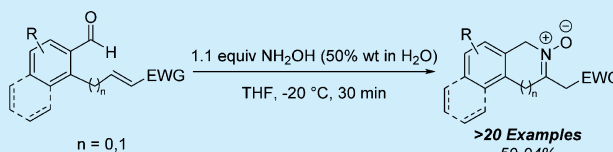


Simple Aza-Conjugate Addition Methodology for the Synthesis of Isoindole Nitrones and 3,4-Dihydroisoquinoline Nitrones

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S Supporting Information

ABSTRACT: Aryl-aldehydes containing *ortho*-substituted α,β -unsaturated carboxylic acid derivatives react with hydroxylamine to afford reactive *N*-hydroxy-carbinolamine intermediates that undergo intramolecular *aza*-conjugate addition reactions to afford isoindole nitrones and 3,4-dihydroisoquinoline nitrones in good yield. Conditions have been developed to reduce these isoindole nitrones to their corresponding hydroxylamine, enamine, and amine derivatives. Isoindole nitrones react with dimethyl acetylenedicarboxylate (DMAD) via a [4 + 2]-cycloaddition/deamination pathway to afford substituted naphthalene derivatives, while 3,4-dihydroisoquinoline nitrones react with DMAD via a [1,3]-dipolar cycloaddition pathway to afford tricyclic heteroarenes.



Nitrones are an important class of organic compound that are traditionally prepared via oxidation of imines, amines, and hydroxylamines using a variety of oxidants and catalysts.¹ A number of nonoxidative methods for their synthesis have also been developed, including condensation of *N*-monoalkylated hydroxylamines with carbonyl compounds² or *N*-alkylation of oximes using alkene derivatives.³ Nitrones are versatile substrates for a wide range of reactions¹ and are also useful as free radical spin traps for electron paramagnetic resonance (EPR) studies on biological systems.⁴ For example, the isoindole-derived nitrones DMPO (5,5-dimethyl-pyrroline-*N*-oxide), TMINO (1,1,3-trimethyl-isoindole-*N*-oxide), and 3-TF-TMINO (1,1,3-trimethyl-isoindole-*N*-oxide) have proven to be particularly useful for detecting oxidative radical species in biological systems, due to the improved stability of their derived radical adducts.⁵ 3,4-Dihydroisoquinoline derived nitrones have been employed as synthetically versatile substrates for a range of reactions,¹ including enantioselective [1,3]-dipolar cycloaddition and nucleophilic addition reactions,⁶ as well as free radical trapping agents for the treatment of stroke.⁷ Given this utility, we now report efficient cyclization methodology for the synthesis of isoindole nitrones and 3,4-dihydroisoquinoline nitrones that contain carboxylate side chains that are potentially useful for bioconjugation.

As part of a research program directed toward the synthesis of novel heterocyclic ring systems for drug discovery and sensing applications, we found that reaction of the aldehyde functionality of α,β -unsaturated ester **1a** with $\text{NH}_2\text{OH}\cdot\text{HCl}$ and excess sodium acetate (or Et_3N) in water/EtOH at rt resulted in clean formation of isoindole nitron **7a** in 78% yield. Under these conditions, it is proposed that hydroxylamine reacts reversibly with the aldehyde functionality of α,β -unsaturated ester **1a** to

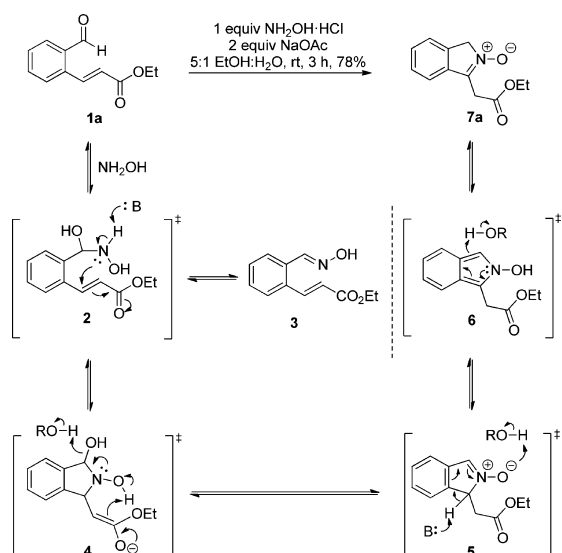
give a *N*-hydroxy-carbinolamine intermediate **2** that is in equilibrium with oxime **3**. The *N*-hydroxy-amino functionality of **2** then undergoes a 5-*exo*-trig *aza*-conjugate addition reaction to afford bicyclic enolate intermediate **4**. Elimination of water from isoindoline **4** then occurs to afford nitron **5** which undergoes a series of tautomerization events (*via N*-hydroxy-2*H*-isoindole **6**) to afford the thermodynamically more stable nitron **7a** (Scheme 1).

A series of reactions were then carried out in an attempt to provide evidence for this mechanistic rationale. First, it was found that aldehyde **1a** reacted with $\text{NH}_2\text{OH}\cdot\text{HCl}$, in the absence of sodium acetate, to give the stable oxime **3**, which only cyclized to afford nitron **7a** on exposure to excess sodium acetate. We also found that addition of *N*-methyl-hydroxylamine to a mixture of aldehyde **1a** and Et_3N in water/THF at rt afforded *N*-methyl-carbinolamine-*N*-oxide **8** (*cf.* intermediate **4**) as a mixture of diastereomers (Scheme 2a).

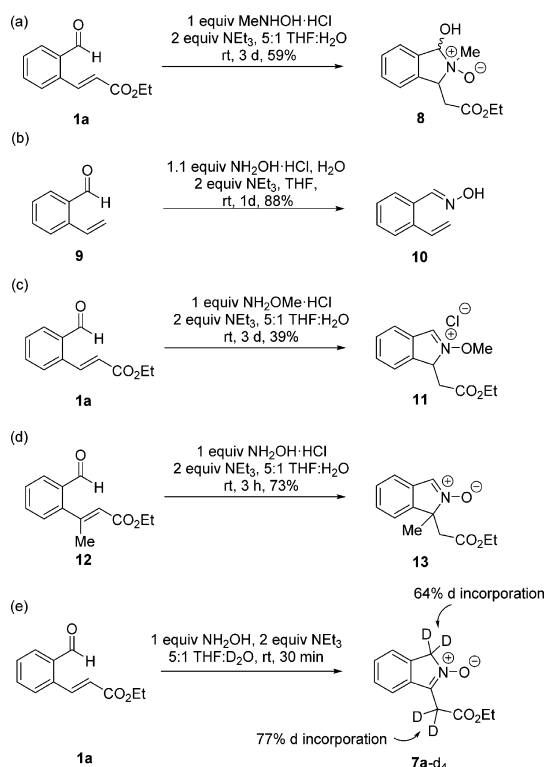
Although *N*-hydroxy-carbinolamine **2** could potentially afford intermediate **4** *via* a *reverse*-Cope mechanism, these type of intramolecular cyclization reactions are normally favored by substrates containing relatively electron-rich alkenes.⁸ Further evidence against a *reverse*-Cope reaction was obtained by reacting styrene aldehyde **9** with $\text{NH}_2\text{OH}\cdot\text{HCl}$ under basic conditions, which cleanly afforded its corresponding oxime **10** (*cf.* oxime **3**), with no evidence of any cyclic nitron product being produced (Scheme 2b). Furthermore, treatment of aldehyde **1a** with *O*-methyl-hydroxylamine resulted in clean formation of the nitron salt **11** (*cf.* intermediate **5**), consistent with an *aza*-conjugate

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Scheme 1. Reaction of the Aldehyde Functionality of α,β -Unsaturated Ester **1a with Hydroxylamine To Afford Nitrone **7a****



Scheme 2. Range of Reactions Employed To Probe the Mechanism of the Cyclization Reaction of **1a To Afford Nitrone **7a****



addition reaction operating under these conditions (Scheme 2c). All of these observations are consistent with ring closure being initiated by conjugate addition of the sp^3 N-atom of *N*-hydroxycarbinolamine **2**, which is more nucleophilic than the sp^2 N-atom of oxime **3**.⁹

Further support for the intermediacy of **5** in the formation of nitrone **7a** was obtained by treatment of aryl-aldehyde **12**, with hydroxylamine under basic conditions which cleanly afforded the regioisomeric nitrone **13** (Scheme 2d). Indeed, carrying out the

cyclization reaction of **1a** with hydroxylamine in the presence of D_2O resulted in a nitrone product **7a-d₄** with 77% deuterium incorporation α to its ester group and 64% deuterium incorporation at its benzylic position (Scheme 2e). Furthermore, treatment of unlabeled nitrone **7a** with NaOAc in a 5:1 mixture of EtOD/ D_2O also resulted in deuterium incorporation α to its ester functionality and at its benzylic position. These results clearly reveal the presence of a tautomeric equilibrium between **5** and **7a** in solution (via **6**) under basic conditions.¹⁰

The conditions employed to carry out cyclization of aldehyde **1a** were then optimized by screening different bases, solvents, and sources of hydroxylamine, which enabled us to identify that use of 1.1 equiv of hydroxylamine (50% solution in water) in THF at $-20^\circ C$ gave nitrone **7a** in 91% yield. These optimal conditions were then applied to the cyclization of a series of 19 α,β -unsaturated carboxylic acid derivatives **1b–t** that gave their corresponding nitrones **7b–t** in 59–94% yields (Table 1). Therefore, aryl-aldehydes **1b–h** containing both electron-donating and -withdrawing substituents cyclized cleanly to afford their corresponding isoindole-nitrones **7b–h**, with the structure of fluorinated isoindole-nitrone **7g** being confirmed by X-ray crystallographic analysis (see Supporting Information (SI)). Pyridine derived aryl-aldehyde ester **1i** cyclized cleanly to afford its expected isoindole nitrone **7i**. However, the regioisomeric pyridine substrate **1j** afforded its tautomeric *N*-hydroxy-2*H*-isoindole **7j** isomer (*cf.* intermediate **6**). Cyclization of alkene substrates containing alternative electron-withdrawing groups proceeded cleanly, with amide **1k**, nitrile **1l**, and thioester **1m** affording their corresponding isoindole-nitrones **7k–m** in 59–79% yield. Reaction of thioester **1m** with hydroxylamine over an extended 24 h period afforded the corresponding acid **7n** in 68% yield that is presumably formed from hydrolysis of the thioester functionality of nitrone **7m** *in situ*. The ketones **1o** and **1p** gave their regioisomeric nitrone **7o** and **7p** respectively (*cf.* nitrones **11** and **13**), while the γ -aryl- α,β -unsaturated esters **1q–t** all cyclized cleanly to afford the synthetically versatile 3,4-dihydroisoquinoline nitrones **7q–t** in good 77–92% yield.

All of the nitrones **7a–t** proved to be stable when stored at $0^\circ C$ under nitrogen. However, they rapidly decomposed on standing in air at rt. The potential synthetic utility of cyclic nitrone **7a** as a substrate for a series of reduction reactions was then explored. Hydrogenation of the parent nitrone **7a** over palladium on charcoal in acidic methanol resulted in reduction/deoxygenation to afford the corresponding isoindoline **14** in 69% yield.¹¹ Alternatively, treatment of **7a** with samarium and cobalt chloride in THF afforded enamine **15** in 39% yield,¹² while reduction of **7a** with $NaBH_3CN$ in acidic methanol afforded *N*-hydroxy-isoindoline **16** in 86% yield (Scheme 3).¹³

Attempts to employ isoindole nitrone **7a** as a substrate for a range of known nitrone reactions (see SI) proved unsuccessful,¹ affording either recovered starting material, nitrone products from a competing reaction of their ester functionalities, or colored polymeric material. We reasoned that this unusual reactivity profile was likely to be due to the relatively unstable isoindole nitrone **7a** preferentially reacting via its *N*-hydroxy-2*H*-isoindole tautomer **6**.¹⁴ We therefore decided to investigate whether **6** could be used as a diene component in a Diels–Alder reaction with an appropriate dienophile.¹⁴ Isoindole nitrone **7a** was reacted with dimethyl acetylenedicarboxylate (DMAD) in THF at rt, which resulted in a clean [4 + 2]-cycloaddition reaction to afford an unstable bridged *N*-hydroxy-1,4-dihydronaphthalene-1,4-imine **17** (observed by 1H NMR spectroscopic analysis). This unstable cycloadduct underwent facile deami-

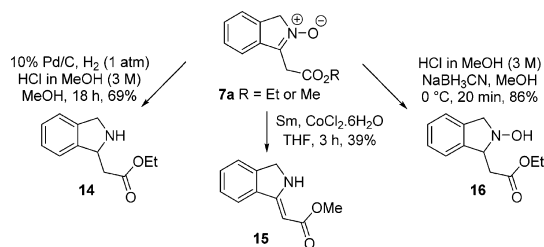
Table 1. Synthesis of a Range of Nitron Analogues 7a–t

Reaction scheme: α,β -unsaturated ester + 1.1 equiv NH_2OH (50% wt in H_2O) in THF, $-20\text{ }^\circ\text{C}$, 30 min \rightarrow Nitron Analogue 7

entry	α,β unsaturated ester ^a	nitron	yield (%)	entry	α,β unsaturated ester ^a	nitron	yield (%)
1			91	12			79
2			74	13			59
3			83	14 ^b			68
4			79	15			87
5			83	16			94
6			85	17			92
7			72	18			86
8			74	19			82
9			89	20			77
10			76				
11			79				

^aProtocols for the synthesis of α,β -unsaturated esters 1a–1t are reported in the SI. ^bCyclization reaction carried out over a period of 24 h.

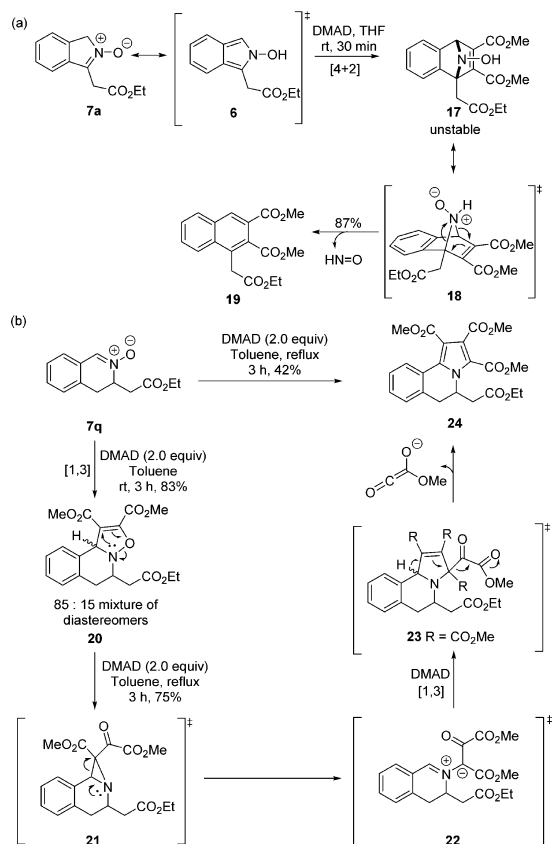
Scheme 3. Reduction of Nitron 7a To Afford Amine 14, Enamine 15, and Hydroxylamine 16



native aromatization (via elimination of a nitroxyl ($\text{HN}=\text{O}$) equivalent from *N*-oxide 18) on standing, to afford naphthyl triester 19 in 87% yield (Scheme 4a).^{4,5} In contrast, 3,4-

dihydroisoquinoline nitron 7q reacted with DMAD via its expected [1,3]-dipolar cycloaddition pathway, to afford dihydroisoxazole 20 as an inseparable 85:15 mixture of diastereomers in 83% yield.¹⁶ Repeating the reaction of nitron 7q with DMAD in toluene at reflux resulted in formation of tricyclic pyrrole 24 in 42% yield, which was also formed in 75% yield by treating dihydroisoxazole 20 with DMAD in toluene at reflux.¹⁶ A reasonable mechanism for formation of pyrrole 24 is shown in Scheme 4b, whereby intramolecular *aza*-conjugate addition of the nitrogen lone pair of dihydroisoxazole 20 first affords a reactive aziridine intermediate 21. Aziridine 21 then undergoes thermal ring opening to afford an azomethine ylide 22 that participates in a second [1,3]-dipolar cycloaddition reaction with DMAD to afford dihydropyrrole 23 that then eliminates a methyl glyoxylate equivalent to afford tricyclic pyrrole 24.¹⁶

Scheme 4. (a) [4 + 2]-Cycloaddition Reactions of Isoindole 7a with DMAD; (b) [1,3]-Dipolar Cycloaddition Reactions of 3,4-Dihydroisoquinoline 7q with DMAD



In conclusion, we have shown that aryl-aldehydes containing *ortho*-substituted α,β -unsaturated carboxylic acid fragments react with hydroxylamine via a tandem nucleophilic addition–*aza*-conjugate addition–elimination pathway to afford a series of 20 cyclic nitrones.¹⁷ These nitrones can be reduced to their corresponding amine, enamine, and hydroxylamine derivatives and used as substrates in [4 + 2]- and [1,3]-dipolar cycloaddition reactions for the synthesis of naphthalenes and tricyclic heteroarenes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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