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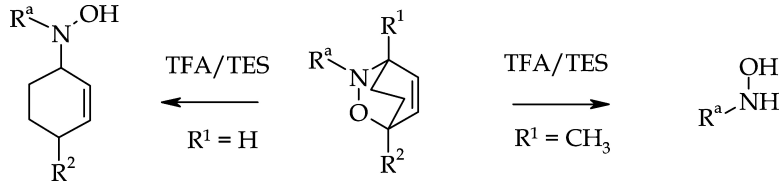

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Solid-Supported Nitroso Hetero-Diels–Alder Reactions. 3. Acid-Mediated Transformation of Cycloadducts by Scission of the Oxazine C−O Bonds

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Polymer-supported dihydro[1,2]oxazine derivatives were prepared by acyl- and arylnitroso hetero-Diels–Alder reactions and exposed to strong (trifluoroacetic) acid during cleavage from resin-bound linkers. Cycloadducts prepared from cyclic dienes containing electron-donating substituents at the C6 oxazine carbon promoted formation of carbocations by cleavage of the C−O bond. The carbocations were quenched by nucleophilic reagents including triethylsilane, water, and alcohols and provided access to novel derivatives of *N*-alkyl hydroxamates. Products were submitted to biological assays, and the results are reported.

Introduction

An inherent last step in solid-phase syntheses is the release of target compounds from the polymer-supported linker (unless resin-bound compounds are the targets of the syntheses).[1] The most frequently used linkers are acid cleavable,[2] and thus the target compounds need to tolerate the relevant acid-containing cleavage cocktails. Alcohols, phenols, acids, and amides prepared from acid-sensitive ethers, esters, and amides, respectively, were frequently immobilized using benzyl-type linkers for solid-phase synthesis.[2,3] The release of target compounds was facilitated by cleavage of the nitrogen/oxygen−carbon bond and the propensity toward cleavage depends on the potential to stabilize intermediate carbocationic species. However, the formation of carbocations is detrimental to products amenable to alkylation. This problem has been addressed on frequent occasions, particularly, for the solid-phase syntheses of peptides, and numerous cleavage cocktails containing carbocation scavengers, such as thiols[4] or trialkylsilanes,[5,6] have been advocated and widely used. The purpose of using scavengers was to eliminate the reactive species and prevent the target compound from unwanted transformations. Here, we wish to report deliberate use of scavengers to create novel compounds from acid-sensitive acyl- and arylnitroso hetero-Diels–Alder (HDA) cycloadducts.

In our previous papers dedicated to polymer-supported HDA reactions using immobilized acyl and aryl dienophiles,[7,8] we also assessed the stability of HDA adducts toward conditions typically used for solid-phase synthesis, in particular TFA-mediated release of target HDA cycloadducts from acid-labile linkers in Wang and Rink resins. We observed acid-instability of certain target adducts in acid–based cocktails. To prepare acid-labile products, we used linkers cleavable by mild nonacidic reagents such as tetra-*n*-butylammonium fluoride (TBAF) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In this article, we address the cause of the acid sensitivity and report exploitation of the instability to prepare novel derivatives of *N*-alkyl hydroxamates by the scission of the C−O oxazine bond. We have already reported our findings concerning the acid lability of 9,10-dimethylanthracene HDA adducts, used in retro-HDA reactions, in our previous paper.[7]

Transformation of the oxazine ring by scission of the C−O bond using different reagents has been studied and generated valuable synthetic intermediates: Cycloalkene-derived hydroxamates were prepared by Lewis acids (iron(III),[9,10] copper(II),[10] and palladium(0)[9]) mediated ring opening in the presence of an alcohol. The copper-catalyzed reaction of cyclopentadiene HDA adducts with Grignard reagents[11] and palladium(0)/indium iodide-mediated allylic additions to aldehydes and ketones[12] led to controlled formation of new C−C bonds.

Results and Discussion

We examined the tendency toward acid-mediated transformation of polymer-supported acyl- and arylnitroso HDA adducts on silyloxy and Wang linkers. HDA adducts synthesized on those two linkers are cleavable by mild reagents, TBAF and DDQ, respectively, but nevertheless are also susceptible to acid-mediated cleavage as well.

Solid-Supported Synthesis of HDA Adducts. Acyl- and arylnitroso HDA adducts were synthesized from polymer-supported nitroso dienophiles and dienes using recently described procedures.[7,8] Briefly, the acylnitroso HDA adducts on silyloxy linker- and Wang linker-derived ethers were prepared by immobilization of Fmoc-ethanolamine to the

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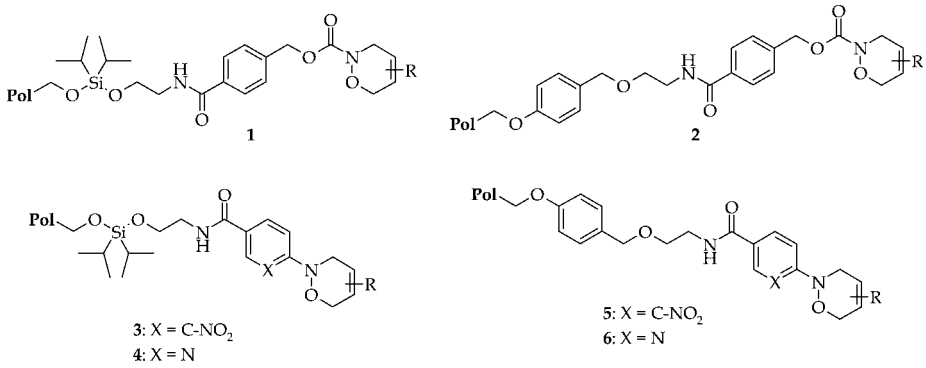
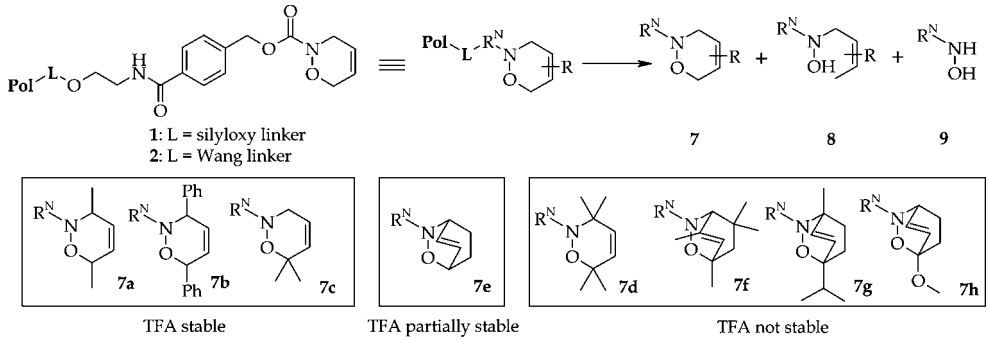


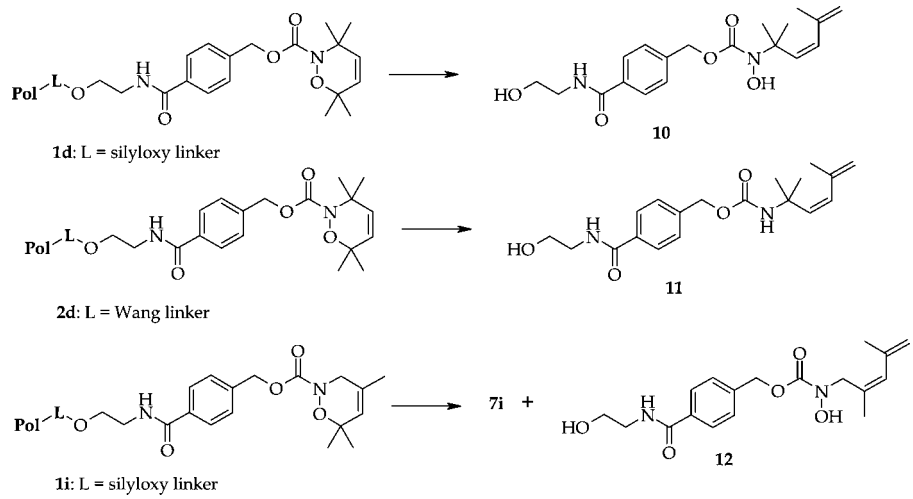
Figure 1. Polymer-supported HDA adducts. R refers to any substitution pattern on oxazine carbons, including bridged adducts.

Scheme 1. Release of HDA Adducts[a]



[a] Refer to the text for cleavage conditions.

Scheme 2. Cleavage of Resin-Bound HDA Adducts **1d**, **2d**, and **1i**



respective linkers, followed by Fmoc group removal and acylation with 4-hydroxymethylbenzoic acid. The hydroxamate was introduced by reaction of the polymer-supported benzyl alcohol with carbonyldiimidazole, followed by exposure to hydroxylamine. The oxidation was carried out in the presence of a diene that trapped the transient acylnitroso species to yield HDA adducts **1** and **2**. Both resins **1** and **2**, cleavable by different reagents TBAF and DDQ, respectively, afforded identical HDA adducts. In addition to mild nonacid reagents, the HDA adducts were cleaved also by TFA.

The arylnitroso dienophiles were prepared from 4-fluoro-3-nitrobenzoic and 6-fluoronicotinic acids immobilized via ethanolamine to silyloxy and Wang linkers (Figure 1). Fluorine was replaced by nucleophilic aromatic substitution with hydroxylamine, followed by oxidation with tetrabutylammonium periodate.[8] Both dienophiles represent electron-deficient arylnitroso species, the major differences were the presence of a nitro group ortho to the nitroso group in HDA adducts **3** and **5** and the presence of a protonatable pyridyl nitrogen in cycloadducts **4** and **6**, structural differences that turned out to have more profound effects than originally expected.

Polymer-Supported Transformations. First, we describe our results from studies with acylnitroso HDA adducts. We compared the acid stability of HDA adducts prepared using eight dienes (Figure 2): 2,4-hexadiene (diene **a**), 1,4-diphenyl-1,3-butadiene (**b**), 4-methyl-penta-1,3-diene (**c**), 2,5-dimethyl-2,4-hexadiene (**d**), 1,3-cyclohexadiene (**e**), 1,3,5,5-tetramethyl-cyclohexadiene (**f**), α-terpinene (**g**) and 1-methoxy-1,3-cyclohexadiene (**h**). The dienes were selected on the basis

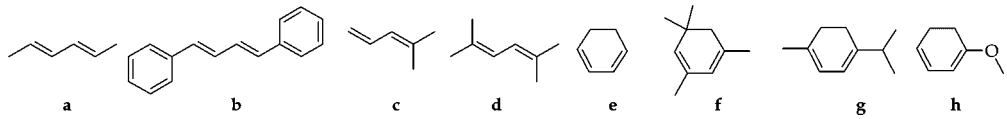
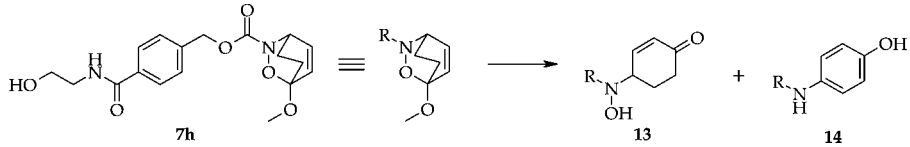


Figure 2. Dienes evaluated for acid-mediated transformations of their HDA adducts.

Scheme 3. Transformation of the HDA Adduct with 1-Methoxy-1,3-cyclohexadiene[a]



[a] Refer to the text for reaction conditions.

of our previously published data[7,8] to cover a range of sensitivities toward acid-mediated transformations of the corresponding HDA cycloadducts: dienes **a**, **b**, and **e** contained one alkyl/aryl group at both olefin terminal carbons, the other dienes contained two substituents (both alkyls or alkyl and methoxy in **h**) at one olefin terminus and none (**c**) one (**f** and **h**) and two (**d** and **g**) alkyls at the opposite end of the olefin. Both acyclic and cyclic dienes were included. The cyclic dienes formed bridged oxazine derivatives that influenced reactivity of the respective cycloaducts in acid-containing environment. In our experiment, we used dienes with symmetrical and unsymmetrical substitutions. Unsymmetrical dienes can form two regioisomers, as expected. Using appropriate NMR techniques, we determined that the tested dienes afforded one major isomer having the bulkier group at the C6 oxazine carbon.[8]

Polymer-supported HDA adducts **1** and **2** were synthesized using eight dienes according to the published procedure,[7] and the cycloadducts were cleaved by TBAF and DDQ, respectively. With the exception of 2,5-dimethyl-2,4-hexadiene (**d**) and 1-methoxy-1,3-cyclohexadiene (**h**), we isolated and characterized all HDA adducts **7** (Scheme 1).

The 2,5-dimethyl-2,4-hexadiene adduct **1d** afforded one major product upon cleavage with TBAF that revealed the expected *m*/*z* ion in the mass spectrum (Scheme 2). However, the ^{1}H and ^{13}C NMR spectra were consistent with an acyclic product **10** having the oxazine C−O bond cleaved, presumably from base-catalyzed elimination. The HDA adduct **2d**, immobilized via a Wang ether linkage, was released by treatment with DDQ and provided **11**, a N−O cleaved analog of the acyclic product.

Intrigued by this observation, particularly in the view of the fact that the HDA adduct derived from 4-methyl-penta-1,3-diene (**c**) provided, upon TBAF cleavage, the expected adduct, we also carried out the HDA reaction with 2,4-dimethyl-1,3-pentadiene (diene **i**, not included in our original set), followed by cleavage of the resin-bound product with TBAF. Two major components were identified in a cleaved sample that corresponded to the expected HDA adduct **7i** and the C−O bond-cleaved product **12** in ratio of 4:6.

The HDA adduct with 1-methoxy-1,3-cyclohexadiene, an acetal **7h**, was not stable and decomposed during HPLC purification in aqueous ammonium acetate buffer. Two components of decomposition were formed and isolated. The first product corresponded to α,β-unsaturated ketone **13** (Scheme 3). While this transformation was expected, the second compound formed by decomposition of the HDA adduct was 4-aminophenol derivative **14**. The α,β-unsaturated ketone **13** was also formed as a single product during cleavage with 10% TFA. Analogous behavior was reported in similar reactions of the HDA adduct of nitrosobenzene with 1-methoxy-1,3-cyclohexadiene.[13] Interestingly enough, the 1-methoxy-1,3-cyclohexadiene motif is contained in thebain, one of the first dienes applied in the acylnitroso HDA reaction.[14] Kirby isolated the thebain HDA adduct, and only treatment with aqueous HCl yielded the α,β-unsaturated ketone derivative.[15]

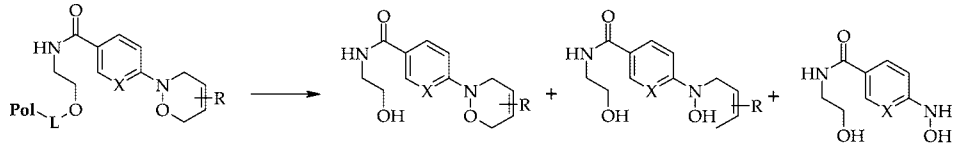
Table 1. Exposure of Acid-Sensitive HDA Adducts **1** to Various Cleavage Reagents

HDA adduct	cleavage TBAF		cleavage 10% TFA/TES		cleavage 50% TFA/TES	
	product	yield	product	yield	product	yield
1e	**7e**	82%	**7e**	73%	**8e**	28%
1e	**7f**	77%	**7f**	34%	**8f**	81%
1g	**7g**	87%	**7g**	25%	**9**	ND

HDA adducts **7** were also able to be released from resins **1** and **2** by treatment with TFA, and this enabled direct comparison of cleavage outcome by acidic reagent with TBAF and DDQ cleavages. HDA adducts **7** derived from 2,4-hexadiene, **7a**, 1,4-diphenyl-1,3-butadiene, **7b**, and 4-methyl-penta-1,3-diene, **7c**, were present as the major components in crude preparations obtained by cleavage with 50% TFA in dichloromethane (DCM) (Scheme 1). LCMS analysis of the cleaved sample derived from the HDA reaction with 1,3-cyclohexadiene revealed a mixture containing five components, including the expected product **7e**. Milder cleavage conditions, 10% TFA for 30 min, cleanly provided the expected product **7e**, indicating the instability of the HDA adduct toward more concentrated TFA. When 50% TFA was used, the HDA adducts **7f** and **7g** anticipated from the HDA reactions of 1,3,5,5-tetramethyl-cyclohexadiene and α-terpinene were not detected. Lowering the concentration of TFA to 10% only resulted in partial decomposition, and we detected the expected HDA adducts. When compared to mild TBAF cleavage, yields of HDA adducts with 1,3,5,5-tetramethyl-cyclohexadiene, **7f**, and α-terpinene, **7g**, from the corresponding resin forms of **1** were substantially reduced (Table 1).

The presence of a carbocation scavenger, 10% triethylsilane (TES) in a 50% TFA cleavage cocktail, led to the formation of *N*-alkyl hydroxamates **8e** and **8f** as the major products in the case of 1,3-cyclohexadiene and 1,3,5,5-

Scheme 4. Cleavage of Polymer-Supported Arylnitroso HDA Adducts



3, 4: L = silyloxy linker
5, 6: L = Wang linker
3, 5: X = C-NO_2
4, 6: X = N

16: X = C-NO_2
17: X = N

18: X = C-NO_2
19: X = N

20: X = C-NO_2
21: X = N

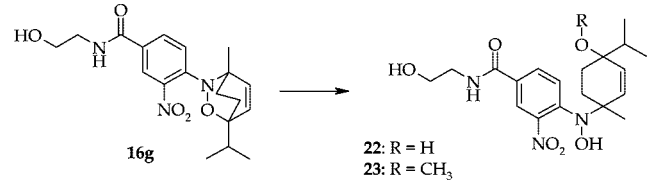
tetramethyl-cyclohexadiene HDA adducts (Scheme 1). However, 2,5-dimethyl-2,4-hexadiene and α-terpinene adducts exposed to identical conditions resulted in detection of the hydroxamate **9** as the major component in the cleaved sample.

Because C−O reduced product **8f** was obtained by direct treatment of polymer-supported HDA adduct with TES-containing TFA cleavage cocktail, we also tested the HDA adduct prepared on 4-hydroxymethylbenzoic acid directly attached to the Rink resin. The reaction expectedly afforded the corresponding C−O reduced HDA adduct **15f**.

For comparison, we now describe the results of various conditions to cleave arylnitroso HDA adducts from solid supports. Two sets of arylnitroso HDA adducts were prepared using dienes on the same silyloxy and Wang linkers (Scheme 4). The tendency toward the acid instability remained unchanged; however, there were marked differences in reactivity of individual HDA adducts with respect to the pendant *N*-aryl substituents. Cleavage of acid-sensitive resin-bound HDA adducts **3** and **5** with 10% TFA afforded HDA adducts **16f** and **17f**, albeit in lower yields. Treatment with 50% TFA yielded products in the case of adducts derived from 2,4-hexadiene (**a**), 1,4-diphenyl-1,3-butadiene (**b**), 4-methyl-penta-1,3-diene (**c**), and 1,3-cyclohexadiene (**e**). HDA adducts derived from 1,3,5,5-tetramethyl-cyclohexadiene (**f**) and α-terpinene (**g**) were decomposed, and the corresponding arylhydroxylamines **20** and **21** were detected. The addition of TES to the cleavage cocktail led to quantitative conversion to the *N*-alkyl-*N*-aryl hydroxylamine **19f** in the case of HDA adduct formed from 1,3,5,5-tetramethyl-cyclohexadiene; however, the reaction time had to be extended to 2 h to achieve quantitative conversion. Surprisingly, the corresponding *N*-alkyl-*N*-aryl hydroxylamine **18f** was not present. HDA adducts from 2,5-dimethyl-2,4-hexadiene and α-terpinene were decomposed, and the corresponding hydroxylamine derivatives were detected as major products.

Off-Resin Transformations. Preparative useful acid-mediated transformations of HDA adducts having two alkyl groups on both the C3 and the C6 oxazine carbons is problematic because of the instability of both the C−N and C−O bonds. Since the *t*-Bu-type of protecting group attached to oxygen is less acid-stable when compared to the same protection of an amide nitrogen,[16] we attempted to find conditions for cleavage of the C−O bond without affecting the C−N bond. The application of linkers cleavable with nonacidic reagents facilitated release of HDA adducts by mild reagents and provided the opportunity to expose the model α-terpinene HDA adducts to milder acidic conditions when compared to conditions required for acid-mediated release from the resin. We exposed the HDA adduct to diluted trifluoroacetic acid in THF-containing water as a potential carbocation scavenger and compared reactivity of three HDA adducts **7g**, **16g**, and **17g** with α-terpinene to assess the effect of the N-substituent. The nitroaryl-derived adduct **16g** was almost instantaneously converted into the expected product **22** in high yield in a THF/water mixture containing 3% TFA (Scheme 5). The product was isolated, purified, and characterized. The ^{1}H NMR spectrum revealed the presence of two olefinic protons, thus unequivocally confirming the structure of the 1,4-hydroxylamino alcohol **22**. Because of the partial acid-lability of the HDA adduct with cyclohexadiene, we also evaluated the tendency toward C−O bond scission of this adduct synthesized using 3-nitro-4-nitroso-benzoate directly attached to Rink resin (i.e., adduct **16e** missing the ethanolamine appendage) and isolated the corresponding *N*-alkyl-*N*-aryl hydroxylamine derivative (compound **15e**).

Scheme 5. Transformation of α-Terpinene HDA Adduct in Solution[a]



16g

22: R = H
23: R = CH_3
24: R = CH_2-CH_2OH

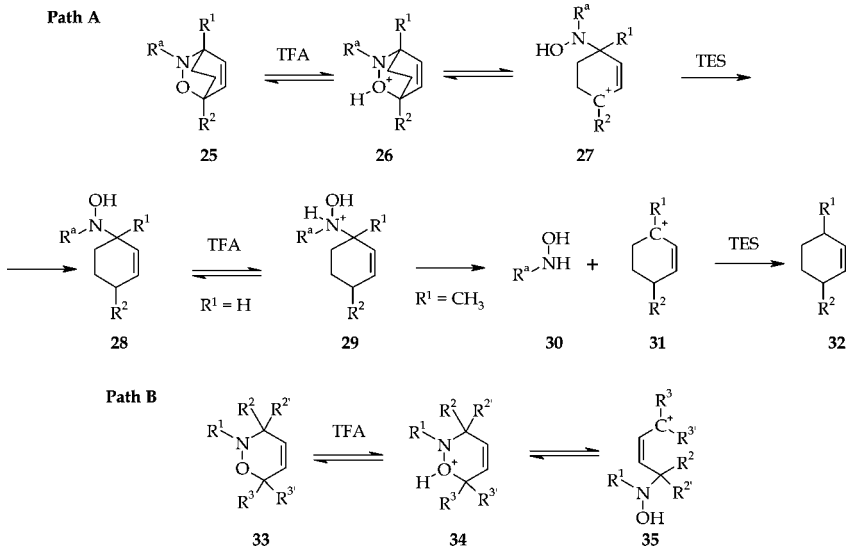
[a] Refer to the text for reaction conditions.

Encouraged by this result, we explored the possibility of quenching the carbocation with alcohols. The conversion to ether **23** was instantaneous in the presence of methanol. In addition to methanol, we also evaluated the reaction in ethanol, *n*-propanol, and 1,3-propanediol. While the conversion to 1,3-propanediol adduct **24** was complete in 30 min, lengthening the alkyl chain of the alcohol decelerated the reaction rate substantially (not complete overnight).

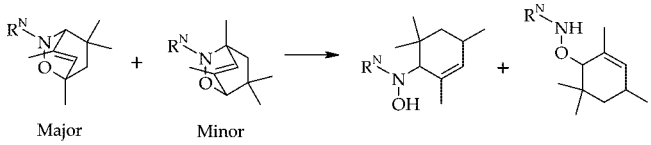
The acylnitroso-derived adduct **7g** was still stable in 10% TFA in methanol/THF overnight, whereas exposure to 10% TFA in water/THF mixture overnight caused cleavage of the oxazine C−O bond and formation of the alcohol. However, the C−N bond was cleaved under those conditions as well, and the major component of the reaction mixture was the corresponding hydroxamate.

Pyridyl adduct **17g** decomposed upon exposure to 3% TFA without forming a detectable amount of the corresponding *N*-alkyl hydroxylamine derivative. The pyridyl-derived HDA adduct **17g** was the most acid-sensitive of all substrates studied, and we detected the formation of the reduced product among several components of a complex reaction mixture

Scheme 6. Acid-Mediated Transformation of Oxazines



Scheme 7. Cleavage of Two Regioisomers of 1,3,5,5-Tetramethyl-cyclohexadiene HDA Adducts



only when exposed to THF/methanol solution containing a Lewis acid ($BF_3 \cdot Et_2O$). The different reactivity of HDA adducts was attributed to different electronic properties of the N-substituent: the electron-deficient acyl derivative **7g** was the most resistant (among three compounds tested) toward protonation required for subsequent transformation. On the other end of the reactivity scale, the pyridyl derivative **17g**, was especially prone to protonation and, consequently, was amenable to cleavage of both the C−O and C−N bonds.

Discussion

Analysis of experimental results indicated that the acid stability of HDA adducts was predominantly influenced by substituents at the C3 and C6 carbons of the oxazines and to lesser extend by the N-substituent. In addition, bridged oxazines, prepared from cyclic dienes, were considerably less stable than the unbridged analogs obtained from acyclic dienes. Thus, not surprisingly, the fate of oxazines in acidic milieu was found to depend on the substituents and on the presence of a bicyclic or single-ring structure.

TFA, a relatively strong acid that promotes formation of cationic species, is thus capable of cleaving the C−O and C−N oxazine bonds. In TFA, the oxazine oxygen of **25** and **33** is protonated, and the fate of the corresponding protonated species **26** and **34** was found to depend on the propensity to stabilize carbocations **27** and **35** (Scheme 6, paths A and B for bridged and single-ring oxazines). The presence of one alkyl group on the C6 carbon was not sufficient to induce carbocation formation, and the related oxazines were determined to be stable in TFA-based solutions typically used for liberating target compounds from acid-labile linkers. The presence of two alkyl groups or one alkyl and one methoxy group on the C6 carbon increased the stability of the corresponding carbocations, and the oxazine C−O bond was cleaved. The presence of one phenyl group did not induce the C−O bond cleavage; however, the HDA adduct containing a phenyl group with electron-donating alkoxy groups is not acid stable (Krchňák and Miller, manuscript in preparation).

The eventual fate of the cationic species depended on the structure of the HDA adduct. We observed substantial differences in the stability of HDA adducts **25** and **33** prepared from cyclic and acyclic dienes. Cyclic dienes afforded less-stable bridged oxazines **25** (Scheme 6, path A). Cleavage of the C−O bond of bridged oxazines yielded forms of carbocation **27** on a carbocyclic six-membered ring that do not have a high propensity to reclose to bridged compounds and can be quenched by addition of carbocation scavengers. Scavengers, such as TES, present in reaction mixtures, quenched the cyclic carbocations represented by **27** and led to formation of *N*-alkylhydroxamates/hydroxylamines **28**.

On the other hand, cleavage of monocyclic oxazines formed carbocations **35** as linear species with a high tendency to reclose to six-membered ring systems such as **26**. In fact, precedence has shown that formation of a carbocation from a tertiary alcohol can be used to prepare an oxygen-containing six-membered ring.[17] The formation of cationic species **35** was proven by formation of a reduced HDA adduct in the presence of TES, but not water or alcohols. There is substantial difference between TES and water/alcohol scavengers. TES-mediated formation of a C−H bond is not reversible, whereas the formation of alcohols and ethers formed by scavenging with water and alcohols, respectively, is a reversible process.

The presence of two alkyl groups on the C3 carbon also labilized the C−N bond, and exposure of those compounds to TFA led to scission of both the C−O and the C−N bonds and complete decomposition of the HDA adduct with formation of hydroxylamine **30**. The protonated species **29**, derived from 1,3,5,5-tetramethyl-cyclohexadiene adducts (R^1 = H), was stable toward C−N bond scission. However, the α-terpinene

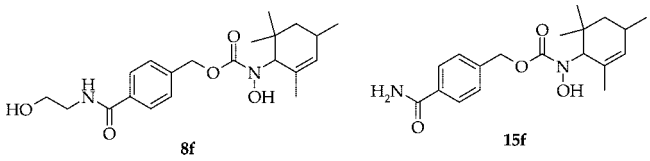


Figure 3. Structures of reduced HDA adducts.

Table 2. Exposure of HDA Adducts **5** and **6** to Various Cleavage Reagents[a]

HDA adduct	cleavage TBAF		cleavage 10% TFA		cleavage 50% TFA/TES	
	product	yield	product	yield	product	yield
5f	**16f**	83%	**16f**	26%	**20**	ND
5g	**16g**	83%	**16g**	~3%	**20**	ND
6f	**17f**	85%	**17f**	65%	**19f**	69%
6g	**17g**	84%	**17g**	~3%	**21**	ND

[a] Major component in samples cleaved by 10% TFA were arylhydroxylamines **20** and **21**, respectively. ND refers to not determined

analog was cleaved because of the stabilizing effect of the additional methyl group (R^1 = Me). Thus, bridged oxazines containing alkyl substituents on both C3 and C6 carbons were completely decomposed to hydroxamates (or hydroxylamines, depending on the nature of the substituent). This behavior can be exploited, for example,for conservation of reactive arylnitroso compounds in a form of acid-labile α-terpinene HDA adducts and release either by acid cleavage, followed by oxidation, or retro-HDA reaction at elevated temperature (Krchňák and Miller, manuscript in preparation).

Because the major regioisomer formed by the HDA reaction with unsymmetrical dienes contained the bulkier substituent at the C6 carbon,[8] we did not test any compound that would have two alkyl groups on the C3 carbon and only one on the C6 carbon. Such compounds would be prone to cleavage of the C−N bond and formation of the *O*-alkyl hydroxamates/hydroxylamines. We observed formation of the minor isomers in HDA adducts generated from 1,3,5,5-tetramethyl-cyclohexadiene, and treatment with a TES containing cleavage cocktail resulted in two compounds having the *m*/*z* ions corresponding to two isomeric products. However, because of the minute quantities of the minor isomer, we did not isolate and characterize it.

All synthesized compounds were subjected to a panel of biological assays that included tests for antimicrobial, antiinflammatory, antiproliferative, and cytotoxicity activities. Assay details are described in the Supporting Information.

Antimicrobial activity was determined by agar diffusion tests using a panel of Gram-positive and Gram-negative bacteria, yeasts, and fungi. The *N*-alkyl-*N*-aryl hydroxylamine derivative **23** showed weak but broad antimicrobial activity against all groups of microorganisms used. Compound **19f** displayed selective activity against Gram-positive bacteria but not against mycobacteria.

Antiinflamatory activity in the horse radish peroxidase assay, comparable to the standard, *N*-acetylcystein, was exhibited by compounds **10** and **22** and at weaker potency by compounds **12**, **23**, and **24**.

Compound **11** exhibited moderate antiproliferative efficacy against K-562 cells. Compound **19f** showed moderate antiproliferative efficacy on L-929. Strong cytotoxicity in HeLa cells, but not antiproliferative activity, was exhibited by the *N*-alkyl-*N*-aryl hydroxylamine derivative **15e**.

Conclusion

Acid-instability of dihydro[1,2]oxazines prepared by the acyl- and arylnitroso HDA reactions is influenced by three factors: substituents at the C3 and C6 carbons, presence of a bridge between the C3 and C6 carbons, and to lesser extent by the *N*-substituent. Acid-mediated transformations of acid-labile oxazines were used to access novel *N*-alkyl hydroxamate/hydroxylamine derivatives by cleavage of the oxazine C−O bond and subsequent quenching of the cationic species by nucleophiles including TES, water, and alcohols. Assays indicated that even simple products generated from acid-mediated openings possess hints of activity that might be useful as leads in the development of biologically active compounds.

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Supporting Information Available. Details of experimental procedures and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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