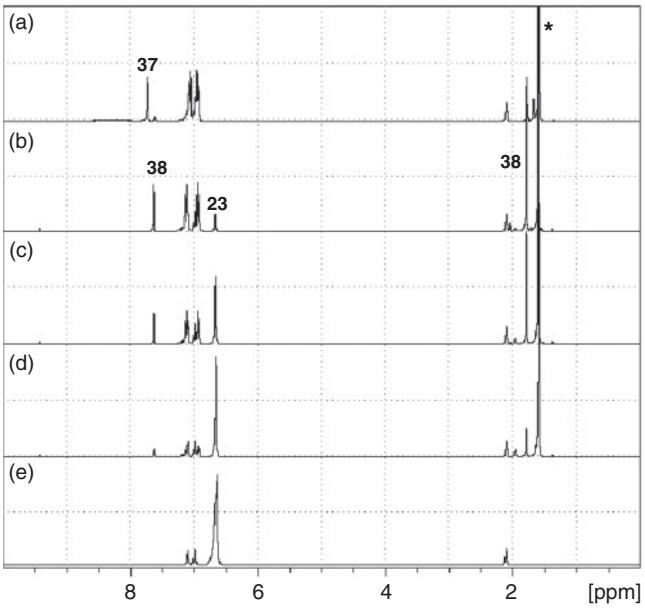
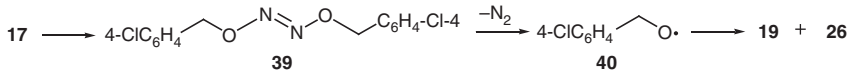


Fig. 8. Conversion of 4-chlorobenzaldoxime **37** to 4-chlorobenzonitrile **23** at 90°C in [D8]toluene; (a) 4-chlorobenzaldoxime with added acetic anhydride (*); (b) after 1 h; (c) after 6 h; (d) after 23 h; (e) reference 4-chlorobenzonitrile.

Anhydride Formation

The presence of low yields of acetic benzoic anhydride in the decomposition mixture of *N*-acetoxy-*N*-(4-chlorobenzyloxy) benzamide was confirmed using ^{1}H NMR spectroscopy and GC-MS, with the use of a standard. However, the HERON reaction is expected to produce equal amounts of acetic benzoic anhydride and 4-chlorobenzyloxynitrene. The anhydride **16** was synthesized and ultimately found to redistribute to a mixture of benzoic anhydride and acetic anhydride in line with known behaviour of mixed anhydrides on heating.[46,47] Furthermore, in the presence of 4-chlorobenzyl alcohol **26**, both 4-chlorobenzyl acetate **24** and to lesser extent 4-chlorobenzyl benzoate **21** were generated, as illustrated in Fig. 10. The relative yields are in line with the pK_As of acetic and benzoic acids (pK_A 4.8 and 4.2 respectively).

Whereas in the decomposition of **15** most anhydride appears to be consumed, in other analogous reactions, anhydrides and mixed anhydrides are detectable, even in significant quantities (Scheme 7). For instance, along with dioxazole **47a**, *N*-benzoyloxy-*N*-butoxybenzamide **41a** afforded benzoic anhydride **22** and the single ester butyl benzoate **45a**, which were readily detectable by both NMR spectroscopy and GC-MS (Fig. 11). *N*-Butoxy-*N*-heptanoyloxybenzamide **41b** produced significant quantities of the unsymmetrical benzoic heptanoic anhydride **42b**, which, although not observed in the ^{1}H NMR spectrum of



Scheme 6.

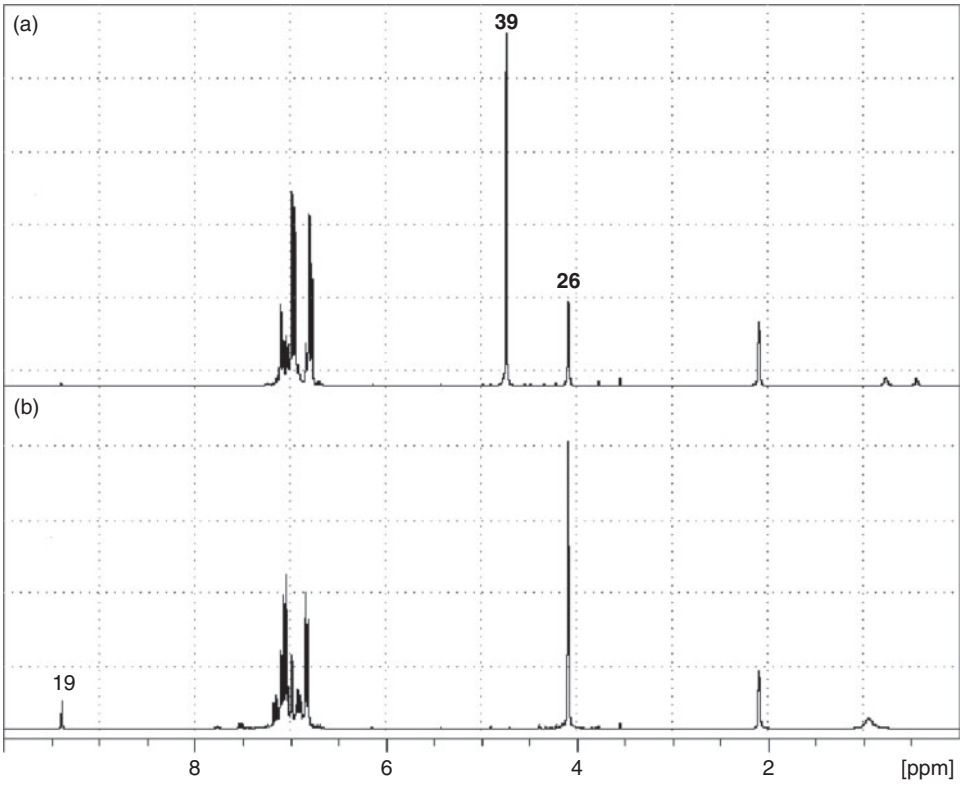


Fig. 9. ^{1}H NMR spectra in [D8]toluene of (a) 4-chlorobenzyl hyponitrite **39** with 4-chlorobenzyl alcohol **26** and (b) 4-chlorobenzaldehyde **19** and 4-chlorobenzyl alcohol **26** after complete decomposition at 90°C.

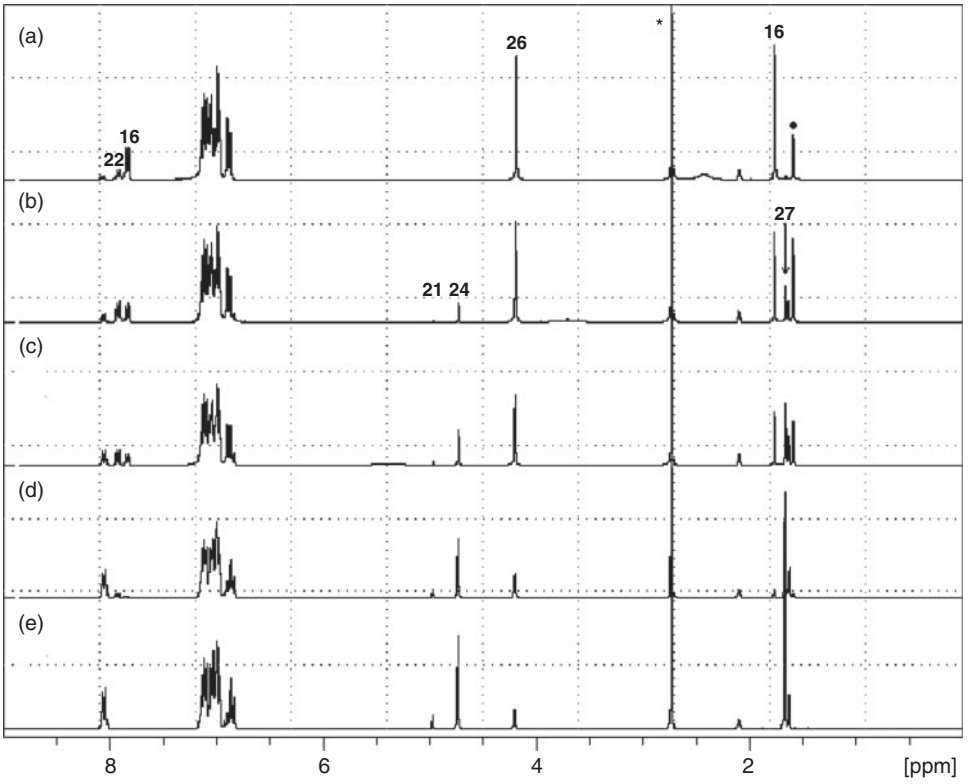
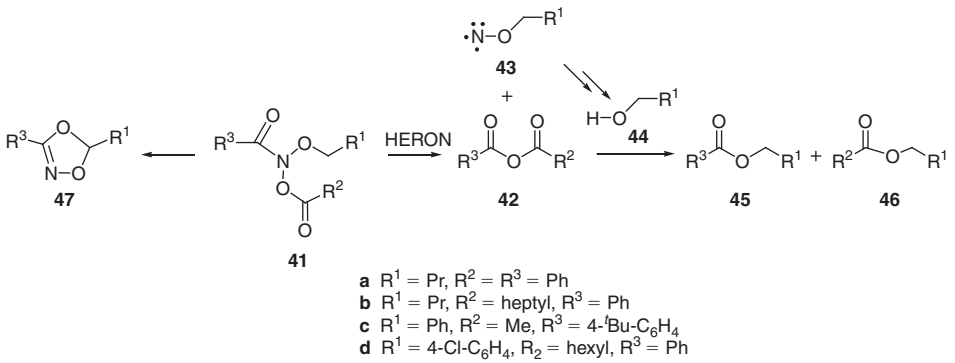


Fig. 10. ^{1}H NMR spectra in [D8]toluene of the reaction between acetic benzoic anhydride **16** and 4-chlorobenzyl alcohol **26** to form benzoic acid **20**, acetic acid **27**, 4-chlorobenzyl benzoate **21** and 4-chlorobenzyl acetate **24**. Benzoic anhydride **22** and acetic anhydride (•) can also be detected with internal standard diphenylethane (*); (a) 0 min; (b) 0.25 h; (c) 0.5 h; (d) 4.5 h; (e) 18 h.



Scheme 7.

the reaction mixture, was detectable by GC-MS together with butyl benzoate and butyl heptanoate **46b**. Anhydride formation in all cases is clearly attributable to HERON reactions.

The formation of two esters in all reactions where unsymmetrical anhydrides are generated as primary HERON products is the consequence of an intermolecular reaction between alcohols **44**, derived from the corresponding alkoxynitrenes **43**, and mixed anhydrides **42** (Scheme 7). To confirm this, a 'crossover' decomposition reaction was carried out with equimolar quantities of *N*-acetoxy-*N*-benzyloxy-4-*tert*-butylbenzamide **41c** and *N*-(4-chlorobenzyloxy)-*N*-heptanoyloxybenzamide **41d** in [D8] toluene. Decomposition at similar rates should produce in the reaction two mixed anhydrides, **42c** and **42d**, and two alcohols, 4-chlorobenzyl alcohol **26** and benzyl alcohol **44c**, from dimerization and decomposition of the 4-chlorobenzyloxynitrene **17** and benzyloxynitrene **43c** respectively. Formation of the esters by intermolecular reactions between the alcohols and both mixed anhydrides should yield eight esters. The resultant reaction mixture from the decomposition was analyzed by GC-MS and shown to contain all eight esters, identified from their individual mass spectra (Fig. 12). Four of these, **45c** with **46c** and **21** with **46d** were esters that were formed from the individual starting materials, but these were accompanied by all four crossover esters, 4-chlorobenzyl esters **24** and **48** and benzyl esters **49** and **50**. This route to ester formation was therefore confirmed (Chart 2).

From the GC-MS trace in Fig. 12, it is clear that there is a preponderance of two esters, namely benzyl 4-*tert*-butyl benzoate **45c** and 4-chlorobenzyl benzoate **21** and this was also observed in the ^{1}H NMR spectrum of the reaction mixture

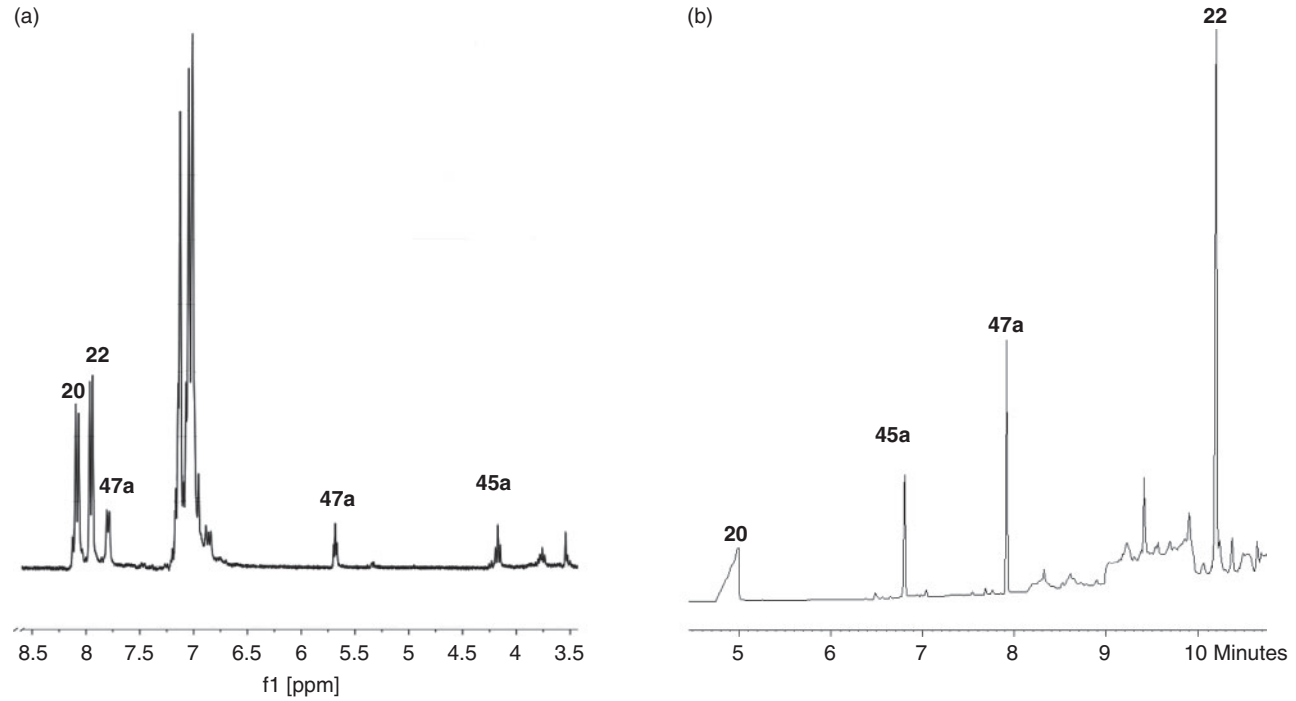


Fig. 11. (a) ^{1}H NMR spectrum in [D8]toluene and (b) GC-MS trace of fully decomposed *N*-benzoyloxy-*N*-butoxybenzamide **41a**.

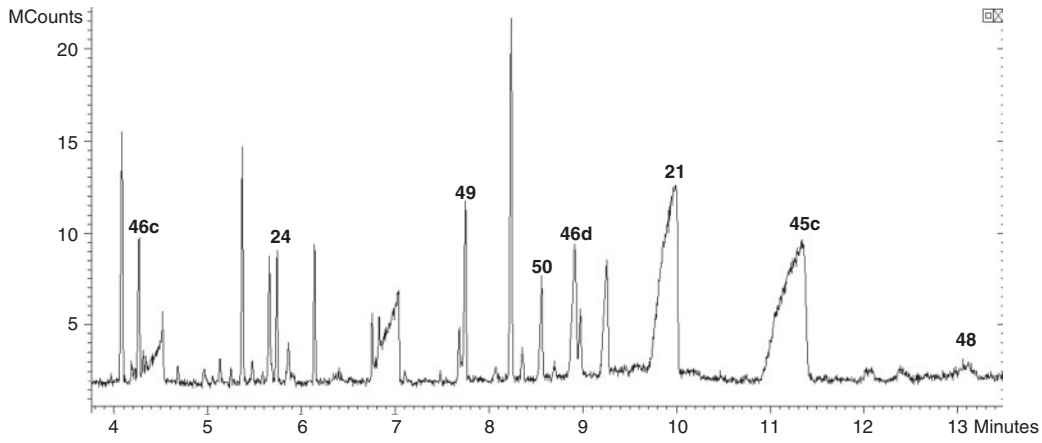
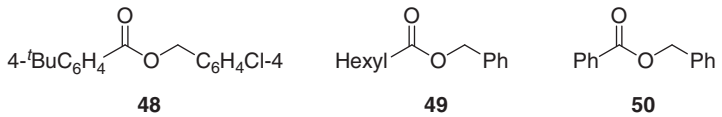


Fig. 12. GC-MS chromatogram of the reaction mixture from a joint decomposition of *N*-acetoxy-*N*-benzyloxy-4-*tert*-butylbenzamide **41c** and *N*-(4-chlorobenzyloxy)-*N*-(heptanoyloxy)benzamide **41d** in [D8]toluene showing all eight esters. Mass spectral data for each ester are presented in Table 1.



48 **49** **50**

Chart 2.

(see Accessory Publication). Furthermore, the reaction of 4-chlorobenzyl alcohol with anhydrides from acetic benzoic anhydride afforded a significantly greater yield of 4-chlorobenzyl acetate than 4-chlorobenzyl benzoate (Fig. 10). Although the reaction of the nitrene-derived alcohol with mixed anhydride must be a source of the non-crossover esters **45**, it is clearly not the only source.

*Formation of (5*H*)-1,4,2-Dioxazoles*

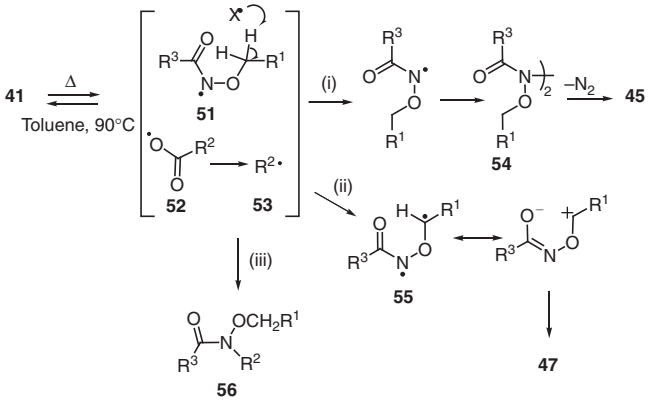
Dioxazoles are formed in low yields in parallel with other products in these reactions. They are characterized in the ^{1}H NMR spectra ($CDCl_3$) by the low-field benzylic methine at ~δ 6.9[40] and the *ortho* protons on the 2-phenyl ring at δ 7.5, as well as by the methine carbon at δ 107–110 in the ^{13}C NMR spectrum. Although **18**, from decomposition of the parent **15** in [D8]

toluene, was not readily detectable by GC-MS under the conditions, it was clearly observable by ^{1}H NMR spectroscopy at similar chemical shifts (δ 6.32 and δ 7.75, Fig. 6). While **18** has been synthesized previously, limited NMR data were reported. In the present study, it was isolated from a large-scale decomposition of **15** in toluene and we report here its full characterization together with data for several other analogues.

Aspects of dioxazole formation have been published in preliminary form elsewhere.[2,3] Experiments in these laboratories support a free-radical reaction process outlined in Scheme 8, which involves solvent-cage formation of a 1,3-diradical **55** by benzylic hydrogen abstraction from alkoxyamidyl **51** (by either acyloxyl radical **52** or its decarboxylation product radical **53**) (Scheme 8ii). In certain cases, low yields of adducts **56** have been detected and these must arise from a competitive reaction between alkoxyamidyls **51** and alkyl radicals **53** (Scheme 8iii). For instance, *N*-butoxy-*N*-heptanoyloxybenzamide **41b** gave, in addition to 3-phenyl-5-propyl-(5*H*)-1,4,2-dioxazole **47b**, half as much *N*-butoxy-*N*-hexylbenzamide (**56**, $R^1 = Pr$, $R^2 = n$-hexyl, $R^3 = Ph$) identified by comparison with a synthetic reference sample.

Calculations on the structure of the model diradical **55** ($R^1 = R^3 = H$) predict the singlet state to be more stable than the triplet state by 110 kJ mol^{-1} and to be strongly dipolar in character, which would facilitate cyclization to the dioxazole.[2,3]

In a detailed study of the decomposition of *N*-acetoxy-*N*-butoxybenzamide **57** and *N*-acetoxy-*N*-(1,1-dideuteriobutoxy) benzamide **58**, a primary deuterium isotope effect of 3.5 has been observed in the formation of 3-phenyl-5-propyl-(5*H*)-1,4,2-dioxazole **47a**, confirming that the ease of cleavage of an oxymethylenic C–H bond is integral to dioxazole formation (S. A. Glover, D. S. Pankhurst, unpubl. data). In the same experiment, an inverse isotope effect was found for formation of butyl benzoate **45a**, indicating that the processes are in competition with one another. Alkoxyamidyls are long-lived radicals owing to stabilization of the nitrogen-centred radical by the neighbouring oxygen,[48–53] and their generation by a variety of methods leads to dimerization to hydrazines.[44,49,52,54] Diffusion of **51** from the solvent cage (Scheme 8i) would therefore be expected to lead to hydrazines **54** and ultimately to the esters **45** through double HERON reactions that we, and others, have shown to occur.[4,23,25,38,39] The preponderance of the esters **45** over **46** can therefore be attributed to this second route to ester formation.



Scheme 8.

Dioxazole formation involves homolysis of the N–OAc bond in competition with the HERON pathway, leading to anhydrides together with alkoxynitrenes, and experiments with various *N*-acetoxy-*N*-(4-substituted-benzyloxy)benzamides support this. With a 4-methoxyl substituent on the benzyloxyl group in **59b**, dioxazole **60b** was not observable by ^{1}H NMR spectroscopy or by GC-MS, but along with **18** from **15**, the heterocycle **60a** was a significant product with a 4-nitro substituent in **59a**. As benzoate esters can be formed by two processes (from alcohol derived from alkoxynitrene or from dimerization of alkoxyamidyls), the extent of radical reactivity can only be estimated at between 25–36% for **15** and 31–43% for **59a**. Little dioxazole was detected from the 4-methoxy substrate **59b**. It is clear that more dioxazole is generated with the electron-withdrawing *para* nitro group (Chart 3).

These substituent effects are in accord with the properties of the HERON reactions; the HERON transition state generates positive charge at the alkoxyl oxygen adjacent to the benzylic position, which would be stabilized and destabilized by electron-donor and electron-withdrawing groups respectively (Fig. 13). The *para* substituents would have a much smaller effect on the homolysis of the N–OAcyl bond.

While a donor alkoxyl group would be expected to promote the HERON reaction giving anhydride in competition with homolysis, the opposite effect would be expected with an electron-withdrawing group.

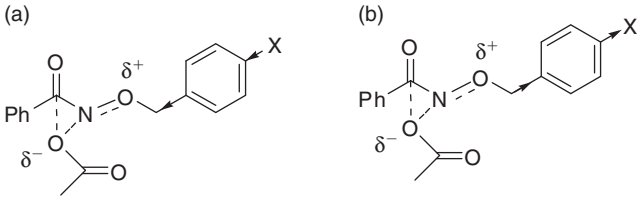
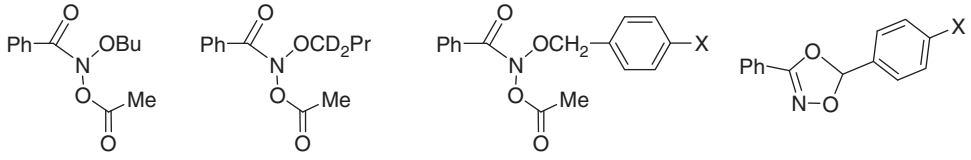


Fig. 13. Electronic effects in the HERON transition state: (a) stabilization by *para* electron-donor groups and (b) destabilization by *para* electron-withdrawing groups.



57 **58** **59** **60**

a X = NO_2
b X = OMe

a X = NO_2
b X = OMe

Chart 3.

Conclusion

Thermal decomposition reactions of *N*-acyloxy-*N*-alkoxyamides generate complex reaction mixtures by two competing mechanisms: a HERON reaction leads to anhydrides and alkoxynitrenes, whereas homolysis of the N–OAcyl bond affords alkoxyamidyl radicals. The three primary products are all reactive under the reaction conditions. The alkoxynitrenes can be captured by oxygen, yielding nitrate esters in competition with rearrangement to oximes or dimerization to unstable hyponitrites. The latter are sources of alkoxyl radicals that disproportionate to alcohols and aldehydes. The anhydride reacts with both oximes and alcohols, giving stable nitriles and esters. Alkoxyamidyls are sources of dioxazoles and hydrazines, which are an alternative route to esters by HERON reactions.

Substituent effects control the competition between these two processes in a predictable manner. An electron-donor methoxyl group on the *para* position of a benzyloxy group promotes the HERON reaction at the expense of homolysis, the converse of the impact of an electron-withdrawing NO_2 group.

Although synthetically of limited value for the generation of alkoxynitrenes, we have demonstrated that the heterolytic decomposition pathway of *N*-acyloxy-*N*-alkoxyamides, at elevated temperature and without the influence of a polar solvent, is another clear-cut example a HERON reaction of an anomeric amide. Under these conditions, heterolysis of the N–OAcyl bond giving alkoxynitrenium ions is disfavoured and, under the influence of a moderate n_O–σ^*_{NOAcyl} anomeric destabilization, the acyloxyl group migrates from nitrogen to the carbonyl carbon, resulting in alkoxynitrene formation. The elevated temperature required for this rearrangement also promotes a competitive homolysis of the N–OAcyl bond.

The reaction is in accord with theoretical attributes of the HERON reaction pathway for *N*-formyloxy-*N*-methoxyformamide, which predicts acyloxyl migration to be more favourable than alkoxyl migration. No evidence could be found for a reverse HERON reaction that would lead to esters and acyloxynitrenes, although the chemistry of such electron-deficient species is unknown.

The most likely route to formation of dioxazoles, in some cases in reasonable yields, most probably involves a 1,3-diradical generated from the alkoxyamidyls in a solvent cage. The details of this reaction process will be the subject of a future paper from these laboratories.

Experimental

Materials and Methods

Infrared spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrophotometer as chloroform solutions. Mass spectra were recorded on a Varian 1200 L triple quadrupole mass spectrometer coupled to a Varian CP-3800 gas chromatograph; the column used was a FactorFour Capillary Column, VF-5 ms, 30 m × 0.25 mm, 0.25 μm. Samples were injected into the column at 100°C, which was held for 2 min before increasing by 40°C per minute to the maximum temperature of 250°C, which was maintained until the end of each run. The injector was at 523 K and the sample was subjected to a capillary voltage of 70 eV. NMR spectra were recorded in $CDCl_3$ or [D8]toluene on a Bruker Avance 300P FT NMR spectrometer with a 5-mm ^{1}H inverse/BB z gradient probe, operating at 300.13 MHz (^{1}H) or 75.46 MHz (^{13}C). Centrifugal chromatographic separations were performed on a 7294T model Harrison Research Chromatotron with plates coated with 2.0 mm of silica gel 60 F_{254} (Merck).

Synthesis of N*-Acyloxy-*N*-alkoxyamides*

Synthesis of *N*-butoxy-*N*-benzoyloxybenzamide **41a**,[33] *N*-benzyloxy-*N*-chloro-4-*tert*-butylbenzamide,[36] *N*-chloro-*N*-(4-chlorobenzyloxy)benzamide, *N*-butoxy-*N*-chlorobenzamide, *N*-acetoxy-*N*-(4-chlorobenzyloxy)benzamide **15**, *N*-acetoxy-*N*-(4-nitrobenzyloxy)benzamide **59a**, and *N*-acetoxy-*N*-(4-methoxybenzyloxy)benzamide **59b** have been described before, as have precursors butyl benzohydroxamate and 4-chlorobenzyl benzohydroxamate.[29,31] All mutagenic *N*-acyloxy-*N*-alkoxyamides from this and previous studies are characterized spectroscopically.

N*-Butoxy-*N*-heptanoyloxybenzamide **41b***

N-Butoxy-*N*-chlorobenzamide (0.5 g, 2.24 mmol) and sodium heptanoate (0.48 g, 3.13 mmol) were stirred in dry acetone (15 mL), in the dark at room temperature, for 48 h. On completion of acyloxylation, the mixture was filtered and concentrated under vacuum. Purification by centrifugal chromatography using 5% ethyl acetate/hexane afforded pure *N*-butoxy-*N*-heptanoyloxybenzamide (0.51 g, 1.59 mmol, 71%) as a pale yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 1782s (C=O), 1724s (C=O). δ_H 7.78 (d, 2H), 7.54 (t, 1H), 7.43 (t, 2H), 4.19 (t, 2H), 2.34 (t, 2H), 1.63 (quin, 4H), 1.38 (sextet, 2H), 1.26 (t, 8H), 0.91 (t, 6H). δ_C 174.2, 171.1, 132.5, 132.0, 129.0, 128.2, 75.5, 32.1, 31.3, 30.1, 28.5, 24.2, 22.4, 19.0, 13.9, 13.7.

N*-Acetoxy-*N*-benzyloxy-4-*tert*-butylbenzamide **41c***

N-Benzyloxy-*N*-chloro-4-*tert*-butylbenzamide (0.5 g, 1.57 mmol) was stirred in the dark with anhydrous sodium acetate (0.18 g, 2.20 mmol) in dry acetone for ~14 h. The mixture was filtered and concentrated under vacuum. Purification via centrifugal chromatography with 10% ethyl acetate/hexane and concentration under vacuum afforded *N*-acetoxy-*N*-benzyloxy-4-*tert*-butylbenzamide (0.42 g, 1.23 mmol, 78%) as a yellow oil. δ_H 7.70 (d, 2H, *o*-ArCO), 7.42 (d, 2H, *o*-ArCH_2), 7.34 (m, 5H), 5.18 (s, 2H, ArCH_2O), 2.05 (s, 3H, CH_3CO), 1.33 (s, 9H, $(CH_3)_3$). δ_C 174.01, 168.21, 156.71, 134.90, 129.18, 128.64, 125.32, 128.47, 77.46, 35.13, 31.07, 18.78.

N*-(4-Chlorobenzyloxy)-*N*-heptanoyloxybenzamide **41d***

N-Chloro-*N*-(4-chlorobenzyloxy)benzamide (0.5 g, 1.69 mmol) was stirred in the dark with anhydrous sodium heptanoate (0.36 g, 2.36 mmol) in dry acetone for ~16 h. The mixture was filtered and concentrated under vacuum. Purification via centrifugal chromatography with 10% ethyl acetate/hexane and concentration under vacuum afforded *N*-(4-chlorobenzyloxy)-*N*-heptanoyloxybenzamide (0.46 g, 1.15 mmol, 68%) as a yellow oil. δ_H 7.71 (d, 2H), 7.56 (t, 1H), 7.42 (t, 2H), 7.30 (d, 2H), 7.21 (d, 2H), 5.13 (s, 2H), 2.25 (t, 2H), 1.53 (quin, 2H), 1.21 (complex m, 6H), 0.86 (t, 3H). δ_C 174.32, 171.09, 134.61, 133.16, 132.66, 131.77, 130.47, 129.00, 128.66, 128.26, 32.03, 31.27, 28.53, 24.49, 22.38, 13.94.

Reference Standards

4-Chlorobenzonitrile, 4-chlorobenzaldehyde, 4-chlorobenzyl alcohol, benzoic anhydride, benzoic acid, and acetic acid are commercially available. 4-Chlorobenzyl acetate and 4-chlorobenzyl benzoate were also available from previous studies.

4-Chlorobenzyl Nitrate[55] **25**

p-Chlorobenzyl bromide was stirred with silver nitrate (equal molar quantities) in acetonitrile for 24 h at room temperature. Silver bromide precipitate was filtered off and the remaining solution was concentrated under vacuum, producing approximately an 80% yield of *p*-chlorobenzylnitrate. Distillation at 110°C, 10 mm Hg, afforded pure *p*-chlorobenzylnitrate (lit.[55] 72°C, 2 mm Hg). δ_H 7.34 (q, 4H), 5.37 (s, 2H).

4-Chlorobenzaldoxime[56] **37**

p-Chlorobenzaldehyde (0.5 g) and hydroxylamine hydrochloride (0.5 g), in ethanol (5 mL) and pyridine (0.5 mL), were refluxed until reaction was complete (monitored by TLC). Excess ethanol was removed under vacuum. Water was added (5 mL) and the mixture was cooled in an ice bath, with stirring, until crystallization was complete. The crystals were isolated by filtration and then recrystallized from a minimal amount of hot ethanol. mp 106–108°C (lit.[56] 104–106°C). δ_H 8.11 (s, 1H), 7.51 (d, 2H), 7.36 (d, 2H).

1,2-Bis(4-chlorobenzyloxy)diazene[57,58] **39**

Silver hyponitrite was synthesized according to literature protocol.[57] 4-Chlorobenzyl bromide (1 g) was stirred in a 2:1 benzene/hexane solution (8 mL) in an ice bath. Over a period of 40 min, an excess of silver hyponitrite was added and the mixture was then stirred for 1 h at room temperature (at which time there were no further changes in the appearance of the precipitate). The precipitate was filtered off and washed with a small portion of the reaction solvent. The remaining solution was concentrated under vacuum, and the resulting crystals were recrystallized from methanol in an acetone/liquid nitrogen slush bath. The white crystals were collected, dried under vacuum, and stored at −20°C. δ_H 7.31 (complex m, 8H), 5.20 (s, 4H). δ_C 129.94, 128.82, 128.69, 128.26, 74.71.

N-*Butoxy*-N-*hexylbenzamide*

N-butoxybenzamide (0.50 g, 2.59 mmol) and 1-bromohexane (0.36 g, 2.18 mmol) were dissolved in 10% aqueous methanol solution (10 mL), followed by the addition of potassium hydroxide (0.17 g, 3.04 mmol). The mixture was stirred for 24 h, followed by the removal of methanol under vacuum and the addition of an extra 20 mL of distilled water. The aqueous mixture was extracted with dichloromethane (DCM) (3 × 20 mL), followed by washing of the organic layer with dilute HCl solution (20 mL), distilled water (20 mL), and 10% Na_2CO_3 solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to afford the crude product. Purification by centrifugal chromatography, using 5% ethyl acetate/hexane, afforded pure *N*-butoxy-*N*-hexylbenzamide as a brown oil. δ_H 7.66 (d, 2H), 7.44 (t, 1H), 7.38 (t, 2H), 3.74 (t, 2H), 3.68 (t, 2H), 1.69 (m, 8H), 1.30 (m, 4H), 0.92 (t, 3H), 0.83 (t, 3H). δ_C 169.8, 130.0, 129.3, 128.3, 127.8, 73.8, 46.5, 31.5, 29.7, 27.2, 26.4, 22.6, 19.0, 14.0, 13.6. *m*/*z* (EI) 277 (w), 176, 135, 105.

General Decomposition Procedure

Thermal decompositions of *N*-acyloxy-*N*-alkoxyamides in [D8] toluene (typically 1.75×10^{-1} M) were carried out in NMR tubes, with a known amount of diphenylethane as internal standard. Unless otherwise specified, the solutions were degassed with nitrogen, which was bubbled through the solution using a fine capillary tube for a period of 20 min. The NMR tubes were sealed with a cap and paraffin film and suspended in an oil bath at a 90°C. The decompositions were monitored using ^{1}H NMR, and were continued until the decomposition was complete. Reactions were analyzed directly by NMR and GC-MS.

Isolation of Dioxazoles

General Method

Dioxazoles **18**, **47a**, and **60a** were separated from large-scale reaction mixtures using TLC prep plates, coated with 2.0 mm of silica gel 60 F_{254} (Merck), and using 10% ethyl acetate/hexane as solvent. Further purification was achieved using centrifugal chromatography and 2.5% ethyl acetate/hexane as solvent.

*5-(4-Chlorophenyl)-3-phenyl-(5*H*)-1,4,2-dioxazole* **18** was isolated as colourless crystals; mp 50–52°C. ν_{max} ($CHCl_3$)/cm^{-1} 1624 (CN), 1081 and 1050 (CO). δ_H 7.85 (d, 2H), 7.54 (t, 3H), 7.46 (m, 4H), 6.89 (s, lH). δ_C 159.1, 136.6, 133.6, 131.8, 129.0, 128.8, 128.1, 127.0, 122.6, 107.8. *m*/*z* (EI) 259 ($M^{+\bullet}$), 140, 139, 119 (M – (4-chlorobenzaldehyde)), 105, 91. (Lit.[40] 259 [$M^{+\bullet}$], 140, 139, 119, 105.) Calc. for $C_{14}H_{l0}O_2NCl$: C 64.01, H 3.88, N 5.33, Cl 13.49%. Found: C 64.41, H 3.97, N 5.33, Cl 13.74%.

*5-(4-Nitrophenyl)-3-phenyl-(5*H*)-1,4,2-dioxazole* **60a** was isolated as pale yellow crystals; mp 127–130°C (lit.[40] 130°C). ν_{max} ($CHCl_3$)/cm^{-1} 1624 (CN), 1087 and 1060 (CO). δ_H 8.33 (d, 2H), 7.86 (d, 2H), 7.80 (d, 2H), 7.56 (t, 1H), 7.48 (t, 2H), 7.02 (s, 1H). δ_C 159.0, 149.2, 141.8, 132.1, 128.9, 127.6, 127.0, 124.0, 122.1, 106.6. *m*/*z* (EI) 270 ($M^{+\bullet}$), 150, 119 (M – (4-NO_2-benzaldehyde)).

*3-Phenyl-5-propyl-(5*H*)-(1,4,2)-dioxazole* **47a** was isolated as a yellow oil. δ_H 7.82 (d, 2H), 7.49 (t, 1H), 7.44 (t, 2H), 6.07 (t, 1H), 1.94 (q, 2H), 1.60 (sextet, 2H), 1.02 (t, 3H). δ_C 131.5, 129.5, 128.6, 126.8, 109.8, 35.4, 16.5, 13.8. *m*/*z* (EI) 191 ($M^{+\bullet}$), 148 (M – propyl), 120. *m*/*z* (ESI) 192 (M + 1), 214 (M + 23), 231 (M + 40).

Crossover Experiment with N-*Acetoxy*-N-*benzyloxy-4-*tert*-butylbenzamide* **41c** *and* N-*(4-Chlorobenzyloxy)-*N*-heptanoyloxybenzamide* **41d**

Equimolar quantities of *N*-acetoxy-*N*-benzyloxy-4-*tert*-butylbenzamide **41c** and *N*-(4-chlorobenzyloxy)-*N*-heptanoyloxybenzamide **41d** were decomposed together according to the standard procedure and the product mixture analyzed by ^{1}H NMR spectroscopy and GC-MS. Esters were identified from their characteristic molecular ions and fragmentation patterns, which are presented in Table 1.

Accessory Publication

A publication is available from the Journal's website that illustrates:

1. The effect of oxygen on the production of 4-chlorobenzylnitrate **25** from thermal decomposition of *N*-acetoxy-*N*-(4-chlorobenzyloxy)benzamide **15** as observed by ^{1}H NMR spectroscopy in [D8]toluene (Fig. S1);
2. The presence of 4-chlorobenzonitrile **23** in the ^{13}C NMR spectrum, in [D8]toluene, of a reaction mixture from thermal decomposition of *N*-acetoxy-*N*-(4-chlorobenzyloxy)benzamide **15** (Fig. S2);
3. The preponderance of non-crossover esters **45c** and **21** in the ^{1}H NMR spectrum from thermal decomposition

Table 1. Ester fragmentations from crossover experiment with *N*-(4-chlorobenzyloxy)-*N*-heptanoyloxybenzamide 41d and *N*-acetoxy-*N*-benzyloxy-4-*tert*-butylbenzamide 41c in [D8]toluene at 90°C

R′CO_2R″	R′	R″	$M^{+\bullet}$	R″–OH^+	R′CO^+	$C_7H_6X^+$ (X = H, Cl)	$C_6H_5^+$	M – $CH_3^{+\bullet}$	M – $^tBu^{+\bullet}$
46c	CH_3	$PhCH_2$	150	108	43	91	77	–	–
24	CH_3	4-$ClPhCH_2$	184	142	43	125	77	–	–
50	Ph	$PhCH_2$	212	–	105	91	77	–	–
21	Ph	4-$ClPhCH_2$	246	–	105	125	77	253	
45c	4-^{t}BuPh	$PhCH_2$	268	–	161	91	77	287	212
48	4-^{t}BuPh	4-$ClPhCH_2$	302	–	161	125	–	–	–
49	Hexyl	$PhCH_2$	220	108	113	91	–	–	–
46d	Hexyl	4-$ClPhCH_2$	254	142	113	125	–	–	–

of *N*-acetoxy-*N*-benzyloxy-4-*tert*-butylbenzamide **41c** and *N*-(4-chlorobenzyloxy)-*N*-heptanoyloxybenzamide **41d** (Fig. S3).

References

[1] S. A. Glover, *Tetrahedron* **1998**, *54*, 7229. doi:10.1016/S0040-4020(98)00197-5

[2] S. A. Glover, in *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids, Part 2* **2009**, p. 839 (Eds Z. Rappoport, J. F. Liebman) (Wiley: Chichester).

[3] S. A. Glover, in *Advances in Physical Organic Chemistry* **2008**, Vol. 42, p. 35 (Ed. J. Richard) (Elsevier: London).

[4] S. A. Glover, G. Mo, A. Rauk, *Tetrahedron* **1999**, *55*, 3413. doi:10.1016/S0040-4020(98)01151-X

[5] O. V. Shishkin, R. I. Zubatyuk, V. G. Shtamburg, A. V. Tsygankov, E. A. Klots, A. V. Mazepa, R. G. Kostyanovsky, *Mendeleev Commun.* **2006**, *16*, 222. doi:10.1070/MC2006V016N04ABEH002195

[6] V. G. Shtamburg, E. A. Klots, A. P. Pleshkova, V. I. Avramenko, S. P. Ivonin, A. V. Tsygankov, R. G. Kostyanovsky, *Russ. Chem. Bull.* **2003**, *52*, 2251. doi:10.1023/B:RUCB.0000011887.40529.B0

[7] V. G. Shtamburg, V. F. Rudchenko, S. S. Nasibov, I. I. Chervin, R. G. Kostyanovskii, *Izv. Akad. Nauk SSSR [Khim]* **1981**, 449.

[8] P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry* **1984**, Vol. 1, p. 4 (Pergamon Press: Oxford).

[9] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds* **1994**, p. 753 (John Wiley & Sons, Inc.: New York, NY).

[10] A. Rauk, *Orbital Interaction Theory of Organic Chemistry* **1994**, p. 102 (John Wiley & Sons, Inc.: New York, NY).

[11] S. A. Glover, A. Goosen, C. W. McCleland, J. L. Schoonraad, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2255. doi:10.1039/P19840002255

[12] S. A. Glover, A. Goosen, C. W. McCleland, J. L. Schoonraad, *Tetrahedron* **1987**, *43*, 2577. doi:10.1016/S0040-4020(01)81665-3

[13] S. A. Glover, A. P. Scott, *Tetrahedron* **1989**, *45*, 1763. doi:10.1016/S0040-4020(01)80041-7

[14] M. Kawase, T. Kitamura, Y. Kikugawa, *J. Org. Chem.* **1989**, *54*, 3394. doi:10.1021/JO00275A027

[15] Y. Kikugawa, M. Kawase, *J. Am. Chem. Soc.* **1984**, *106*, 5728. doi:10.1021/JA00331A053

[16] Y. Kikugawa, M. Shimada, *Chem. Lett.* **1987**, *16*, 1771. doi:10.1246/CL.1987.1771

[17] D. Schroeder, F. Grandinetti, J. Hrusak, H. Schwarz, *J. Phys. Chem.* **1992**, *96*, 4841. doi:10.1021/J100191A023

[18] K. L. Cavanagh, S. A. Glover, H. L. Price, R. R. Schumacher, *Aust. J. Chem.* **2009**, *62*, 700. doi:10.1071/CH09166

[19] S. A. Glover, G. Mo, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1728. doi:10.1039/B111250N

[20] S. A. Glover, *Arkivoc* **2001**, Part xii, Issue in Honour of O.S.Tee, ms. OT-308C, 143.

[21] J. J. Campbell, S. A. Glover, *J. Chem. Res. (M)* **1999**, *8*, 2075.

[22] J. J. Campbell, S. A. Glover, *J. Chem. Res. (S)* **1999**, *8*, 474. doi:10.1039/A903555I

[23] S. A. Glover, A. Rauk, J. M. Buccigross, J. J. Campbell, G. P. Hammond, G. Mo, L. E. Andrews, A.-M. E. Gillson, *Can. J. Chem.* **2005**, *83*, 1492. doi:10.1139/V05-150

[24] J. M. Buccigross, S. A. Glover, *J. Chem. Soc., Perkin Trans. 2* **1995**, 595. doi:10.1039/P29950000595

[25] J. M. Buccigross, S. A. Glover, G. P. Hammond, *Aust. J. Chem.* **1995**, *48*, 353.

[26] S. A. Glover, in *Merck Index, Organic Name Reactions ONR-43* **2006** (Ed. M. J. O'Neil) (Merck & Co., Inc.: Whitehouse Station, NJ).

[27] R. G. Gerdes, S. A. Glover, J. F. Ten Have, C. A. Rowbottom, *Tetrahedron Lett.* **1989**, *30*, 2649. doi:10.1016/S0040-4039(00)99089-0

[28] J. J. Campbell, S. A. Glover, C. A. Rowbottom, *Tetrahedron Lett.* **1990**, *31*, 5377. doi:10.1016/S0040-4039(00)98076-6

[29] J. J. Campbell, S. A. Glover, G. P. Hammond, C. A. Rowbottom, *J. Chem. Soc., Perkin Trans. 2* **1991**, 2067. doi:10.1039/P29910002067

[30] J. J. Campbell, S. A. Glover, *J. Chem. Soc., Perkin Trans. 2* **1992**, 1661. doi:10.1039/P29920001661

[31] A. M. Bonin, S. A. Glover, G. P. Hammond, *J. Chem. Soc., Perkin Trans. 2* **1994**, 1173. doi:10.1039/P29940001173

[32] S. A. Glover, G. P. Hammond, A. M. Bonin, *J. Org. Chem.* **1998**, *63*, 9684. doi:10.1021/JO980863Z

[33] T. M. Banks, A. M. Bonin, S. A. Glover, A. S. Prakash, *Org. Biomol. Chem.* **2003**, *1*, 2238. doi:10.1039/B301618H

[34] A.-M. E. Gillson, S. A. Glover, D. J. Tucker, P. Turner, *Org. Biomol. Chem.* **2003**, *1*, 3430. doi:10.1039/B306098P

[35] L. E. Andrews, T. M. Banks, A. M. Bonin, S. F. Clay, A.-M. E. Gillson, S. A. Glover, *Aust. J. Chem.* **2004**, *57*, 377. doi:10.1071/CH03276

[36] L. E. Andrews, A. M. Bonin, L. Fransson, A.-M. E. Gillson, S. A. Glover, *Mutat. Res.* **2006**, *605*, 51.

[37] S. A. Glover, A. Rauk, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1740. doi:10.1039/B204232K

[38] M. V. De Almeida, D. H. R. Barton, I. Bytheway, J. A. Ferriera, M. B. Hall, W. Liu, D. K. Taylor, L. Thomson, *J. Am. Chem. Soc.* **1995**, *117*, 4870. doi:10.1021/JA00122A018

[39] L. M. Thomson, M. B. Hall, *J. Phys. Chem. A* **2000**, *104*, 6247. doi:10.1021/JP000623Z

[40] A. Selva, A. Citterio, E. Pella, R. Tonani, *Org. Mass Spectrom.* **1974**, *9*, 1017. doi:10.1002/OMS.1210091008

[41] M. S. Platz, in *Reactive Intermediate Chemistry* **2004**, p. 501 (Eds R. A. Moss, M. S. Platz, M. Jones) (Wiley Interscience: Hoboken, NJ).

[42] A. Srinivasan, N. Kebede, J. E. Saavedra, A. V. Nikolaitchik, D. A. Brady, E. Yourd, K. M. Davies, L. K. Keefer, J. P. Toscano, *J. Am. Chem. Soc.* **2001**, *123*, 5465. doi:10.1021/JA002898Y

[43] W. A. Wasylenko, N. Kebede, B. M. Showalter, N. Matsunaga, A. P. Miceli, Y. Liu, L. R. Ryzhkov, C. M. Hadad, J. P. Toscano, *J. Am. Chem. Soc.* **2006**, *128*, 13142. doi:10.1021/JA062712G

[44] R. O. C. Norman, R. Purchase, C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1972**, 1701. doi:10.1039/P19720001701

[45] E. M. Y. Quinga, G. D. Mendenhall, *J. Org. Chem.* **1985**, *50*, 2836. doi:10.1021/JO00216A005

[46] S. R. Sandler, W. Karo, *Organic Functional Group Preparations* **1972**, Vol. III (Academic Press: New York, NY).
[47] C. D. Hurd, M. F. Dull, *J. Am. Chem. Soc.* **1932**, *54*, 3427. doi:10.1021/JA01347A066
[48] K. U. Ingold, J. C. Walton, in *Landolt Börnstein II 17c* **1987** (Springer Verlag: Berlin).
[49] S. A. Glover, A. Goosen, C. W. McCleland, J. L. Schoonraad, *J. Chem. Soc., Perkin Trans. 2* **1986**, 645. doi:10.1039/P29860000645
[50] A. R. Forrester, E. M. Johansson, R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1* **1979**, 1112. doi:10.1039/P19790001112
[51] A. R. Forrester, H. Irikawa, *J. Chem. Soc. Chem. Commun.* **1981**, 253. doi:10.1039/C39810000253
[52] T. Koenig, J. A. Hoobler, W. R. Mabey, *J. Am. Chem. Soc.* **1972**, *94*, 2514. doi:10.1021/JA00762A057
[53] T. Koenig, J. A. Hoobler, C. E. Klopfenstein, G. Heddon, F. Sunderman, B. R. Russell, *J. Am. Chem. Soc.* **1974**, *96*, 4573. doi:10.1021/JA00821A036
[54] J. H. Cooley, M. W. Mosher, M. A. Khan, *J. Am. Chem. Soc.* **1968**, *90*, 1867. doi:10.1021/JA01009A032
[55] K. M. Koshy, R. E. Robertson, *Can. J. Chem.* **1974**, *52*, 2485. doi:10.1139/V74-362
[56] C. H. Hauser, D. S. Hoffenberg, *J. Am. Chem. Soc.* **1955**, *20*, 1491.
[57] G. D. Mendenhall, *J. Am. Chem. Soc.* **1974**, *96*, 5000. doi:10.1021/JA00822A054
[58] C. A. Ogle, S. W. Martin, M. P. Dziobak, M. W. Urban, G. D. Mendenhall, *J. Org. Chem.* **1983**, *48*, 3728. doi:10.1021/JO00169A023