



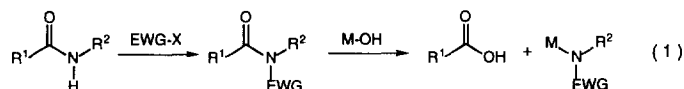
Mild Nitrosation and Hydrolysis of Polyfunctional Amides

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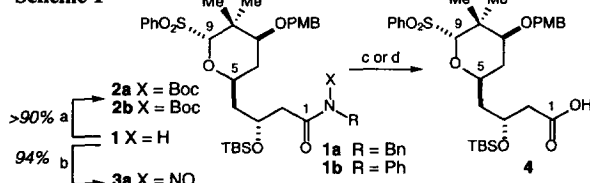
Abstract: Secondary amides may be hydrolyzed *via* a mild, high-yielding sequence consisting of *N*-nitrosation, treatment with lithium hydroperoxide, and reduction with sodium sulfite. These operations may be executed in the presence of an array of functional groups, including other amide functionality. © 1997 Elsevier Science Ltd.

Secondary amides are advantageous carboxylic acid protecting groups due to their acid and base stability, resistance to nucleophilic attack, and good chromatographic behavior. Despite these properties, they are infrequently employed in this capacity, primarily because conventional amide hydrolysis under either strongly basic or acidic conditions is a difficult operation to carry out in a polyfunctional setting.¹ It has been shown previously that derivatization of secondary amides to either imides (EWG=CO₂R)² or *N*-nitrosamides (EWG=NO)³ facilitates hydrolysis (eq 1).⁴ In this Letter, we disclose our studies on the synthetic utility of these reactions, and describe a mild procedure for the hydrolysis of secondary amides consisting of amide nitrosation followed by basic peroxide mediated hydrolysis. This procedure may be executed reliably in the presence of sensitive functionality, which we demonstrate in the context of two different synthetic studies.



Bryostatin Studies. In our efforts⁵ directed toward the synthesis of the marine macrolide bryostatin 1,⁶ sulfonylamide **1** (Scheme 1) serves as a C₉ carbonyl anion equivalent.⁷ The terminal amide functions admirably in C₉-C₁₀ bond constructions with the lithiated dianion of sulfone **1b**. However, in our attempts to hydrolyze the C₁ amide of more advanced intermediates, we found that application of standard methods such as nitrosation/thermolysis⁸ or direct amide hydrolysis⁹ resulted in extensive substrate decomposition.

Scheme 1



entry	substrate	conditions	% acid ^a	T °C	time
A	2a (Boc)	LiOH	51	25	17 h
B	2b (Boc)	LiOH	70	25	14 h
C	3a (N=O)	LiOH	90	0	50 min
D	2a (Boc)	LiOOH	94	25	12 h
E	3a (N=O)	LiOOH	>95	0	<5 min

^a % conversion, as assayed by 500 MHz ¹H NMR.

(a) Boc₂O, DMAP, MeCN, 2 h, 25 °C. (b) NaNO₂, 1:2 AcOH:Ac₂O, 30 min, 0→25 °C. (c) 10 equiv. LiOH, 3:1 THF:H₂O, time, T °C. (d) 10 equiv. LiOH, 20 equiv. 30% H₂O₂, 3:1 THF:H₂O, time, 0→T °C; Na₂SO₃, 5 min, 0 °C.

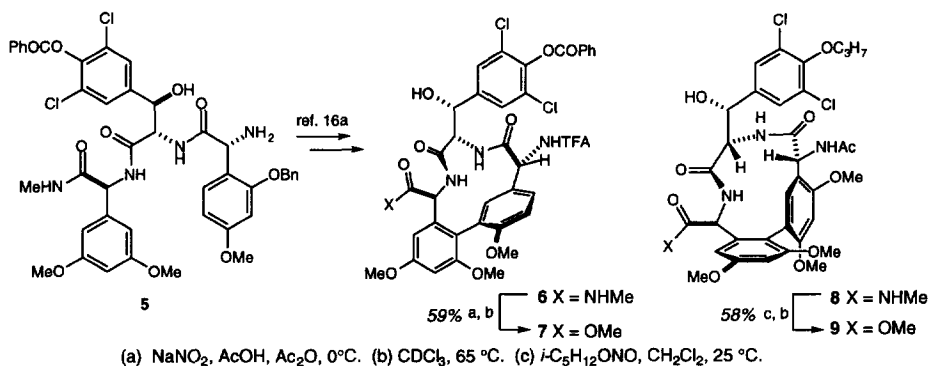
On the basis of these results, we investigated the two-step process of amide activation and hydrolysis on amide **1** (Scheme 1).¹⁰ Activation of **1** through *N*-carboxylation^{2,11} or *N*-nitrosation¹² was accomplished in good yield. Saponification of the imide **2a** with lithium hydroxide (THF-H₂O, 25 °C) according to the Grieco procedure² (entry A) was sluggish and complicated by the base-promoted elimination of the C₃ silyloxy group. This reaction could be improved by lowering the pK_a of the leaving group, through the use of either the anilide or nitrosamide derivatives **2b** (entry B) or **3a** (entry C) respectively; however, these reactions were still flawed

by the base-induced elimination of the C₃ protected alcohol. In analogy to our earlier work with the hydrolysis of *N*-acyloxazolidinones,¹³ we explored the use of lithium hydroperoxide (LiOH, excess 30% H₂O₂) as a less basic alternative to lithium hydroxide. In accord with our expectations, this reagent combination afforded nearly quantitative conversion to the carboxylic acid **4** in each instance (entries D & E).

Several aspects of the above study deserve comment. First, these data again demonstrate the advantage of lithium hydroperoxide¹³ in the cleavage of base-sensitive activated esters. Second, it is noteworthy that the reaction of *N*-nitrosamide **3a** was several orders of magnitude more rapid than that of the imide **2a** under both of these hydrolysis conditions (entry C vs. A, and entry E vs. D), suggesting that the nitrosamide is both a more effective leaving group and a better carboxyl activating agent than the corresponding *N*-Boc imide.¹⁴ Finally, the mild hydrolysis of *N*-nitrosamide **3a** stands in stark contrast to previous examples from the literature,¹⁵ where strongly basic conditions and high temperatures (60-100 °C) are employed to effect *N*-nitrosamide hydrolysis.

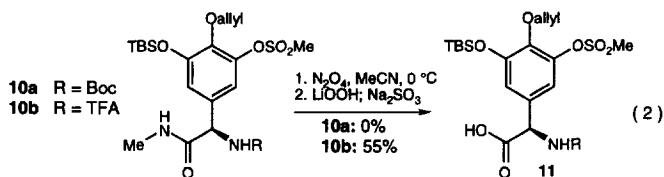
Vancomycin Studies. During the course of our studies on the synthesis of the vancomycin class of glycopeptide antibiotics,¹⁶ we have also employed an *N*-methyl amide protection strategy for the carboxyl terminus to circumvent epimerization of the terminal arylglycine residue (Scheme 2). In contrast to the bryostatin studies, the use of the two-step amide activation sequence for the deprotection of a C₁ amide requires differentiation of the C-terminal amide from other amide functionality in the peptide backbone during both the activation and cleavage steps.

Scheme 2



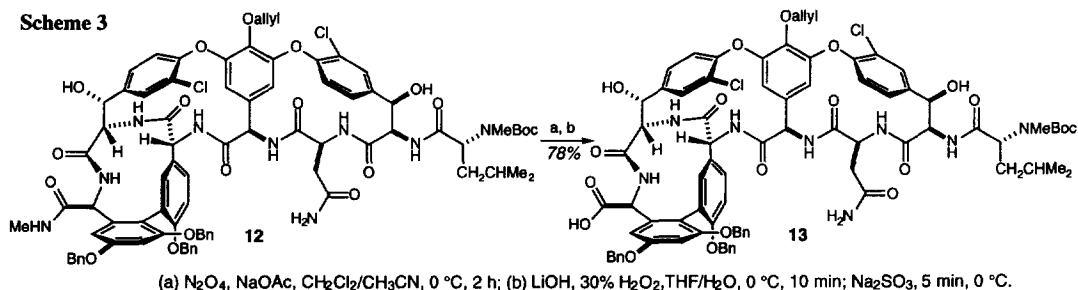
Our initial work focused on the selective derivatization of the macrocyclic tripeptides **6** and **8** (Scheme 2). While it proved impossible to selectively acylate the terminal *N*-methyl amide with Boc₂O, nitrosation under a variety of conditions (NaNO₂, AcOH; or *i*-C₅H₁₂ONO)^{12,17} afforded good selectivity for the C₁ amide over the hydroxyl¹² and backbone secondary amide groups. Since a carboxylic acid was not yet required in the synthesis, we utilized White's thermal rearrangement^{8a} to obtain the methyl esters **7** and **9**. Although Vilarrasa has shown that *N*-nitrosation with nitrogen dioxide is sensitive to steric effects in peptide systems,¹⁸ we were surprised by the level of selectivity noted for these reactions (Scheme 2).

Additional studies from our lab have indicated that the origins for this selectivity may be at least partly electronic in nature (eq 2). While selective nitrosation of the *N*-methyl amide could not be achieved with carbamate **10a**, the trifluoroacetamide analog **10b** could be nitrosated with high (>95:5) selectivity. Subsequent saponification using lithium hydroperoxide¹³ was the most effective method for cleaving the intermediate nitrosamide.



Although results from these and other laboratories have indicated that the competition between carbamates and amides during nitrosation is subject to a number of factors,¹⁹ it would appear that the use of a more electron-deficient acetamide protecting group (as in **10b**) provides for selective amide nitrosation.

With these data in hand, we then focused our attention on substrates relevant to the late stages of the vancomycin total synthesis. Degradation of vancomycin through a straightforward four-step sequence afforded amide **12** (Scheme 3), a suitable substrate with which to test our nitrosation/hydrolysis strategy. Although primary amides are known substrates for the nitrosative deamination reaction,²⁰ model studies revealed that *nitrosation of methyl amides is more rapid than nitrosation of primary amides*.²¹ In the event, nitrosation under carefully controlled conditions,²² followed by cleavage with lithium hydrogen peroxide and reduction of the acylperoxide with sodium sulfite afforded acid **13** in 78% yield.



Conclusion. We have developed a mild method for the saponification of secondary amides involving *N*-nitrosation and cleavage of the resultant nitrosamide with lithium hydroperoxide. This investigation illustrates the following points: (1) *N*-nitrosamide derivatives react as active esters in hydrolysis reactions,⁴ and are much more reactive than the corresponding imide partners;² (2) the lithium hydrogen peroxide/sodium bisulfite reagent combination¹³ is superior to other standard hydrolysis procedures for *both* imides and *N*-nitrosamides; and (3) this method may be employed to selectively hydrolyze unhindered methyl amides in the presence of primary amides and sterically crowded secondary amides. The availability of this method has allowed us to employ secondary amides for carboxylic acid protection in complex synthetic efforts, and thereby avoid the complications arising from the base sensitivity of esters.

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