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Full Paper

Formation and HERON Reactivity of Cyclic *N,N*-Dialkoxyamides

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Cyclic *N,N*-dialkoxyamides have been made, for the first time, by hypervalent iodine oxidation of β- and γ-hydroxyhydroxamic esters **17**, **19**, and **21**. The fused γ-lactam products, *N*-butoxy- and *N*-benzyloxybenzisoxazolones (**22a** and **22b**), are stable while alicyclic γ-lactam and δ-lactam products, **24** and **25**, although observable by NMR spectroscopy and ESI-MS are unstable at room temperature, undergoing HERON reactions. The γ-lactam **24** undergoes exclusive ring opening to give a butyl ester-functionalised alkoxynitrene **28**. The δ-lactam **25**, instead, undergoes a HERON ring contraction to give butyrolactone (**27**). The structures of model γ- and δ-lactams **6**, **7**, and **8** have been determined at the B3LYP/6-31G(d) level of theory and the γ-lactams are much more twisted than the acyclic *N,N*-dimethoxyacetamide (**5**) resulting in a computed amidicity for **6** of only 25 % that of *N,N*-dimethylacetamide (**3**). The HERON reactions of *N,N*-dimethoxyacetamide (**5**) and alicyclic models **6** and **8** have been modelled computationally. The facile ring opening of **6** ($E_A = 113\ kJ\ mol^{-1}$) and ring contraction of **8** ($E_A = 145\ kJ\ mol^{-1}$) are predicted well, when compared with the HERON rearrangement of **5** ($E_A = 178\ kJ\ mol^{-1}$).

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Introduction

Recently we reported an efficient synthesis, the structure, and the thermal reactivity of an unusual class of amide derivatives, *N,N*-dialkoxyamides **1** (Chart 1).[1,2] These are the least studied members of the class of anomeric amides **2** (Chart 1), amides bearing two heteroatoms at the amide nitrogen.[1–26] In general, bisheteroatom-substituted amides are characterised by a reduced amide resonance on account of the electron demand of the electronegative atoms on nitrogen. The amide nitrogen lone pair, which normally resides in a $2p_z$ orbital on an sp^2 hybridised nitrogen and strongly interacts with the corresponding orbital on the carbonyl carbon, gains 's' character and not only do the nitrogens tend towards pyramidality, but the lone pair is localised on nitrogen with attendant loss of amide resonance.[6,16,17] Bisalkoxyl substitution results in the largest loss of resonance of all the classes of anomeric amides we have studied to date.[2]

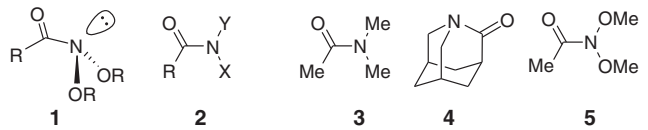


Chart 1.

Crystallographic studies[2] confirm that *N,N*-dialkoxyamides possess highly pyramidalised nitrogens (average angles at nitrogen of 110.4° and 111.5°) and long N–C bonds (1.42 and 1.41Å). In addition a reduced amide resonance is evident from dynamic ^{1}H NMR studies in which the amide rotational barrier is too low to measure and infrared data reveal high carbonyl vibrational frequencies (between 1710–1715 cm^{-1}).[1,2,6,17] As with almost all anomeric amides, the nitrogen lone pair, while residing in an sp^3 hybrid orbital, is still largely aligned with the amide carbon $2p_z$ orbital as crystal structures demonstrate that the twist angles are small (14° and 7°).[2]

These properties of *N,N*-dialkoxyamides are well predicted computationally at the B3LYP/6-31G(d) level of theory.[2,5] Furthermore, we have recently devised a quantitative measure of amide character for a wide range of amides and lactams.[2,27] Relative to the iconic *N,N*-dimethylacetamide (**3**), which we and others[28] have designated as having 100 % amidicity, and the completely twisted amide 1-aza-2-adamantanone (**4**), with by definition 0 % amidicity, *N,N*-dimethoxyacetamide (**5**) is computed to have an amidicity of just 46 % and to have lost more than half the resonance embodied in *N,N*-dimethylacetamide.[2] It is interesting that, while amide character is diminished by reduced overlap as a consequence of the change in hybridisation at nitrogen, this does not account for all of the decrease in amidicity. Loss of resonance energy in *N,N*-dimethylacetamide as a result of complete pyramidalisation at nitrogen is estimated at ~25 $kJ\ mol^{-1}$ or about one-third that of the planar structure.[27] The additional loss of resonance in *N,N*-dialkoxyamides

is a result of further localisation of the nitrogen lone pair on nitrogen as a consequence of the inductive effect of both oxygen atoms.[2]

Thermal reactivity of *N,N*-dialkoxyamides involves homolysis to generate alkoxyl and *N*-alkoxyamidyl radicals.[1] Certain bisheteroatom-substituted amides have been found to undergo the unusual HERON (from *He*teroatom *r*earrangements *o*n *n*itrogen) reaction† (Fig. 1).[14,15,29] *N*-Alkoxy-*N*-aminoamides generate esters and aminonitrenes in a concerted process involving anomerically driven migration of the alkoxyl group from nitrogen to the carbonyl.[4,8,9,14] The high energy nitrogen lone pair strongly destabilises the adjacent N–O bond and these reactions occur at room temperature. *N*-Acyloxy-*N*-alkoxyamides also undergo HERON reactions yielding anhydrides and alkoxynitrenes but these reactions occur at higher temperatures and in competition with homolytic reactions.[18] The HERON in this case is driven by the weak N–O-acyl bond. *N,N*-Dialkoxyamides studied to date do not undergo HERON reactions.[1] Migration of an alkoxyl group requires anomeric destabilisation of an N–O bond and the geminal oxygen atom lone pairs are too low in energy in this case.

In this paper we describe the first synthesis of cyclic *N,N*-dialkoxyamides which, in certain cases, undergo thermal HERON reactions. These reactions are described along with the theoretical differences between acyclic and cyclic forms of these anomeric amides.

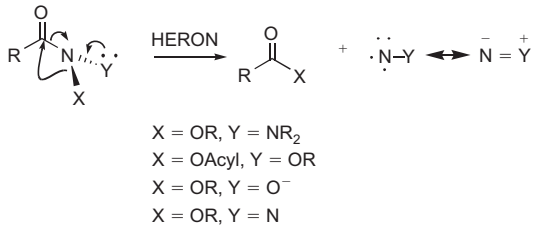


Fig. 1. The generalised HERON reaction of anomeric amides.

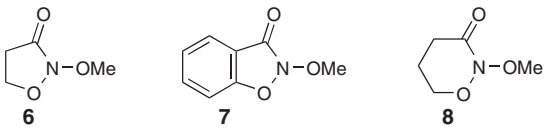


Chart 2.

Results and Discussion

Several cyclic forms of *N,N*-dialkoxyamides **6**–**8** (Chart 2), together with *N,N*-dimethoxyacetamide (**5**)[2] have been studied computationally and structures of the B3LYP/6-31G(d)-optimised geometries for **6**, **7**, and **8**, together with that of **5** are presented in Table 1. The Winkler–Dunitz amide twist parameter (τ) and nitrogen pyramidality index (χ) are defined in Fig. 2.[30,31]

While they possess broadly similar properties to acyclic *N,N*-dimethoxyacetamide (**5**) in that all lactam nitrogens are strongly pyramidal, the extent of twist in the γ-lactam forms is significantly greater than in the acyclic analogue. The twist angle (τ) for model *N*-methoxy γ-and δ-lactams **6**, **7**, and **8** are respectively

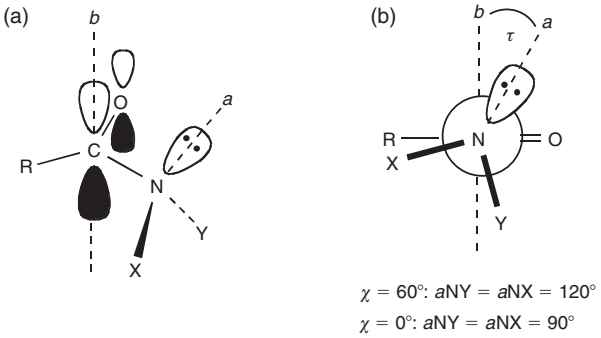


Fig. 2. Interpretation of the Winkler–Dunitz twist and pyramidality indices, τ and χ.[30,31] (a) Orbital axes in an anomeric amide and (b) angular projections along the N–C bond.

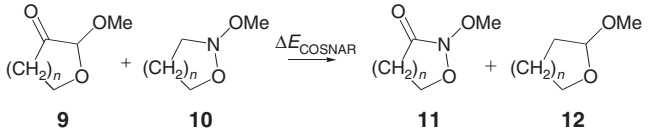
Table 1. B3LYP/6-31G(d) optimised geometries for *N,N*-dimethoxyacetamide (5), γ-lactams 6 and 7, and δ-lactam 8

Compound	τ^A [deg.]	χ^B [deg.]	θ^C [deg.]	N–C [Å]	C–O [Å]	N–O_{exo} [Å]	N–O_{endo} [Å]
5[D]	8.5	48.1	114.3	1.415	1.214	1.388(*syn*)	1.412(*anti*)
6	−36.7	64.6	106.8	1.465	1.200	1.428	1.419
7	−17.9	61.2	109.3	1.461	1.210	1.373	1.477
8	12.6	60.7	110.3	1.427	1.209	1.379	1.46

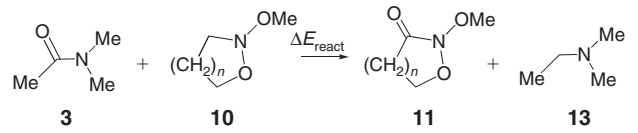
[A]Winkler–Dunitz twist parameter (Fig. 2).[30,31]
[B]Winkler–Dunitz pyramidality index (Fig. 2).[30,31]
[C]Average angle at nitrogen.
[D]Previously published data.[2]

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

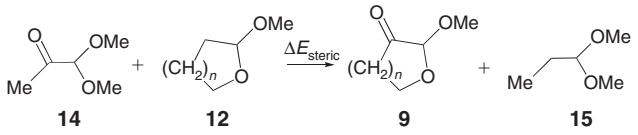
37°, 18° and 12° as compared with 8° for **5**. We recently reported that amidicities of amides can be estimated computationally by two independent isodesmic reactions, carbonyl substitution nitrogen atom replacement (COSNAR) and a *trans*-amidation process.[27] COSNAR, as applied to lactams **6** and **8**, measures the stabilisation derived from the isodesmic reaction in Eqn 1 and is a direct measure of resonance stabilisation.[32–34] The *trans*-amidation reaction in Eqn 2 measures the destabilisation in the lactams relative to *N,N*-dimethylacetamide (**3**).[27] Total loss of resonance for fully twisted lactam 1-aza-2-adamantanone (**4**) equates with a loss of 76.0 kJ mol^{-1},[27] thus for lactams **6** and **8** the residual resonance stabilisation is the negative of the difference between this value and that determined from Eqn 2. By this method, a further destabilisation of the carbonyl owing to the inductive effect of two β-oxygens ($\Delta E_{inductive}$, estimated previously at 17.88 kJ mol^{-1})[2] and specific steric effects, (ΔE_{steric}) must be offset to give the residual resonance stabilisation from Eqn 4.[27] For *N,N*-dimethylacetamide (**3**) the COSNAR and *trans*-amidation resonance energies are respectively −77.53 and −76.01 kJ mol^{-1} and amidicities for **6** and **8** by each method are determined as a percentage of these values. The steric correction for each lactam is estimated from the isodesmic equation in Eqn 3. From B3LYP/6-31G(d) data in Table 2 the amidicity for γ-lactam **6** is less than half that of *N,N*-dimethoxyacetamide (**5**) by both the COSNAR and *trans*-amidation methods while that for **8** is similar to that of *N,N*-dimethoxyacetamide (**5**). As has been demonstrated for a range of amides and lactams, amidicities by the COSNAR and *trans*-amidation methods are similar, as found for both lactam forms.



9 **10** **11** **12** (1)



3 **10** **11** **13** (2)



14 **12** **9** **15** (3)

$$\text{Residual resonance (kJ mol}^{-1}) = -76.01 + (\Delta E_{react} - \Delta E_{steric} - \Delta E_{inductive}) \quad (4)$$

The reduction in amidicity in the γ-lactam **6** can be largely attributed to the significant degree of twist about the N–C bond in this case ($\tau = 37°$, Table 1). Fig. 3 illustrates the B3LYP/6-31G(d) energy surface generated by deformation of *N,N*-dimethoxyacetamide (**5**). It differs markedly from that computed for *N,N*-dimethylacetamide (**3**) where the lowest energy form is planar ($\chi = \tau = 0°$).[27] The lowest energy form for *N,N*-dimethoxyacetamide has a Winkler–Dunitz pyramidality index of $\chi = 48°$ and twist index of $\tau = 8°$ and a twist of ~40° about the N–C axis in the pyramidal structure would further reduce resonance by an estimated 20 kJ mol^{-1}. In the case of **6**, the twist manifests in a very long N–C bond of 1.465 Å for **6** as opposed to 1.415 Å for *N,N*-dimethoxyacetamide (**5**) (Table 1).

Not surprisingly, the δ-lactam amidicity is very similar to that of the acyclic form *N,N*-dimethoxyacetamide (47 %[2]) since the amide moiety in this lactam exhibits a very similar twist and pyramidality to the acyclic form. The N–C bond lengths in δ-lactam (1.427 Å) and *N,N*-dimethoxyacetamide (1.415 Å) are similar.

Table 2. B3LYP/6–31G(d) energies for lactams 6 and 8 and relevant COSNAR and *trans*-amidation structures, reaction energies from Eqns 1–4, and amidicities

Structure	Energy [au]	Energy [kJ mol^{-1}]	Amidicities [%]
N-Methoxy-γ-lactam **6** [**11** ($n = 1$)]	−436.939062		
2-Methoxy-3-tetrahydrofuranone (**9**) ($n = 1$)	−420.984956		
N-Methoxyisoxazolidine (**10**) ($n = 1$)	−362.928153		
2-Methoxytetrahydrofuran (**12**) ($n = 1$)	−346.981671		
N,N-Dimethylacetamide (**3**)	−287.830189		
N,N-Dimethylethylamine (**13**)	−213.788638		
1,1-Dimethoxypropanone (**14**)	−422.190664		
1-Methoxy-1-propyl methyl ether (**15**)	−348.185186		
N-Methoxy-δ-lactam **8** [**11** ($n = 2$)]	−476.254615[A]		
2-Methoxy-4,5-dihydro-(2*H*)pyran-3-one (**9**) ($n = 2$)	−460.29646[A]		
N-Methoxy-3,4,5,6-tetrahydrooxazine (**10**) ($n = 2$)	−402.241932[A]		
2-Methoxy-3,4,5,6-tetrahydropyran (**12**) ($n = 2$)	−386.298084[A]		
Eqn 1 ($n = 1$)	−0.007624	−20.01	25.8
Eqn 2 ($n = 1$)	0.030642	80.44	
Eqn 3 ($n = 1$)	0.002193	5.76	
Eqn 4 ($n = 1$)		−19.22	25.3
Eqn 1 ($n = 2$)	−0.014307	−37.56	49.4
Eqn 2 ($n = 2$)	0.028868	75.78	
Eqn 3 ($n = 2$)	0.007102	18.65	
Eqn 4 ($n = 2$)		−36.76	48.4
Eqn 4 *N,N*-dimethoxyacetamide (**5**)[B]		−35.87	47.2

[A]For comparison with δ-lactam **8**, all structures bear an equatorial methoxy group.
[B]Previously published data.[2]

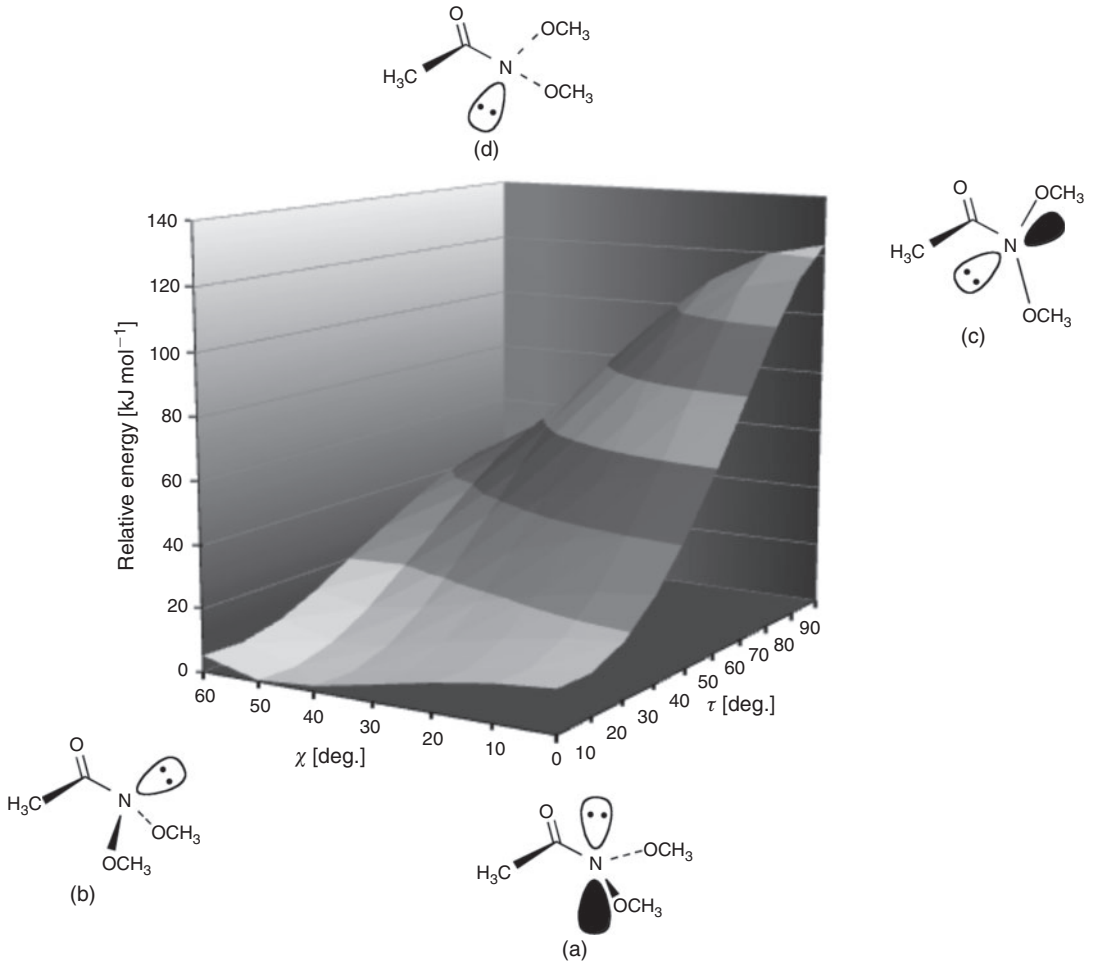


Fig. 3. B3LYP/6-31G(d) energy surface for deformation of *N,N*-dimethoxyacetamide (**5**). χ and τ are the Winkler–Dunitz pyramidalisation and twist parameters in degrees. Structures correspond to (a) the planar untwisted form with an sp^2 hybridised nitrogen; (b) an untwisted conformer with an sp^3 hybridised nitrogen; (c) a fully twisted form with sp^2 hybridised nitrogen; and (d) a fully twisted form with an sp^3 hybridised nitrogen.

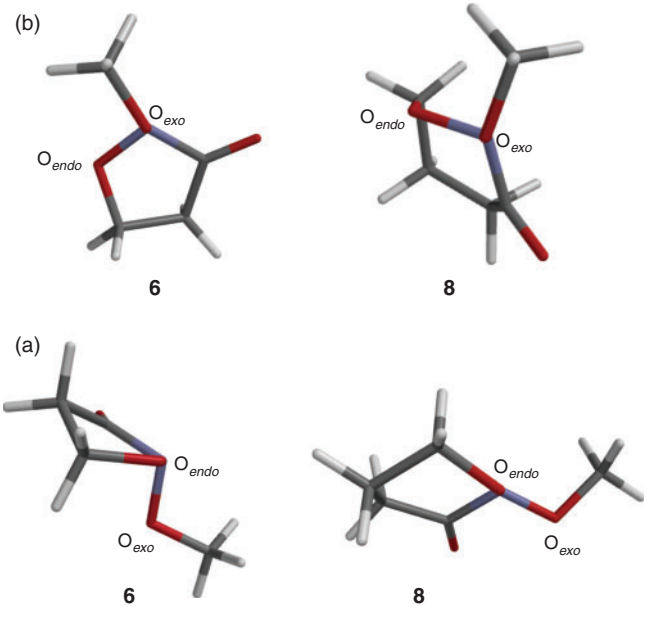
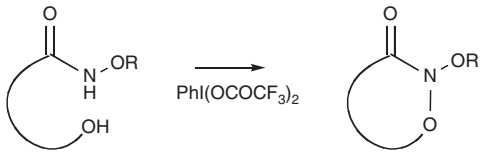


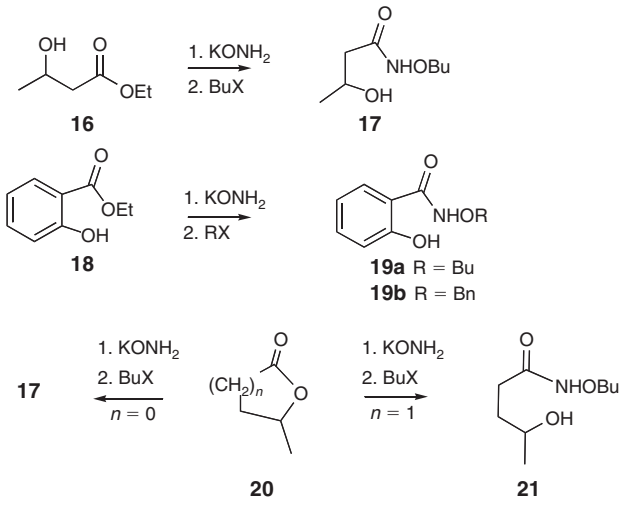
Fig. 4. Optimised geometries for model γ-lactams **6** and **8** with projections along the (a) O_{endo}–N and (b) O_{exo}–N bonds.



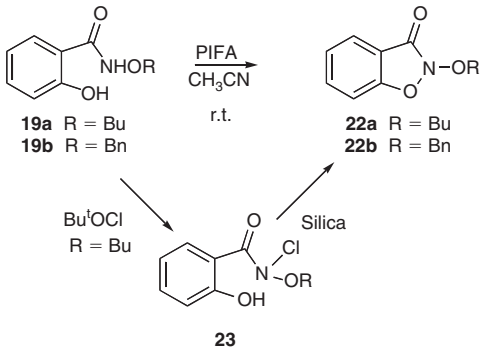
Scheme 1.

From projections illustrated in Fig. 4a and b, it is clear that in the γ-lactam form, there is a mutual n_O–σ^*_{NO} anomeric overlap. Both p-type oxygen lone pairs are nicely aligned with the adjacent N–O σ-bond and the exocyclic and endocyclic NO bonds differ in length by only 0.01 Å. However, in the δ-lactam, one anomeric alignment is dominant; that between a p-type lone pair on the exocyclic oxygen and the endocyclic N–O bond. The p-type lone pair on the endocyclic oxygen is actually orthogonal to the exocyclic N–O bond. Consistent with this, the exocyclic N–O bond is 0.08 Å shorter than the endocyclic N–O bond.

Since *N,N*-dialkoxyamides are readily synthesised by phenyliodine bis(trifluoroacetate) (PIFA) oxidation of hydroxamic esters in the presence of alcohols,[1] attempted generation of cyclic systems employed oxidative intramolecular cyclisation of β- and γ-hydroxyhydroxamic esters according to Scheme 1.



Scheme 2.



Scheme 3.

Alkoxyamination of ethyl 3-hydroxybutanoate (**16**), ethyl salicylate (**18**), and β-butyro- and γ-valerolactones **20** ($n = 0$ and 1) afforded the hydroxamic ester precursors **17**, **19**, and **21** (Scheme 2).

PIFA oxidation of *N*-butoxysalicamide (**19a**) in acetonitrile afforded a 30% yield of the γ-lactam 2-butoxy-3(*2H*)-benzisoxazolone (**22a**) together with a large quantity of unidentified polymeric material which may be accounted for by oxidation of the phenolic group. Similarly, benzyloxysalicamide (**19b**) afforded 2-benzyloxy-3(*2H*)-benzisoxazolone (**22b**) in 20% yield (Scheme 3). γ-Lactams **22a** and **22b** exhibited a characteristically high carbonyl stretch frequency at 1740 and 1743 cm^{-1} as well as a carbonyl carbon resonance at 173 ppm very close to the chemical shift of those in acyclic *N*,*N*-dialkoxybenzamides (174 ppm).[1] The cyclic dialkoxyamide **22a** could also be accessed by the *N*-chloroamide **23**. Chlorination of *N*-butoxysalicamide with *tert*-butylhypochlorite afforded **23**, which cyclised cleanly to lactam **22a** upon stirring with, or elution on, silica gel (Scheme 3).

Treatment of β- and γ-hydroxyhydroxamic esters **17** and **21** with PIFA afforded unstable intermediates which were consistent with cyclised forms **24** and **25** respectively (Chart 3). NMR analysis of the product mixture from oxidation of β-hydroxyhydroxamic ester **17** immediately after workup indicated the expected formation of iodobenzene, consumption of starting material, and generation of γ-lactam **24** as evidenced by a clear ABX spin system centred on δ4.65 (5-H^X as a ddq, *J* 9.7, 5.7, and 6.1), δ2.74 (4-H^A as a dd, *J* 17.1 and 5.7) and δ2.42 (4-H^B as a dd, *J* 17.1 and 9.7) (Fig. 5a, Fig. 6a). The 5-methyl group and the 1′-oxymethylene on the butyl chain appeared as a new doublet at δ1.41 and a new triplet at δ4.00 respectively. γ-Lactam **24** decomposed rapidly and completely upon standing at room temperature or in $CDCl_3$ giving a mixture of diastereomers of **26**, each of which exhibited an ABX spin system centred on δ5.5–5.6 (overlapping 3-H^X), δ2.9−3.1 (overlapping 2-H^A, dd, J_{AB} 17.1 and 16.6 and J_{AX} 9.3 and 8) and δ2.5−2.6 (overlapping 2-H^B, dd, J_{BA} 17.1 and 16.6 and J_{BX} 4.7 and 6.3) (Fig. 5b, Fig. 6b). The 1′-oxymethylenes of both diastereomers overlapped at δ4.0–4.13 and the 4-methyl protons shifted to lower frequency and appeared as overlapping doublets at δ1.35. Analysis of the reaction mixture by electrospray ionisation–mass spectrometry (ESI-MS) indicated two prominent ions at *m/z* 347.2 and 715.5 corresponding exactly to $[M + H]^+$ and $[2M + Na]^+$ for the hyponitrite **26**. The methyne proton shift to higher frequency in **26** is similar to that found for the methylene of 4-chlorobenzylhyponitrite, which resonated ~0.8 ppm higher than that in 4-chlorobenzyl alcohol.[18] A typical ester carbonyl carbon was evident at 169.8 ppm in a ^{13}C NMR spectrum of the reaction mixture. Purification of a reaction mixture by centrifugal chromatography afforded a clean diastereomeric mixture (Fig. 5c), the composition of which was confirmed by high resolution ESI-MS. A minor unidentified decomposition product with a similar methine resonance at a slightly lower frequency than that in **26** was also present.

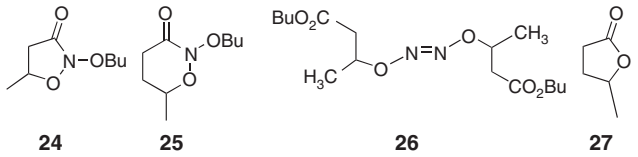


Chart 3.

Further support for formation of γ-lactam **24** came from an NMR study of the reaction of **17** with half an equivalent of PIFA in CD_3CN, which gave immediately a clean 50 : 50 mixture of unreacted hydroxamic ester **17** and γ-lactam **24** together with iodobenzene (Fig. 5d). ESI-MS of this mixture showed ions at *m/z* 176 and 198 attributable to $[M + H]^+$ and $[M + Na]^+$ ions for starting material **17** and *m/z* 196 and 347 attributable to $[M + Na]^+$ and $[2M + H]^+$ for γ-lactam **24**.

Formation of **24** can be accounted for by intramolecular cyclisation of the β-hydroxyl group onto nitrogen as initially proposed. However, **24** appears to be thermally labile at room temperature and an intramolecular HERON rearrangement would afford the alkoxynitrene **28** which upon dimerisation gives two diastereomers of **26** (Scheme 4). Alkoxynitrenes are known to dimerise to hyponitrites although their most stable form has a triplet ground state.[35–37] Formation of **26** must involve a singlet to triplet (S–T) transition after the HERON reaction.

The ring opening of γ-lactam **24** is clearly a more facile process than opening of the corresponding γ-lactam ring in benzisoxazolones **22**. Ring opening in that case would require an $n_{O_{endo}}–\sigma^*_{NO_{exo}}$ anomeric interaction and delocalisation of the endocyclic oxygen lone pair onto the aromatic ring would oppose this effect. The ground state structure of the model **7** supports this as it indicates a strong *exo*-anomeric effect; the exocyclic N–O bond is a full 0.1 Å shorter than the endocyclic N–O bond (Table 1).

Treatment of γ-hydroxyester **21** with PIFA afforded a mixture of iodobenzene and two major components, one of

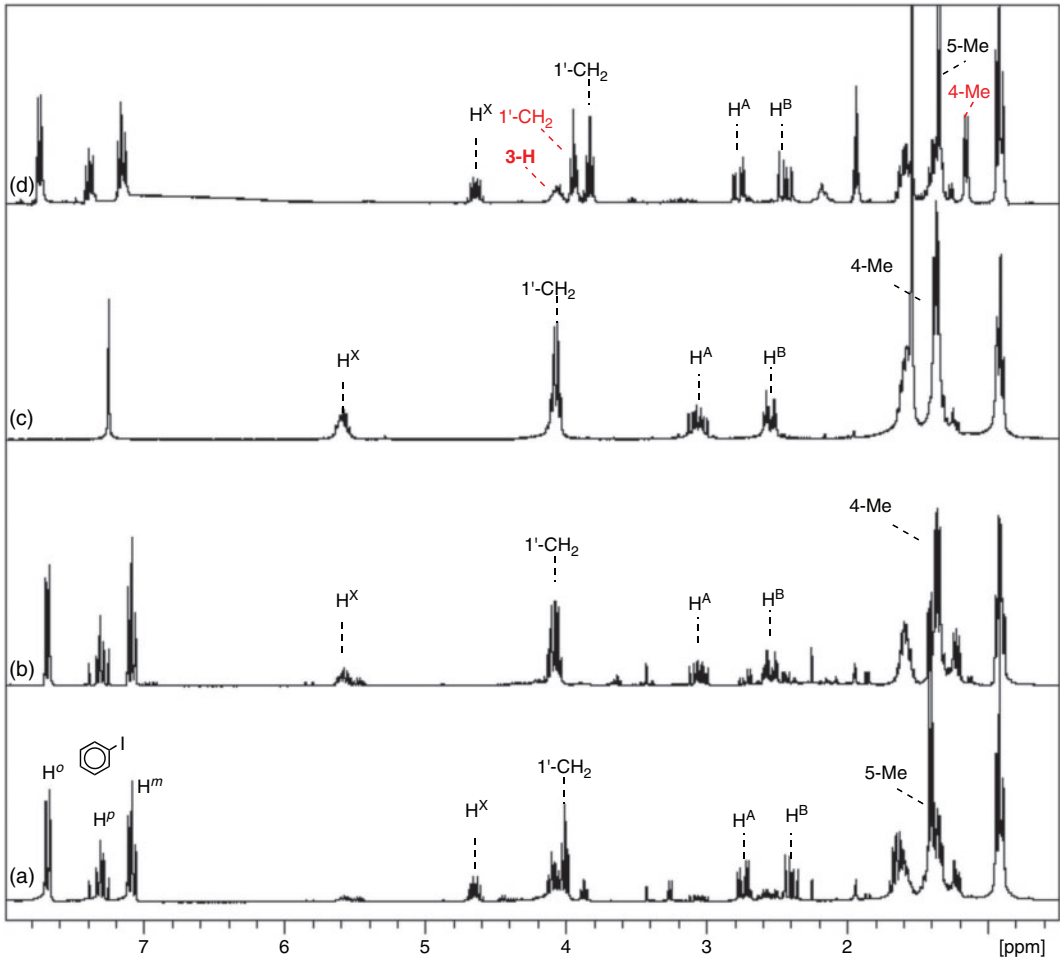


Fig. 5. ^{1}H NMR spectra of mixtures from PIFA oxidation of **17**. (a) Mostly γ-lactam **24** (see Fig. 6a); (b) mostly hyponitrite **26** (see Fig. 6b); (c) clean hyponitrite **26** in $CDCl_3$; and (d) 50 : 50 mix of **17** and **24** in CD_3CN (resonances for **17** in red; see Fig. 6a).

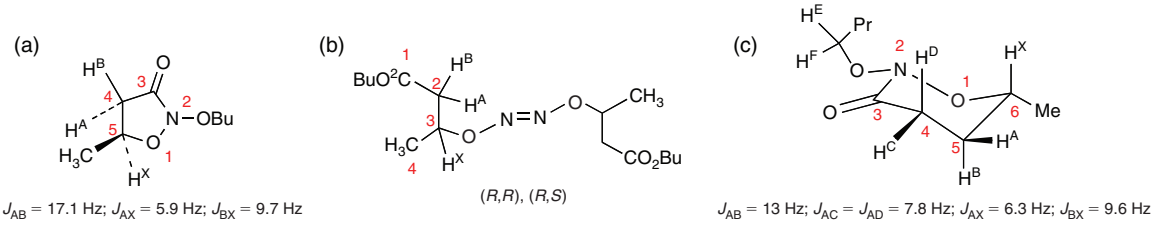
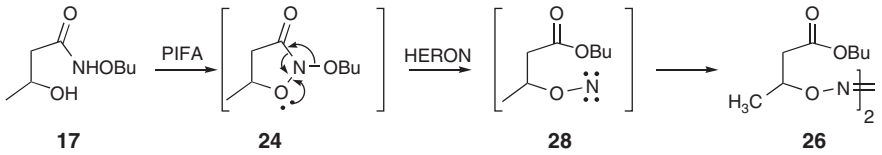


Fig. 6. Proton designations and relevant proton–proton coupling data for (a) γ-lactam **24**, (b) hyponitrite **26** and (c) δ-lactam **25**.



Scheme 4.

which was γ-valerolactone (**27**). An unstable product, from which the lactone **27** formed upon standing, displayed resonances in the ^{1}H NMR spectrum characteristic of δ-lactam **25** (Fig. 7, Fig. 6c). Notably, a methine proton at δ4.3 exhibited similar coupling to that of H^X in the γ-lactam **24**, namely a ddq (*J* 9.6, 6.3 and 6.6) and together with protons centred at δ1.9 and δ2.1 was part of an ABX spin system. The exocyclic 6-methyl group appeared at δ1.34. Interestingly, the oxymethylene protons H^E and H^F (Fig. 6c) at δ4.0 were diastereotopic and resonated as a tight ABX_2 spin system (J_{AB} 10.1, J_{vic} 6.7). This is a further manifestation of the cyclic, chiral nature of **25** as such diastereotopicity is not evident in analogous acyclic *N,N*-dialkoxyamides.[1] Analysis of a clean multiplet at δ2.1, which was attributed to H^A, and a *trans*-diaxial coupling of 9.6 Hz between H^X and H^B indicated that **25** was largely in the chair conformation shown in Fig. 6c and in the B3LYP/6-31G(d)

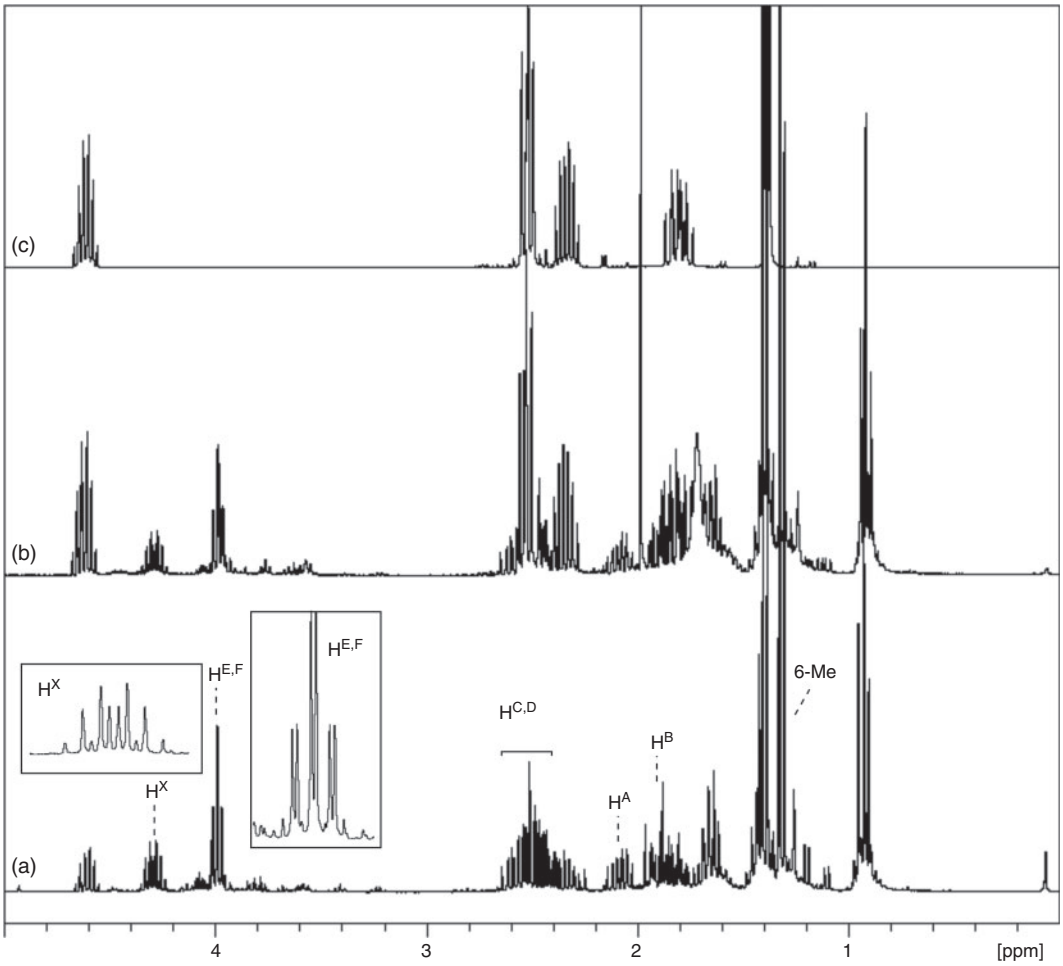
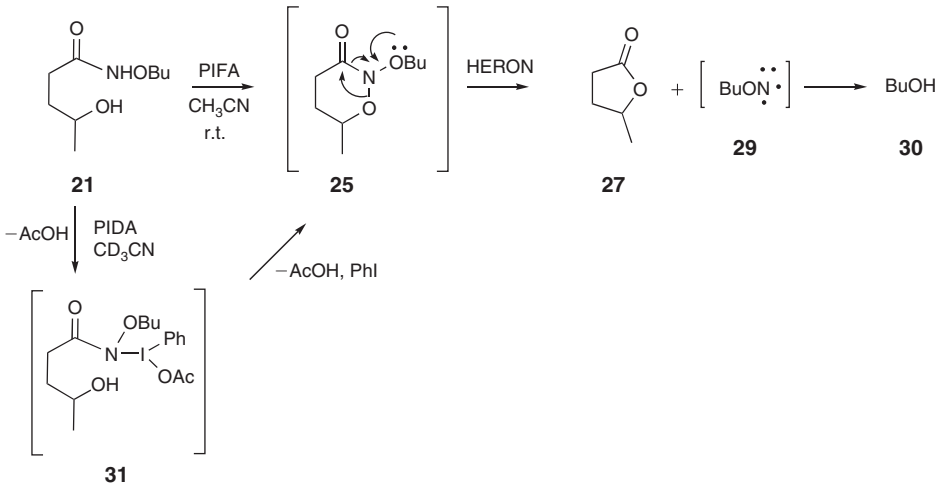


Fig. 7. ^{1}H NMR spectra ($CDCl_3$) of mixtures of δ-lactam **25** and γ-valerolactone (**27**). (a) Directly after PIFA oxidation of **21**; (b) after standing for several hours; and (c) reference γ-valerolactone (**27**).



Scheme 5.

optimised geometry for model δ-lactam **8** depicted in Table 1. Signals attributable to δ-lactam **25** diminished upon formation of the γ-lactone **27**.

A reaction in CD_3CN in the probe of the NMR machine was analysed by ESI-MS directly after addition of PIFA. NMR spectroscopy indicated the presence of δ-lactam **25** and γ-valerolactone (**27**) in a 3 : 1 ratio. ESI-MS indicated a prominent ion for **25** at *m*/*z* 188 ($[M+H]^+$) together with one for the lactone at *m*/*z* 101 ($[M+H]^+$).

The facile transformation of δ-lactam **25** into the γ-lactone **27** suggests that **25** also undergoes a HERON reaction but in this case the endocyclic oxygen migrates in preference to the exocyclic oxygen (Scheme 5). No evidence for formation of the homologue of hyponitrite **26** could be found upon complete

decomposition of **25**. Butoxynitrene products were not observed post workup.

A reaction of **21** with phenyliodine diacetate (PIDA) carried out in CD_3CN and monitored by ^1H NMR spectroscopy led to slower consumption of starting material and formation of two transient intermediates. As in the PIFA reaction, the δ-lactam **25** (labelled in Fig. 8f) was generated, as evidenced by the characteristic methine at δ4.25, oxymethylene triplet at δ3.94, and exocyclic methyl at δ1.27. The δ-lactam **25** was converted into γ-lactone **27** in a consecutive reaction with its formation (Fig. 8d–h). However disappearance of starting material coincided with formation of another intermediate, which was a precursor to the δ-lactam **25** and which was consistent with formation of *N*-(acetoxyiodobenzene)-γ-hydroxyvaleramide (**31**) (Fig. 8a–d). Compound **31** (labelled in Fig. 8d) exhibited a different higher frequency oxymethylene signal at δ4.05 as well as a new exocyclic methyl doublet in a similar position to that of starting material **21**, both of which disappeared in concert with formation of δ-lactam **25** and lactone **27**. Butanol **30** (labelled in Fig. 8g), possibly from nitrene **29**, appeared to form in conjunction with the lactone **27** (labelled in Fig. 8h).

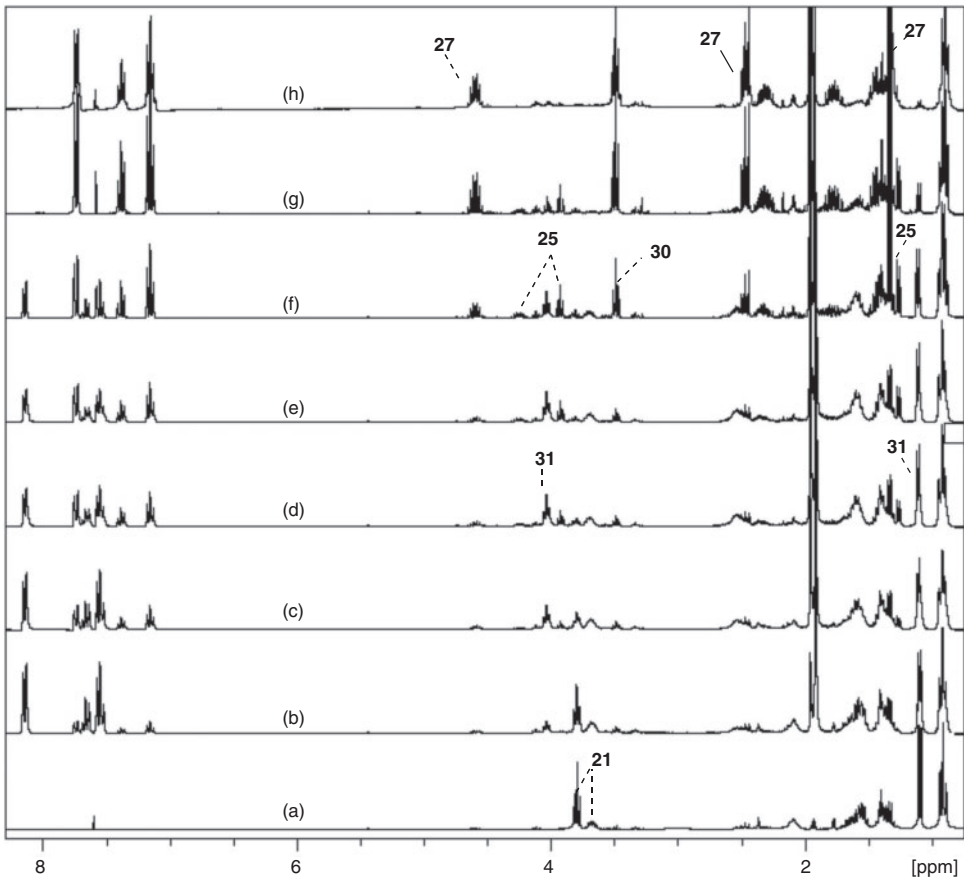


Fig. 8. ^1H NMR spectra (CD_3CN) of the reaction mixtures from PIDA oxidation of **21** over 48 h. (a) Acyclic hydroxamic ester **21**; (b), (c) and (d) formation of adduct **31**; (f) conversion of adduct **31** to δ-lactam **25**; (g) and (h) mostly γ-valerolactone **27**.

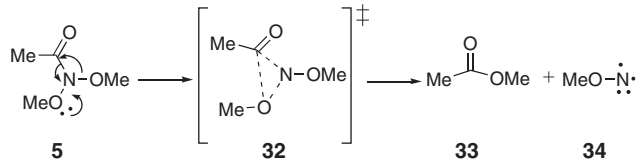
Table 3. B3LYP/6-31G(d) derived energies and properties of HERON reactions of *N,N*-dimethoxyacetamide (5), γ-lactam 6, and δ-lactam 8[A]
Activation energies (E_A), enthalpies ($\Delta H^{\ddagger}$) and free energies of activation ($\Delta G^{\ddagger}$), singlet and triplet reaction energies (ΔE_S and ΔE_T), singlet and triplet reaction enthalpies (ΔH_S and ΔH_T) and singlet and triplet reaction free energies (ΔG_S and ΔG_T) in kJ mol^{-1}; transition state imaginary frequencies (TS_i)

Reactant	E_A	$\Delta H^{\ddagger B}$	$\Delta G^{\ddagger C}$	ΔE_S^D	$\Delta H_S^{B,D}$	$\Delta G_S^{C,D}$	ΔE_T^E	$\Delta H_T^{B,E}$	$\Delta G_T^{C,E}$	TS_i [cm^{-1}]
5 Scheme 6	178.9	171.0	170.7	115.2	101.3	139.3	41.2	29.8	68.0	**32** 321
6 Scheme 7	113.1	108.1	105.5	71.6	68.2	63.2	11.6	9.6	5.2	**35** 256
6 Scheme 8	197.7	192.0	188.1	177.0	166.9	108.2	103.0	95.4	36.9	**37** 326
8 Scheme 9	136.5	131.4	129.5	64.2	54.8	48.3	13.4	9.2	3.5	**39** 336
8 Scheme 10	145.1	139.2	136.0	115.3	105.1	46.0	41.3	33.6	−25.2	**41** 323

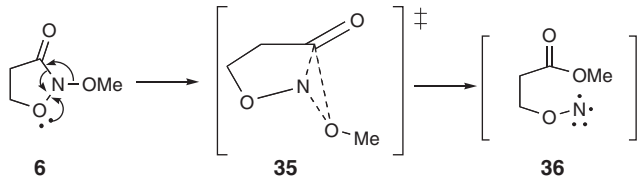
[A]B3LYP/6-31G(d) energies of reactants, transition states, rearrangement products and thermal and entropy corrections are provided as Supplementary Material together with geometries.
[B]Temperature correction at 298.15 K.
[C]Temperature and entropy correction at 298.15 K.
[D]Reaction energies of singlet nitrene.
[E]Reaction energies after nitrene singlet to triplet (S–T) relaxation.

The ring opening of γ-lactam **24** and ring contraction of δ-lactam **25** constitute the first observation of HERON reactivity of *N,N*-dialkoxyamides, which hitherto have been found to undergo thermal N–O homolysis at higher temperatures.[1] The energetics for HERON reactions of models *N,N*-dimethoxyacetamide (**5**), γ-lactam **6**, and δ-lactam **8** computed at the B3LYP/6-31G(d) level are given in Table 3. For the lactams **6** and **8** the energetics of both HERON ring-opening and ring-contraction pathways have been determined. All transition states possessed one imaginary frequency corresponding to the reaction coordinate.

The computed activation barrier for formation of methyl acetate (**33**) and methoxynitrene (**34**) from *N,N*-dimethoxyacetamide (**5**) according to Scheme 6 ($E_A = 179$ or 171 kJ mol^{-1} with enthalpy and entropy correction at 298.15 K) is high when compared with migration of a methoxyl group in bisheteroatom-substituted amides with nitrogen involvement (*N*-methoxy-*N*-(dimethylamino)formamide has a computed barrier of just 89.5 kJ mol^{-1}, which has been experimentally verified[9,14,16]). Migration of methoxyl in *N*-formyloxy-*N*-methoxyformamide has a similar barrier ($E_A = 180$ kJ mol^{-1}) but here the formyloxyl group is predicted to migrate preferentially ($E_A = 163$ kJ mol^{-1}) as has been observed in the thermal reactions of *N*-acyloxy-*N*-alkoxyamides.[14,18]



Scheme 6.



Scheme 7.

The activation barrier to ring opening in **6** to singlet nitrene **36** according to Scheme 7 has been computed to be only 113 kJ mol^{-1} (106 kJ mol^{-1} with enthalpy and entropy correction at 298.15 K) and although it is significantly endothermic, the overall process is slightly endothermic after S–T relaxation.

Analysis of the ground state structure of **6** and the transition state structure **32** for methoxyl migration in *N,N*-dimethoxyacetamide provides a rationale for this difference in activation barriers. At the transition state for methoxyl migration in **5** there is extensive rotation about the N–C bond and loss of most residual stabilisation as a result of conjugation between the nitrogen lone pair and the carbonyl carbon (Fig. 9a, b). This is common to all HERON reactions.[9,14] Fig. 3 illustrates that such rotation (from pyramidal, untwisted form (b) to pyramidal, twisted form (d)) requires ~45 kJ mol^{-1}. The ground-state structure for γ-lactam **6** is depicted in Table 1 and Fig. 4a, b and the transition state for methoxyl migration in γ-lactam **6** is shown in Fig. 10a, b. It is clear that the transition state can be achieved without any significant degree of twist about the N–C bond. Clearly this contribution to the activation barrier in rearrangement of *N,N*-dimethoxyacetamide (**5**) to methylacetate

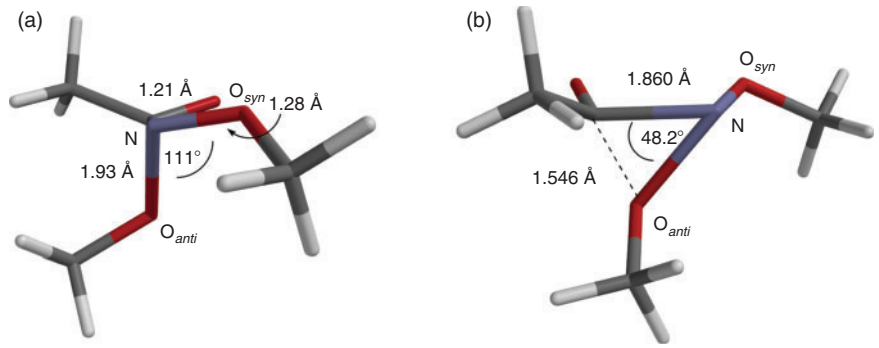


Fig. 9. B3LYP/6-31G(d) transition state geometry for HERON reaction of *N,N*-dimethoxyacetamide (**5**). (a) Projection along the N–C bond; (b) side-on view.

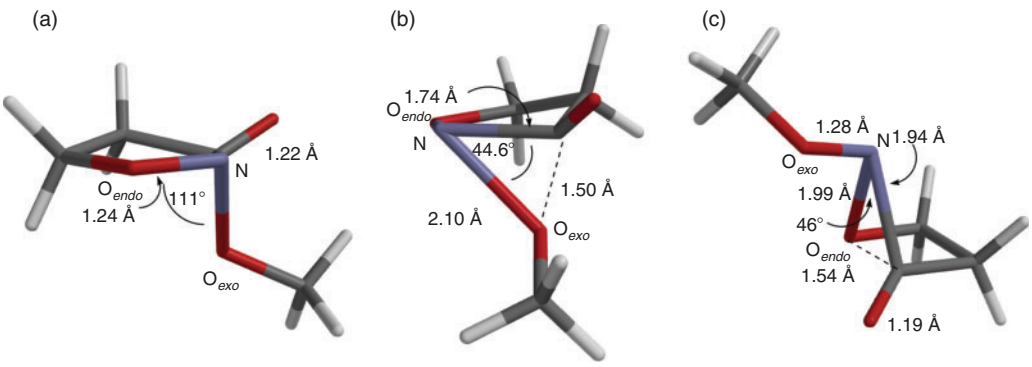
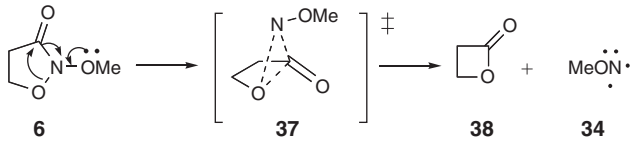


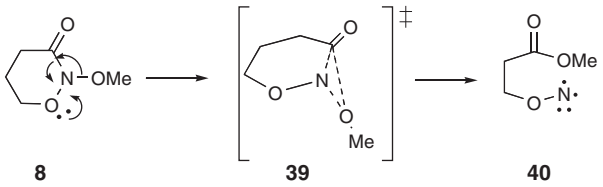
Fig. 10. B3LYP/6-31G(d) transition state geometry for HERON reactions of γ-lactam **6**. (a) Ring opening projection along the N-C bond in **35**; (b) ring opening side-on view; and (c) ring contraction in **37**.

(**33**) is largely absent in the case of **6** resulting in the lower activation barrier. Fig. 4 also shows that anomeric destabilisation of the endocyclic and exocyclic N–O bonds is similar and this is reflected in nearly equivalent bond lengths (Table 1). However, the alternative HERON (Scheme 8) leading to loss of methoxynitrene (**34**) and formation of β-propiolactone (**30**) is computed to have a much larger activation barrier of (198 or 188 kJ mol^{-1} with enthalpy and entropy correction at 298.15 K) and is not competitive with ring opening rearrangement to nitrene **36**. Presumably formation of the four-membered ring in transition state **37** (Scheme 8, Fig. 10c) invokes too much strain for this process to be viable.

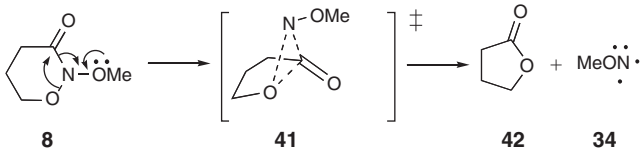
Reactivity of γ-lactam **6** is in contrast to the rearrangement of model δ-lactam **8**. Ring opening and ring contraction HERON processes of **8**, shown in Schemes 9 and 10 respectively, have similar activation barriers (Table 3) and both are measurably lower than that for the HERON reaction of *N,N*-dimethoxyacetamide (**5**). However, two factors favour ring contraction to **42** over ring opening to **40** in this case. First, ring contraction to γ-lactone **42** and singlet methoxynitrene (**34**) is slightly less endothermic than ring opening but collapse of methoxynitrene to the lower energy triplet state results in overall exothermicity. Second, the reaction may be under stereoelectronic control; the chair conformation for **8** in the ground state (Table 1 and Fig. 4b) exhibits an unusually strong anomeric destabilisation of the endocyclic N–O bond by the p-type lone pair on the exocyclic oxygen, as evidenced by the very large difference in the N–O bond lengths (0.08 Å, Table 1). A strong n_Y–σ^*_{NX} interaction in Fig. 1 is intrinsic to the HERON process.[9,14] However, the reverse effect is switched off (Fig. 4a) as the p-type lone pair on the endocyclic oxygen is orthogonal to the exocyclic N–O bond. Transition states for HERON reactions of δ-lactam **8** are shown in Fig. 11. The greatly reduced activation barrier for the γ-lactone formation from δ-lactam **8** relative to the β-lactone formation from γ-lactam **6** is clearly a reflection of the reduced strain in the five-membered ring transition state **41**. A clear reason for the reduced activation barriers for both HERON reactions of δ-lactam **8** relative to *N,N*-dimethoxyacetamide (**5**) as well as the preference of ring contraction over ring opening is not immediately obvious from the ground state or transition state structures.



Scheme 8.



Scheme 9.



Scheme 10.

Conclusion

Hypervalent iodine oxidation of β- and γ-hydroxyhydroxamic esters has been demonstrated to effect ring closure to cyclic *N,N*-dialkoxyamides. Cyclisation of the salicamides **19** afforded the first stable γ-lactams, *N*-alkoxybenzisoxazolones **22**. The γ-lactam **24** formed from the saturated β-hydroxybutanamide (**17**) was however unstable, undergoing an intramolecular HERON ring opening driven by an $n_{O_{endo}}$–$\sigma^*_{NO_{exo}}$ anomeric interaction. This anomeric process is disfavoured in the benzisoxazolones on account of $n_{O_{endo}}$ lone pair delocalisation onto the benzene ring. The δ-lactam **25**, while formed upon PIFA and PIDA oxidation of **21**, is also unstable undergoing the reverse HERON reaction leading to ring contraction to a lactone.

The computed activation barriers for ring opening and ring contraction of γ-lactam **6** support the experimental findings; only ring opening of γ-lactam intermediate **24** to nitrene **28** was observed. In the case of formation of δ-lactam intermediate **25** using PIFA or PIDA, no ring opening in competition with lactone formation was evident. While stereoelectronic factors may be a factor, the influence of substituent effects cannot be discounted.

The search for stable cyclic and bicyclic forms of *N,N*-dialkoxyamides is of interest since structural properties could generate lactams with very low amidicity. We recently showed

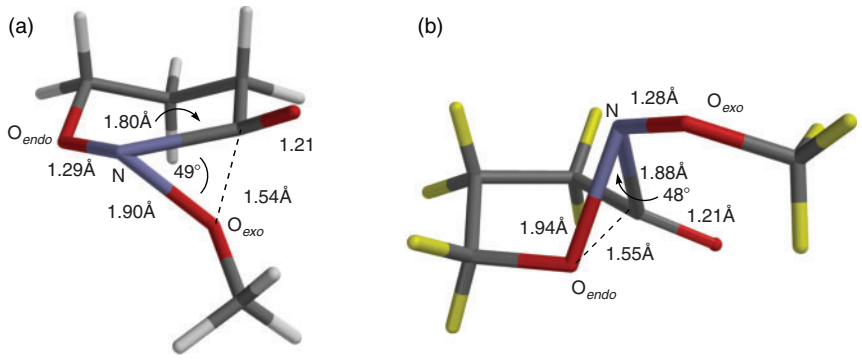


Fig. 11. B3LYP/6-31G(d) transition states for HERON reactions of **8**. (a) Ring opening in **39** and (b) ring contraction in **41**.

that β-lactam antibiotics such as those derived from penam (87 %) and penem (73 %) as well as the cepham (123 %) and cephem (95 %) bicyclic structures possess amide linkages with much higher amidicities.[27] Cyclic and bicyclic *N,N*-dialkoxyamide structures have greater potential to mimic the behaviour of β-lactam antibiotics as serine acylators.[38,39]

Experimental

Materials and Methods

NMR spectra were recorded in $CDCl_3$ or CD_3CN on a Bruker Avance 300P FT NMR spectrometer with a 5 mm ^{1}H inverse/BB *z*-gradient probe, operating at 300.13 (^{1}H) and 75.46 MHz (^{13}C). Mass spectra were recorded by direct injection of samples onto a Varian 1200 L triple quadrupole mass spectrometer with an electrospray ionisation interface using 1 % formic acid in methanol as solvent matrix. Centrifugal chromatographic separations were performed on a 7294T model Harrison Research chromatatron with plates coated with 2.0 mm of silica gel 60 F_{254} (Merck). Flash chromatography columns were charged with Silica gel 60, 230–400 mesh. Hypervalent iodine oxidants, PIFA and PIDA, were available commercially. Potassium salts of hydroxamic acids and hydroxamic esters were synthesised according to established protocols.[7,40–43]

Computational Methods

Fully optimised ground states of models of all structures in Table 1 and those listed in Table 2 and Table 3, as well as the energies of distorted *N*,*N*-dimethoxyacetamide shown in Fig. 3, were computed at the B3LYP/6-31G(d) level using *MacSpartan 10*[44] and *Gaussian 03*.[45] B3LYP/6-31G(d) has been shown to perform well in determinations of structure and properties of a wide range of amides, lactams, and anomeric amides,[2,5,9,10,14,27] and resonance energies at this level have been demonstrated to be in relatively good agreement with those obtained with much larger basis sets and higher levels of correlation energy corrections.[27] Energies of model structures in isodesmic reactions Eqn 1–Eqn 4 were computed without zero point energies (ZPEs) and thermal corrections since these largely cancel. For the HERON processes depicted in Schemes 6–10, the determination of activation energies and reaction energies with ZPE, vibrational, and entropy corrections required full frequency calculations on all reactants, transition states, and singlet and triplet nitrenes and lactone products. Transition states for HERON processes possessed one imaginary frequency. Absolute energies for these reactions as well as those for deformation of *N*,*N*-dimethoxyacetamide (**5**) are provided as Supplementary Material.

*Synthesis of Hydroxamic Esters **17**, **19**, and **21***

*N-Butoxy-2-hydroxybenzamide (**19a**)*

Method 1. 2-Hydroxybenzoyl chloride (1.25 g, 8 mmol) and butoxyamine hydrochloride (1 g, 8 mmol) were added to 100 mL of diethyl ether in a two neck flask in an ice bath. Triethylamine (1.62 g, 0.016 mol) was added dropwise over 1 h so that the temperature remained below 5°C. After stirring overnight, the ether was removed under reduced pressure. The solid was treated with saturated sodium bicarbonate and extracted with diethylether (2 × 15 mL). The extract was washed with 50 mL of HCl (0.1 M), separated, and dried over anhydrous $MgSO_4$. Concentration afforded a yellowy-brown oily compound, which was purified by centrifugal chromatography (15 % ethyl acetate/*n*-hexane) to give *N*-butoxy-2-hydroxybenzamide (**19a**) (0.59 g, 2.8 mmol, 35 %). ν_{max} ($CHCl_3$)/cm^{-1} 3417 (N–H), 3256br (O–H), 1653 (CO), 1607 (Ar). δ_H 8.86 (br, N–H), 7.40 (d, 1H), 7.38 (t, 1H), 7.00 (d, 1H), 6.85 (t, 1H), 4.02 (t, 2H), 1.86 (br, OH), 1.70 (quin, 2H), 1.46 (sextet, 2H), 0.95 (t, 3H). δ_C 168.95(CO), 161.29 (C–OH), 134.75, 125.05, 118.94, 118.80 112.22, 77.20 (C–O), 30.04 (CH_2CH_2O), 19.06 (CH_2CH_3), 13.86 (CH_3). *m/z* (EI), 209, 137, 121, 93, 92, 88, 86, 84; (HR-EI) 209.1052 (M^+), $C_{11}H_{15}NO_3$ requires 209.1052.

Method 2. Potassium 2-hydroxybenzohydroxamate (1 g, 5.9 mmol), butyl bromide (0.81 g, 5.9 mmol), and sodium carbonate (0.75 g, 7.1 mmol) were stirred overnight in 50 % aq. methanol (50 mL) and then refluxed for 2 h. Excess methanol was removed under reduced pressure and the mixture extracted with dichloromethane and the extract was dried over anhydrous sodium sulfate, filtered, and concentrated to give an oil. Purification by centrifugal chromatography (15 % ethyl acetate/*n*-hexane) afforded clean *N*-butoxy-2-hydroxybenzamide (**19a**) (0.57 g, 2.7 mmol, 48 %).

*N-Benzyloxy-2-hydroxybenzamide (**19b**)*

2-Hydroxybenzoyl chloride (1.25 g, 8 mmol) and benzyloxyamine hydrochloride (1 g, 8 mmol) were reacted according to Method 1. Workup produced a brown oil, which was purified by centrifugal chromatography (15 % ethyl acetate/*n*-hexane) to give *N*-benzyloxy-2-hydroxybenzamide (0.34 g, 1.4 mmol, 17.53 %). ν_{max} ($CHCl_3$)/cm^{-1} 3413 (N–H), 3277br (OH), 1654 (CO), 1607 (Ar). δ_H 9.25 (br, 1H), 7.30–7.50 (m, 7H), 6.98 (d, 1H), 6.80 (t, 1H), 5.04 (s, 2H), 0.9 (br, 1H). δ_C 168.72 (CO), 161.25 (C–OH), 134.74, 129.84, 129.39, 129.00, 128.74, 125.60, 118.89, 118.59 112.38, 78.74 (C–O). *m/z* (HR-ESI) 244.0974 ($[M + H]^+$), $C_{14}H_{14}NO_3$ requires 244.0974; 266.0792 ($[M + Na]^+$), $C_{14}H_{13}NO_3Na$ requires 266.0793.

*N-Butoxy-3-hydroxybutanamide (**17**)*

Method 1. To a stirred solution of ethyl 3-hydroxybutanoate[46] (1.0 g, 7.56 mmol) dissolved in methanol (10 mL) was added hydroxylamine hydrochloride (0.53 g, 7.56 mmol) followed by solid potassium hydroxide (0.85 g, 15.1 mmol). The mixture was heated to 65°C for 1 h, allowed to cool followed by addition of butyl iodide (2.78 g, 15.1 mmol) and the mixture was stirred at 25°C for 16 h and then warmed to reflux for 1 h. Removal of the volatiles and purification of the residue by flash chromatography (ethyl acetate) afforded a colourless oil which crystallised upon standing (280 mg, 28 %). Mp 47–49°C. R_f 0.3 (ethyl acetate). ν_{max} (neat)/cm^{-1} 3154, 1661. δ_H 9.71 (br s, 1H, NH), 4.14 (br s, 1H, C*H*(OH)), 4.00 (br s, 1H, OH), 3.86 (br t, 2H, $NOCH_2$), 2.25 (br dd, *J* 14.8, 3.3, 1H, C*H*HCO), 2.18 (br dd, *J* 14.8, 8.5, 1H, CH*H*CO), 1.59 (quintet, 2H, OCH_2CH_2), 1.36 (sextet, 2H, CH_2CH_3), 1.19 (d, *J* 6.2 Hz, 3H, CH(OH)CH_3), 0.89 (t, 3H, CH_2CH_3). δ_C 169.9 (CO), 76.5 (CH_2–O), 64.7 (3–C), 41.56 (2–C), 29.95 (O–CH_2CH_2), 22.95 (4-C), 18.97 (CH_2CH_3), 13.77 (CH_2CH_3). *m/z* (ESI) 176 ($[M + H]^+$), 351 ($[2M + H]^+$), 373 ($[2M + Na]^+$); (HR-ESI) 176.1286 ($[M + H]^+$), $C_8H_{18}NO_3$ requires 176.1287; 198.1105 ($[M + Na]^+$), $C_8H_{17}NO_3Na$ requires 198.1106.

Method 2. Hydroxylamine hydrochloride (4.83 g, 69.5 mmol) in boiling methanol (30 mL) was added to potassium hydroxide (7.8 g, 0.139 mol) in boiling methanol (50 mL) with stirring. The mixture was immediately cooled in an ice bath for 5 min. β-Butyrolactone (5 g, 58.1 mmol) was added to the

mixture with shaking followed by filtration. The filtrate was monitored by TLC until no lactone was observed. Butyl bromide (7.96 g, 58.1 mmol) in methanol (10 mL) and sodium carbonate (6.77 g, 63.9 mmol) in water (40 mL) were added to the filtrate and the resultant mixture was refluxed and monitored by TLC until no further increase in non-baseline material was evident. Excess methanol was removed under reduced pressure and the mixture diluted with brine (50 mL). Extraction with dichloromethane, which was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure, afforded clean *N*-butoxy-3-hydroxybutanamide (**17**) as a white solid (1.75 g, 9.99 mmol, 17.2 %).

*N-Butoxy-4-hydroxypentanamide (**21**)*

Hydroxylamine hydrochloride (4.17 g, 60 mmol) in hot methanol (30 mL) was added to potassium hydroxide (6.73 g, 120 mmol) in boiling methanol. γ-Valerolactone (5 g, 50 mmol) was added and the solution was cooled and filtered. After standing overnight, lactone was not detected by TLC. Butyl bromide (6.84 g, 50 mmol) was added and the reaction mixture was stirred under reflux and monitored by TLC until no further increase in non-baseline material was evident. Most of the methanol was removed under reduced pressure and the mixture diluted with brine. Extraction with dichloromethane, which was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure, afforded clean *N*-butoxy-4-hydroxypentanamide (**21**) as a yellow oil (0.729 g, 3.85 mmol, 8 %). ν_{max} (neat)/cm^{-1} 3500−3200br (NH, OH), 1661. δ_H 3.85 (t, 2H, CH_2–O), 3.8 (m, 1H, CH–O), 2.2–2.5 (br m, 2H, α-CH_2), 1.75–1.9 (m, 1H, β-CH), 1.65–1.75 (m, 1H, β-CH), 1.62 (quin, 2H), 1.4 (sextet, 2H), 1.2 (d, 3H), 0.95 (t, 3H). δ_C 171.42 (CO), 77.3(CH_2–O), 67.2 (4-C), 34.07 (3-C), 29.95 (O–CH_2*C*H_2), 28.03 (2-C), 23.53 (5-C), 18.99 (*C*H_2CH_3), 13.79 (CH_2*C*H_3). *m/z* (ESI) 190 ([M + H]$^+$), 212 ([M + Na]$^+$), 401 ([2M + Na]$^+$); (HR-ESI) 190.1443 ([M + H]$^+$), $C_9H_{20}NO_3$ requires 190.1443; 212.1263 ([M + Na]$^+$), $C_9H_{19}NO_3Na$ requires 212.1263.

*PIFA Cyclisations of **17**, **19**, and **21***

Hydroxamic esters in anhydrous acetonitrile were treated rapidly with similar quantities of PIFA and briefly stirred. The reaction mixture was diluted with saturated sodium carbonate. The aqueous mixture was extracted with dichloromethane, which was washed with brine and concentrated to afford mixtures containing cyclised materials.

*Cyclisation of N-butoxy-2-hydroxybenzamide (**19a**)*

N-Butoxy-2-hydroxybenzamide (**19a**) (0.35 g, 1.7 mmol) in 50 mL of anhydrous acetonitrile was treated with PIFA (1.1 g, 2.5 mmol) and stirred for 5 min. $NaHCO_3$ (10 %, 30 mL) was added with agitation for a further 3 min. The mixture was extracted with portions of dichloromethane (2 × 20 mL), which was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by centrifugal chromatography (15 % ethyl acetate/*n*-hexane) afforded *N*-butoxy-3(*2H*)-benzisoxazolone (**22a**) (0.11 g, 0.5 mmol, 31.43 %). ν_{max} ($CHCl_3$)/cm^{-1} 1742 (CO), 1618. δ_H 7.79 (d, 1H, 4-H), 7.67 (t, 1H, 6-H), 7.18 (t, 1H, 5-H), 7.06 (d, 1H, 7-H), 4.30 (t, O–CH_2), 1.85 (quin, 2H, 2′-CH_2), 1.54 (sextet, 2H, 3′-H), 0.98 (t, 3H, 4′-H). δ_C 173.36 (CO), 164.49 (C_{Ar}–O), 137.00 (6-C), 125.82 (4-C), 123.23 (5-C), 113.06 (*C*–CO), 110.59 (7-C), 77.71 (1′-C), 30.24 (2′-C), 18.83 (3′-C), 13.77 (4′-C). *m/z* (EI) 207, 177, 135, 121, 120, 93, 92; (HR-EI) 207.0893 (M^+), $C_{11}H_{13}NO_3$ requires 207.0895.

*Cyclisation of N-benzyloxy-2-hydroxybenzamide (**19b**)*

N-Benzyloxy-2-hydroxybenzamide (**19b**) (0.24 g, 1 mmol) was dissolved in 15 mL of anhydrous acetonitrile, treated with PIFA (0.42 g, 1.5 mmol), and stirred for 5 min. $NaHCO_3$ (10 %, 20 mL) was added with agitation for a further 3 min. The mixture was extracted with portions of dichloromethane (2 × 20 mL), which were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by centrifugal chromatography (15 % ethyl acetate/*n*-hexane) afforded *N*-benzyloxy-3(*2H*)-benzisoxazolone (**22b**) (0.05 g, 0.2 mmol, 20 %). ν_{max} ($CHCl_3$)/cm^{-1} 1743 (CO). δ_H 7.78 (d, 1H, 4-H, 7.66 (t, 1H, 6-H), 7.51–7.54 (d, 2H, *o*′-H), 7.37–7.43 (m, 3H, *m*′,*p*′-H), 7.18 (t, 1H, 5-H), 7.05 (d, 1H, 7-H) 5.31 (s, 2H). δ_C 173.43 (CO), 164.72 (C_{Ar}–O), 137.11 (6-C), 134.54 (C'_{ipso}), 129.26, 128.93 (C'_p), 128.58, 125.85 (4-C), 123.30 (5-C), 112.93 (*C*–CO), 110.64 (7-C), 79.49 (CH_2). *m/z* (HR-ESI) 242.0815 ([M+H]$^+$), $C_{14}H_{12}NO_3$ requires 242.0817; 264.0638 ([M+Na]$^+$), $C_{14}H_{11}NO_3Na$ requires 264.0637.

*Cyclisation of N-butoxy-3-hydroxybutanamide (**17**)*

Treatment of *N*-butoxy-3-hydroxybutanamide (**17**) (0.027 g, 0.15 mmol) in anhydrous acetonitrile (2 mL) with an equivalent of PIFA (0.066 g, 0.015 mmol) in anhydrous acetonitrile (2 mL) afforded, after workup, a mixture (0.033 g) which was immediately analysed by NMR spectroscopy and was comprised mainly of γ-lactam **24** and iodobenzene (see discussion). Upon standing overnight, **24** decomposed to a diastereomeric mixture of hyponitrite **26**. δ_H 5.5–5.7 (overlapping m, 2H, CH–O), 4.0–4.15 (overlapping t, 4H, CH_2–O), 3.0–3.15 (overlapping dd, 2H, α-H^1), 2.5–2.65 (overlapping dd, 2H, α-H^2), 1.5–1.7 (overlapping quintets, 4H, O–CH_2*C*H_2), 1.4 and 1.38 (overlapping d, 6H, *C*H_3CH), 1.3–1.4 (overlapping sextets, 4H, *C*H_2CH_3), 0.9–0.98 (overlapping t, CH_2*C*H_3). δ_C 169.89 (CO), 64.80 (O–CH_2), 59.90 (β-CH–O), 37.09 (α-CH_2), 30.55 (*C*H_2CH_2–O), 19.04 (*C*H_2CH_3), 16.02 (*C*H_3CH–O), 13.64 (CH_2*C*H_3). *m/z* (ESI) 347.2 ([M + H]$^+$), 715.5 ([2M + Na]$^+$). Purification of a portion by centrifugal chromatography afforded clean diastereomeric mixture **26**. *m/z* (HR-ESI) 347.2182 ([M + H]$^+$), $C_{16}H_{31}N_2O_6$ requires 347.2182; 369.2002 ([M + Na]$^+$), $C_{16}H_{30}N_2O_6Na$ requires 369.2002.

N-Butoxy-3-hydroxybutanamide (**17**) and PIFA in a 2 : 1 ratio were reacted in CD_3CN in the probe of the NMR machine. The reaction produced an immediate 50 : 50 mixture of unreacted **17** and γ-lactam **24** together with iodobenzene. Compound **17**: δ_H (CD_3CN) 4.58–4.70 (ddq, *J* 8.9, 6.1, and 6.1, 1H, CH–O), 3.95 (t, 2H, CH_2–O), 2.78 (dd, *J* 17.8 and 6.1, α-H^1), 2.44 (dd, *J* 17.8 and 8.9, α-H^2), 1.59 (quin, 2H, O–CH_2*C*H_2), 1.38 (sextet, 2H, *C*H_2CH_3), 1.37 (d, 3H, *C*H_3CH), 0.9 (t, 3H, CH_2*C*H_3). *m/z*(ESI) 176 ([M + H]$^+$), 198 ([M + Na]$^+$); Compound **24**: δ_H (CD_3CN) 4.0–4.15 (br m, 1H, CH–OH), 3.83 (t, 2H, CH_2–O), 2.1–2.25 (br m, 2H, α-CH_2), 1.59 (quin, 2H, O–CH_2*C*H_2), 1.38 (sextet, 2H, *C*H_2CH_3), 1.15 (d, 3H, CH*C*H_3), 0.9 (t, 3H, CH_2*C*H_3). *m/z* (ESI) 196 ([M + Na]$^+$).

*Cyclisation of N-butoxy-4-hydroxypentanamide (**21**)*

Treatment of *N*-butoxy-4-hydroxypentanamide (**21**) (0.23 g, 1.2 mmol) in anhydrous acetonitrile (5 mL) with an equivalent of PIFA (0.52 g, 1.2 mmol) in anhydrous acetonitrile (5 mL) at room temperature afforded, after workup, a mixture (0.2 g) which was immediately analysed by NMR spectroscopy and was comprised mainly of δ-lactam **25**, γ-valerolactone (**27**), and

iodobenzene (see discussion). The mixture reverted to lactone upon standing overnight. A repeat reaction in CD_3CN and analysed by NMR spectroscopy contained, along with iodobenzene, lactam **25**, and lactone **27** in a 3 : 1 ratio. The mixture was analysed immediately by ESI-MS. *m/z* (ESI) 101 (**27**, $[M + H]^+$) 188 (**25**, $[M + H]^+$).

N-Butoxy-4-hydroxypentanamide (**21**) (0.02 g, 0.11 mmol) and PIDA (0.034 g, 0.11 mmol) were reacted in CD_3CN (1 mL) in the probe of the NMR machine and the complex mixture analysed by NMR spectroscopy (see discussion).

N-Butoxy-*N*-chloro-2-hydroxybenzamide (*23*)

A solution of *N*-butoxy-*2*-hydroxybenzamide (**19a**) and an equimolar amount of *tert*-butyl hypochlorite[47] in dichloromethane was stirred in the dark for 3 h. The solvent and residual *tert*-butyl hypochlorite were removed under reduced pressure at room temperature to give the *N*-butoxy-*N*-chloro-2-hydroxybenzamide (**23**) in quantitative yield as a yellow oil, which was characterised by ^{1}H NMR spectroscopy. δ_H 10.15 (1H, s, OH), 7.7 (d, 1H), 7.5 (t, 1H), 7.05 (d, 1H), 6.85 (t, 1H), 4.2 (t, 2H), 1.7 (quin, 2H), 1.4 (sextet, 2H), 0.95 (t, 3H). Relative to precursor hydroxamic ester, protons α- to the alkoxyl oxygen undergo a typical downfield shift of around 0.2 ppm in their ^{1}H NMR spectrum upon *N*-chlorination.

Cyclisation of *N*-butoxy-*N*-chloro-2-hydroxybenzamide (*23*)

N-Butoxy-*N*-chloro-2-hydroxybenzamide (**23**) was stirred in $CHCl_3$ with silica gel 60 for 1 h. The mixture was filtered and concentrated to afford clean 2-butoxy-3(2*H*)-benzisoxazolone (**22a**).

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Supplementary Material

B3LYP/6-31G(d) energies of ground state reactants, transition states, singlet and triplet nitrene products and product lactones relating to Schemes 6–10 for HERON reactions of **5**, **6**, and **8**; B3LYP/6-31G(d) energies used in Fig. 3 for deformation of *N*, *N*-dimethoxyacetamide (**5**); B3LYP/6-31G(d) optimised geometries computed for all structures in Table 1 and Table 2 and Schemes 6–10 for HERON reactions of **5**, **6**, and **8** and ^{1}H and ^{13}C NMR spectra of all new reactants and products not presented in the discussion are available on the Journal's website.

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