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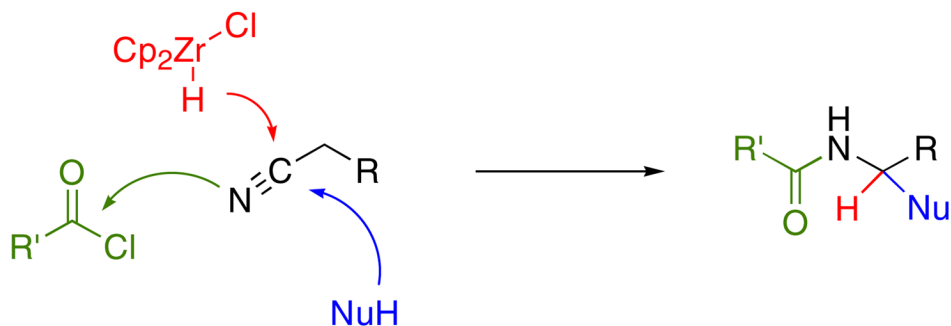
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Multicomponent Approach to the Synthesis of Oxidized Amides through Nitrile Hydrozirconation

Shuangyi Wan, Michael E. Green, Jung-Hyun Park, and Paul E. Floreancig*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

Abstract



“Oxidized” amides, as represented by acyl amins and acyl hemiaminals, are integral subunits of several natural products that exhibit useful biological activity. In this manuscript a multicomponent approach to these groups from acylimine intermediates is demonstrated. The acylimines are accessed through a sequence of nitrile hydrozirconation and acylation, making this highly versatile amide synthesis useful for a range of range of applications in target- and diversity-oriented synthesis.

Natural products that contain “oxidized” amides, in which the carbon bonded to the nitrogen atom has an oxidation state that is higher than the usual (+1) level, effect an impressive range of biological responses. These compounds are represented acyl hemiaminals such as the cytotoxins zampanolide¹ (**1**) and tallysomycin,² and acyl amins such as the protein synthesis inhibitors psymberin (**2**)³ and pederin.⁴ These compounds have evoked substantial synthetic efforts, and several approaches to the synthesis of the oxidized amide groups⁵ and natural product total syntheses⁶ have been disclosed. SAR studies have demonstrated that oxidized amides are important for the biological activities of these natural products.⁷ While these groups have been proposed to serve as latent acyliminium ions⁸ only one report⁹ has appeared in the literature that compellingly establishes protein alkylation through Schiff base formation from an enamide, another important class of oxidized amide. In addition to their roles in conferring biological activity, acyl amins have been used as latent electrophiles in stereoselective carbon–carbon bond forming reactions.¹⁰

In principle oxidized amide groups can be prepared from acylimine intermediates (Scheme 1), with acyl amins being accessed through alcohol addition¹¹ and acyl hemiaminals being accessed through water addition. Additionally, enamides could be accessed through tautomerization. This strategy is limited, however, by the dearth of methods for preparing acylimines. Condensation reactions between aldehydes and amides are ineffective when the aldehyde is enolizable. While this problem can be addressed by adding sulfonates to form α -

sulfonyl amides,¹² regenerating and isolating the acylimine is difficult (though not impossible)¹³ because of the sensitivity of the intermediates.

In consideration of our interests in the synthesis of **1**, **2**, and related structures¹⁴ we sought to develop a universal approach to acylimine construction from easily handled precursors and to establish conditions for the preparation of each class of oxidized amide. Acylating metalloimines¹⁵ is an attractive approach to acylimine formation (Scheme 2). This route can be executed by preparing metalloimines from selective nitrile hydrometallation followed by acid chloride addition. Given the abundant reactions that have been developed for nitrile synthesis and the relatively inert nature of nitriles (compared to other electrophilic groups) to most reaction conditions, this strategy should be useful in the synthesis of complex natural products. Majoral and coworkers have reported¹⁶ that treating sterically hindered nitriles with Schwartz' reagent ($\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$)¹⁷ followed by adding sterically hindered acid chlorides yields isolable acylimines.¹⁸ In this manuscript we demonstrate that the sequence of nitrile hydrozirconation, acylation, and nucleophile addition results in a versatile multicomponent approach to oxidized amides.

In our initial foray into this method (Scheme 3), we exposed cyanohydrin ether **3**, prepared through a BiBr_3 -mediated addition of TMSCN to the corresponding dimethyl acetal,¹⁹ to hydrozirconation, acylation with $\text{PhOC}(\text{O})\text{Cl}$, and MeOH addition. Diastereomers **4** and **5** were isolated from the reaction in a 55% combined isolated yield and with a diastereomeric ratio of 2.4:1. This reaction is consistent with the formation of linear^{18a} metalloimine **6**, which can undergo acylation to provide an acylimine intermediate. Nucleophilic addition of MeOH can proceed through intermediate **7**, in which chelation is enforced through hydrogen bonding with MeOH to form major product **4** or through Felkin-type intermediate **8** to form minor product **5**. The stereochemical assignments for **4** and **5** were established through subjecting **9**, prepared as a single stereoisomer, to a Curtius rearrangement²⁰ and observing the formation of **5** as the sole product.

With the initial reactivity patterns established, we turned our attention to studying the scope of the process (Table 1). Ethoxy nitrile **10** served as the substrate for the initial phases of this study. When isobutyryl chloride is used for the acylation reaction, both CH_2Cl_2 (entry 1) and THF (entry 2) can be employed as reaction solvents. Interestingly, a modest change in stereoselectivity occurs when the solvent is changed from CH_2Cl_2 to THF whereby the major product in CH_2Cl_2 results from chelation control and the major product in THF results from Felkin-type addition.²¹ The capacity of THF to form hydrogen bonds with MeOH is likely the source of diminished chelation control. For reactions that are conducted in CH_2Cl_2 , the entire process can be executed in approximately 30 min since the hydrozirconation and acylation steps proceed to completion within a few minutes and the MeOH addition is instantaneous. Chelation control can be improved ($\text{dr} = 5.7:1$) without sacrificing yield by adding a stoichiometric amount of $\text{Mg}(\text{ClO}_4)_2$ following the acylation step and conducting the MeOH addition at -78°C (entry 3). Notably, the MeOH addition reaction is still instantaneous at -78°C . Metalloimine acylation with α -methoxy acetyl chloride provides an acyl aminal (entry 4) that is electronically similar to the acyl aminal in psymberin. A readily cleaved carbamate can be accessed through acylation with CbzCl (entry 5). Unfortunately sulfonyl aminals could not be prepared in high yields, as shown in entry 6, with substantial amounts of the aldehyde that results from direct nitrile reduction and hydration being isolated.

Nucleophiles other than MeOH also proved to be suitable for the reaction. Steric hindrance does not suppress nucleophilic addition, as demonstrated by the reaction with $t\text{BuOH}$ (entry 7), though the major product results from the Felkin-type pathway. Phenol (entry 8) and thiophenol (entry 9) are also suitable nucleophiles, with phenol reacting through the chelation pathway and thiophenol reacting through the Felkin-type pathway, consistent with their relative

abilities to engage in hydrogen bonding. In addition to the capacity to reverse the stereochemical outcome of the addition reaction, entry 9 represents an excellent method to prepare latent acyliminium ions that can be revealed through oxidation.²²

Structural variations in the nitrile component are also tolerated (Table 2). Benzoylated cyanohydrin **19** can be converted to acyl aminor **20** in 64% yield (entry 1), demonstrating that hydrozirconation can be selective for nitriles in the presence of ester groups.²³ In consideration of the acyl hemiaminal in zampanolide, we simply subjected the acylimine from the hydrozirconation of **19** to a direct aqueous work-up and isolated acyl hemiaminal **21** in 54% yield (entry 2). The stereochemical outcomes of the products from **19** were not determined. Nitriles that are not branched at the α -position can serve as substrates for the sequence, though THF is a superior solvent for inhibiting acylimine tautomerization and subsequent oligomerization. Octyl cyanide can be converted to acyl aminor **23** and acyl hemiaminal **24** in yields that are only modestly lower than those that are observed for branched substrates (entries 3 and 4). Aromatic nitriles, while undergoing hydrozirconation substantially more slowly than aliphatic nitriles, are excellent substrates, with acyl aminor **26** being formed in 73% yield.

To apply this process in a more complex setting that is relevant to the synthesis of psymberin, pederin, and analogs, we prepared (Scheme 4) nitrile **29** from the known^{14b} ketone **27** through a sequence that employs a Lewis acid-promoted reduction with Bu_3SnH ²⁴ to establish relative stereocontrol to provide **28**. Interestingly, the stereochemical outcome of this reaction does not follow from the chelation-control that is generally observed²⁴ in this procedure.

Tetrahydropyran formation through a sequence of ozonolytic alkene cleavage, acylation, and cyanide introduction yielded **29**. Hydrozirconation, acylation with isobutyryl chloride, and MeOH addition in the presence of $\text{Mg}(\text{ClO}_4)_2$ provided acyl aminor **30** in 54% yield, diastereomer **31** in 23% yield, and a small amount (~10%) of the amide that arises from reduction of the intermediate acylimine with the slight excess of Schwartz' reagent that is used in these reactions. Stereochemical assignments were based on ^1H NMR splitting pattern and chemical shift analogies to known compounds²⁵ in the pederin/psymberin family. While chelation controlled addition could not be promoted to the same extent as was observed for **10**, the high overall chemical yield and reasonable stereocontrol provide the desired acyl aminor with the desired stereochemical orientation efficiently and with the potential for extensive structural variation. Also notable in this transformation was the absence of epimerization at the carbon that bears the cyano group, indicating that these conditions do not erode the stereochemical purity of cyanohydrin ethers.

We have described a one pot multicomponent approach to the synthesis of oxidized amides from nitriles. In consideration of the numerous methods that are available for nitrile preparation, the capacity for variation of the nucleophile, electrophile, and nitrile components, the inherent utility of the products as subunits of numerous biologically active compounds, and the ability to employ the products as starting materials in stereoselective transformations, this process is well-suited for applications in target- and diversity oriented²⁶ synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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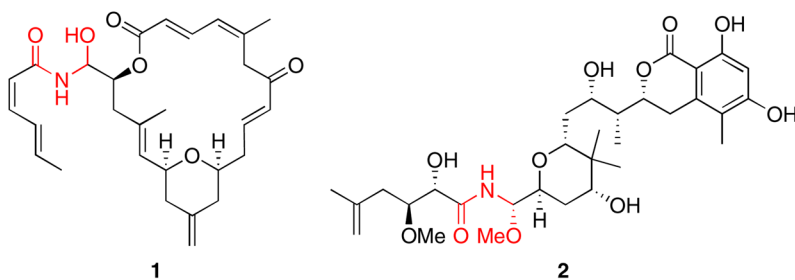
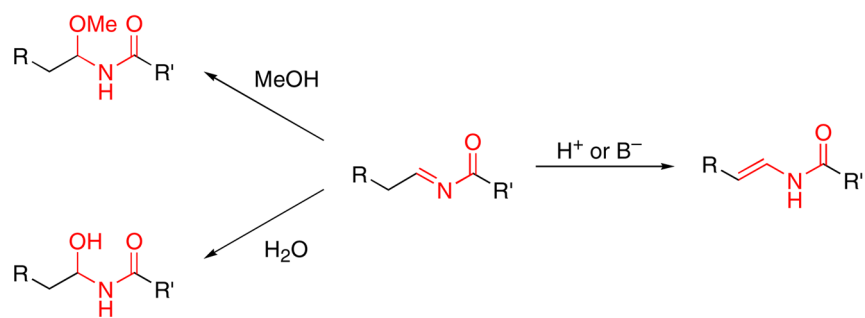
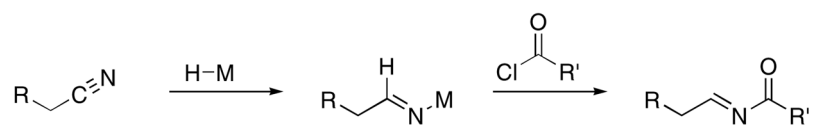


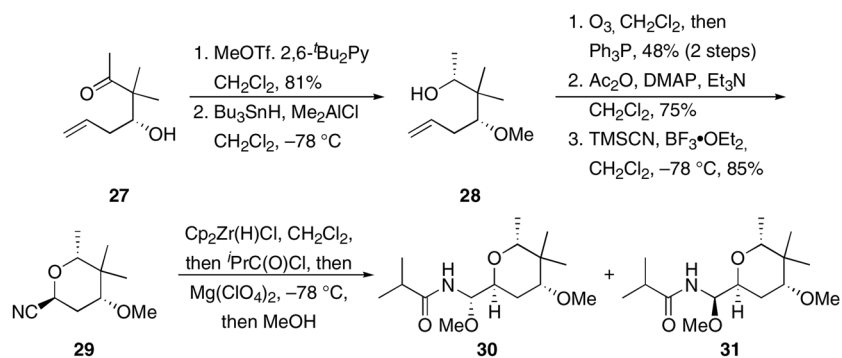
Figure 1.
Natural products that contain oxidized amides.



Scheme 1.
Oxidized amides from acylimines.

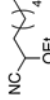
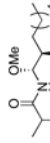
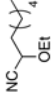
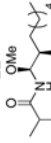
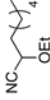
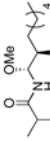
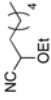
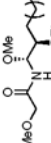
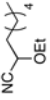
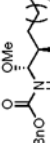
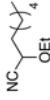
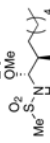
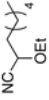
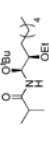
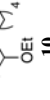
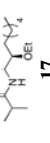
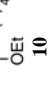
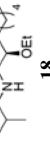
**Scheme 2.**

Acylimine formation through nitrile hydrometallation and acylation.



Scheme 4.
 Synthesis of a tetrahydropyranyl acyl amination.

Table 1
Nucleophile and electrophile scope in acyl amination synthesis.^a

entry	substrate	solvent	electrophile	nucleophile	major product	yield (dr) ^b
1		CH ₂ Cl ₂	^t PrC(O)Cl	MeOH		75% (2:3:1)
2		THF	^t PrC(O)Cl	MeOH		64% (1:4:1)
3 ^c		CH ₂ Cl ₂ /Me ₂ (ClO ₄) ₂	^t PrC(O)Cl	MeOH		71% (5:7:1)
4		CH ₂ Cl ₂	MeOCH ₂ C(O)Cl	MeOH		69% (1:7:1)
5		CH ₂ Cl ₂	ChzCl	MeOH		64% (1:5:1)
6		CH ₂ Cl ₂	Ms ₂ O	MeOH		24% (2:4:1)
7		CH ₂ Cl ₂	^t PrC(O)Cl	^t BuOH		71% (2:0:1)
8		CH ₂ Cl ₂	^t PrC(O)Cl	PhOH		69% (5:6:1)
9		CH ₂ Cl ₂	^t PrC(O)Cl	PhSH		72% (7:0:1)

^aRepresentative procedure: CppZr(H)Cl (1.2 equiv) was added to a solution of the substrate in the solvent (0.1 M). The mixture stirred for 10 min at rt, then was cooled to 0 °C. The electrophile (1.2–1.5 equiv) was added and stirred for 10 min. The nucleophile (20 equiv) was added and the reaction was stirred for a few additional minutes.

^bYields refer to the sum of the yields of the diastereomers.

^cNucleophilic addition was conducted at –78 °C.

Table 2

Nucleophile and electrophile scope in acyl amination synthesis.^a

entry	substrate	solvent	electrophile	nucleophile	major product	yield (dr)
1 ^b		CH ₂ Cl ₂	^t PrC(O)Cl	MeOH		64% (1.4:1)
2 ^b		CH ₂ Cl ₂	^t PrC(O)Cl	H ₂ O		52% (3.0:1)
3		THF	^t PrC(O)Cl	MeOH		62%
4		CH ₂ Cl ₂ /Et ₃ N	^t PrC(O)Cl	H ₂ O		54%
5		THF	^t PrC(O)Cl	MeOH		73%

^a See Table 1 for representative procedures.^b Stereochemical relationships for the major and minor product diastereomers were not determined.