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

Lucy R. Peacock,[†] Robert S. L. Chapman,[†] Adam C. Sedgwick,[†] Mary F. Mahon,[‡] Dominique Amans,[§] and Steven D. Bull*,[†]

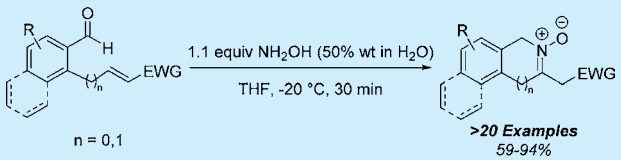
[†]Department of Chemistry, University of Bath, Bath, BA2 7AY, U.K.

[‡]Bath X-ray Crystallographic Suite, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.

[§]Epinova Discovery Performance Unit, GSK, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, U.K.

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 compounds[2] or *N*-alkylation of oximes using alkene derivatives.[3] Nitrones are versatile substrates for a wide range of reactions[1] 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 $NH_2OH{\cdot}HCl$ and excess sodium acetate (or Et_3N) in water/EtOH at rt resulted in clean formation of isoindole nitrone **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 nitrone **5** which undergoes a series of tautomerization events (*via* *N*-hydroxy-2*H*-isoindole **6**) to afford the thermodynamically more stable nitrone **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 $NH_2OH{\cdot}HCl$, in the absence of sodium acetate, to give the stable oxime **3**, which only cyclized to afford nitrone **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 $NH_2OH{\cdot}HCl$ under basic conditions, which cleanly afforded its corresponding oxime **10** (cf oxime **3**), with no evidence of any cyclic nitrone product being produced (Scheme 2b). Furthermore, treatment of aldehyde **1a** with *O*-methyl-hydroxylamine resulted in clean formation of the nitrone salt **11** (*cf.* intermediate **5**), consistent with an *aza*-conjugate

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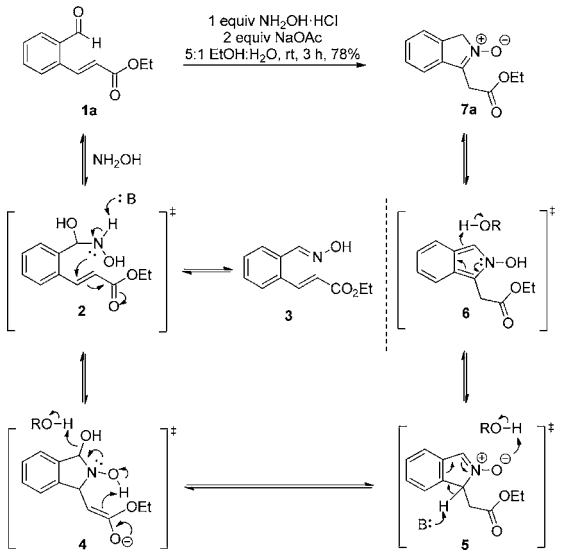
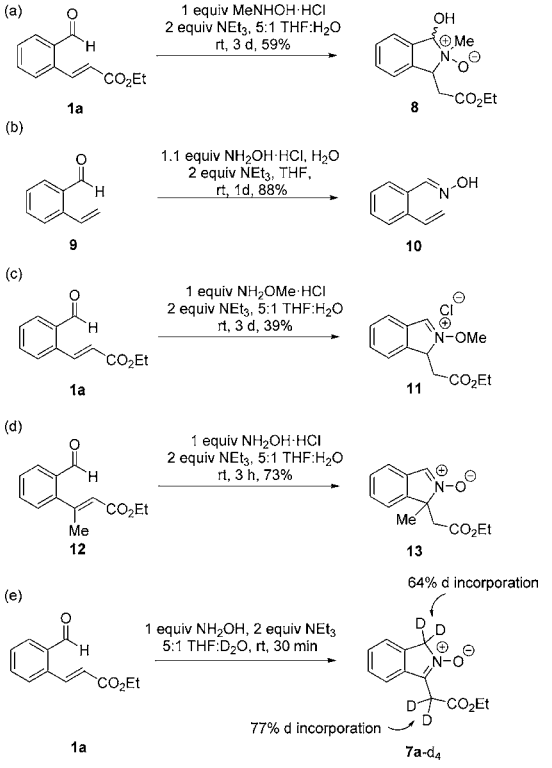
Scheme 1. Reaction of the Aldehyde Functionality of α,β-Unsaturated Ester 1a with Hydroxylamine To Afford Nitrone 7a



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*-hydroxy-carbinolamine **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**-d_4 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 °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 °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-dihydro-naphthalene-1,4-imine **17** (observed by ^1H NMR spectroscopic analysis). This unstable cycloadduct underwent facile deami-

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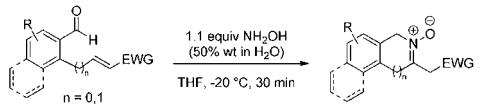
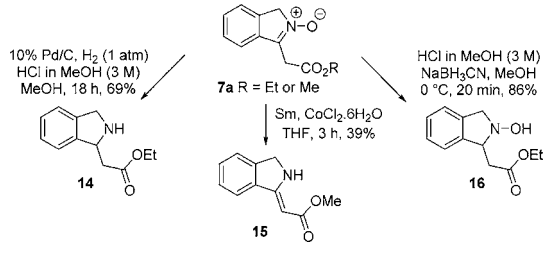
Table 1. Synthesis of a Range of Nitrone Analogues 7a−t



entry	α-β unsaturated ester[a]	nitrone	yield (%)	entry	α-β unsaturated ester[a]	nitrone	yield (%)
1	1a	7a	91	12	1l	7l	79
2	1b	7b	74	13	1m	7m	59
3	1c	7c	83	14[b]	1m	7n	68
4	1d	7d	79	15	1o	7o	87
5	1e	7e	83	16	1p	7p	94
6	1f	7f	85	17	1q	7q	92
7	1g	7g	72	18	1r	7r	86
8	1h	7h	74	19	1s	7s	82
9	1i	7i	89	20	1t	7t	77
10	1j	7j	76				
11	1k	7k	79				

[a]Protocols for the synthesis of α,β-unsaturated esters **1a−1t** are reported in the SI. [b]Cyclization reaction carried out over a period of 24 h.

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



native aromatization (via elimination of a nitroxyl (HN═O) equivalent from *N*-oxide **18**) on standing, to afford naphthyl triester **19** in 87% yield (Scheme 4a).[15] In contrast, 3,4-dihydroisoquinoline nitrone **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 nitrone **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]

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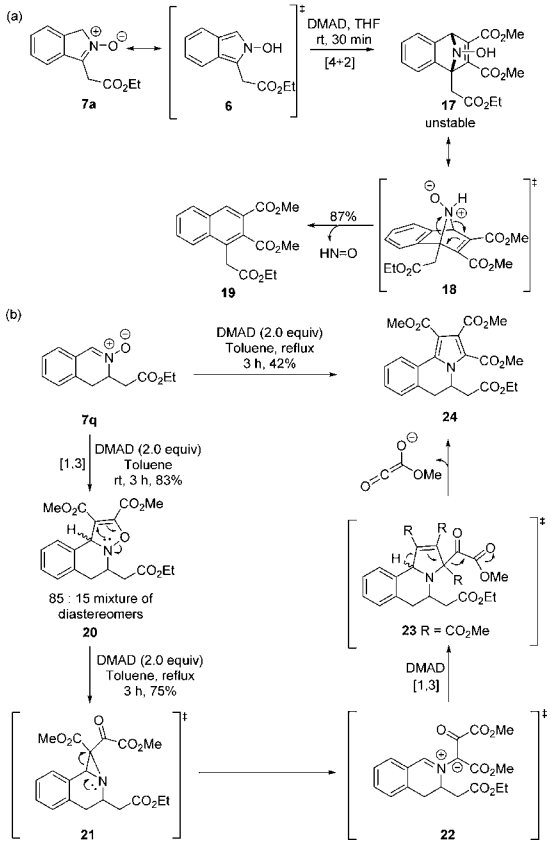
Scheme 4. (a) [4 + 2]-Cycloaddition Reactions of Isoindole 7a with DMAD; (b) [1,3]-Dipolar Cycloaddition Reactions of 3,4-Dihydroisoquinoline 7q with DMAD



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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: s.d.bull@bath.ac.uk.

Notes

The authors declare no competing financial interest.

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