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Thio acid-mediated conversion of azides to amides – Exploratory studies en route to oroidin alkaloids

Apsara K. Herath [a], Manoj R. Bhandari [a], Delphine Gout [a], Muhammed Yousufuddin [b], Carl J. Lovely [a,*]

[a] Department of Chemistry and Biochemistry, 700 Planetarium Place, University of Texas at Arlington, TX 76019, USA
[b] Life and Health Sciences Department, 7400 University Hills Blvd, University of North Texas at Dallas, Dallas, TX 75241, USA

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ABSTRACT

The utility of the thio acid-azide coupling reaction to afford amides is explored in imidazole-containing substrates for application in the total synthesis of examples of oroidin alkaloids. Good yields of the expected amides are obtained in both monomeric and dimeric substrates. Bis azides react preferentially at the 2-azido position but hydrosulfenylation and reduction interfere. 2-Thiophenyl and 2-oxo groups were evaluated as 2-amino surrogates, the thioether delivered the expected amide, whereas 2-imidazolone gave a mixture of the expected amide and the hydrosulfenylation product.

The nagelamide alkaloids[1] (e.g., **1**–**6**, Fig. 1)[2] are a subfamily of the marine-sponge derived pyrrole 2-aminoimidazoles (oroidin)[3] natural products which were first reported in 2004 by Kobayashi and co-workers.[4] Much like their parent family, these alkaloids exhibit a variety of structural frameworks, but are typically characterized by the presence of two oroidin units, i.e., are so-called oroidin dimers.[1a] Our lab has investigated approaches to several members of this family, including nagelamides A, C and D (**1**–**3**) based on a cross-coupling strategy using functionalized vinylimidazoles that may ultimately provide a divergent entry to a plethora of other family members.[5] Such an approach was successful in constructing the reported structure of nagelamide D (**3**)[6] and we wished to extend this chemistry to other family members[5] including the total synthesis of nagelamide A (**2**) and nagelamide C (**1**).[7] Application of our cross-coupling strategy provided access to the frameworks of both molecules (see Scheme 3 for details) but in contrast to nagelamide D,[6] the double Mitsunobu reaction with a masked dibromopyrrole derivative[7b] proceeded with allylic transposition. Extensive experimentation failed to provide a solution to this issue of rearrangement and thus we elected to identify an alternative strategy to address this synthetic roadblock.

One of the attractions of the Mitsunobu strategy was that it permitted the direct incorporation of the pyrrolecarboxamide moiety without the intermediacy and acylation of a polar diamine and if possible we sought to identify a method which retained this design feature.[8] As various possibilities emerged, the reaction of azides and thio acids to provide amides, initially observed by Just,[9] explored by Rosen[10] and subsequently expanded by Williams and co-workers,[11] including the detailed study of the reaction mechanism[12] appeared to be particularly attractive. This chemistry has broad substrate scope in terms of the azide component and the structure of the thio acid and is tolerant of a variety of solvents including water. In light of these observations, application of this reaction in the context of the total synthesis of nagelamides in particular and oroidin alkaloids in general appeared to be of value and thus we report our investigation of this reaction in the context of imidazole derivatives.

The urocanic acid-derived substrate **9**[13] was chosen for preliminary experiments as it was readily available and could be easily elaborated to possess many of the structural features that would be present in advanced intermediates in our planned total synthesis endeavors. Most of the advanced intermediates that we have prepared in previous projects, including our synthesis of the reported structure of nagelamide D (**3**), contain a DMAS (dimethylaminosulfonyl)-protecting group as it confers a nice balance of crystallinity in many intermediates, it activates the C2-position of the imidazole to deprotonation and it can be removed under mildly acidic conditions and thus this was used in all of the of substrates evaluated herein except for one (**20**,[14] entries 7–8, Table 2). The parent allylic azide **9** was prepared from the known alcohol **7**[15]

* Corresponding author.
E-mail address: lovely@uta.edu (C.J. Lovely).

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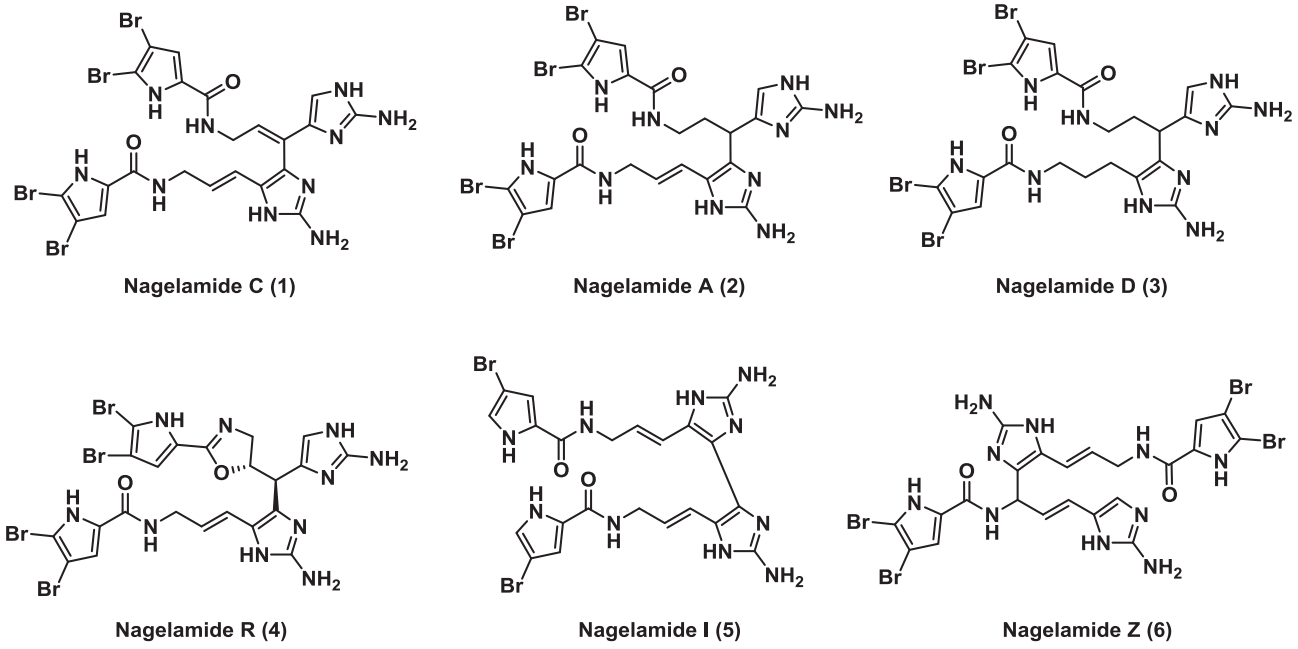
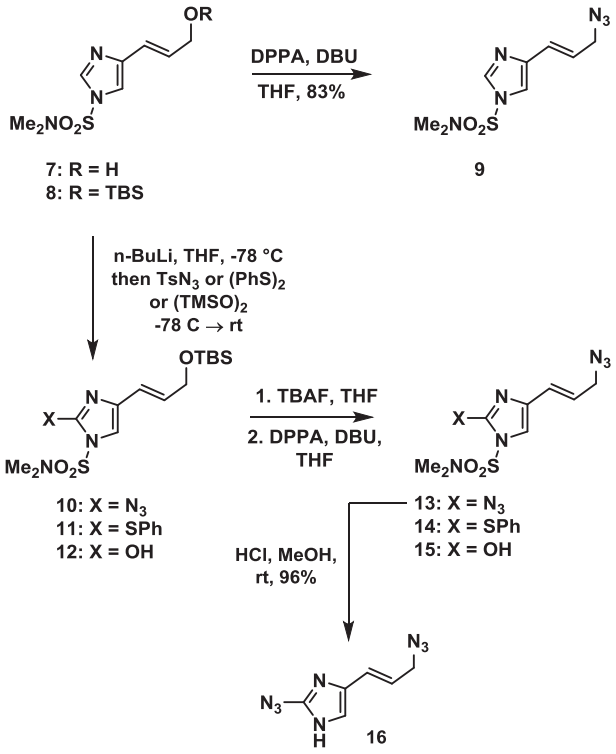


Fig. 1. Representative examples of the nagelamide alkaloids.

by treatment with DPPA and DBU according to the procedure described by Thompson and coworkers (Scheme 1).[16] In addition to these simple allylic azides of critical importance for applications in total synthesis settings was to establish the compatibility of substrates containing a 2-amino group or a 2-oxo group (or surrogates) as these groups are present in many targets of interest. From a pragmatic perspective, however, the unmasking of the 2-amino group prior to removal of the DMAS groups was not an option as we[5,17] and others[7a] have found that the standard conditions for DMAS-deprotection do not result in hydrolysis of the sulfonyl urea and thus we chose to focus on substrates containing a 2-azido, 2-thiophenyl or 2-oxo moiety all as amine surrogates. It should be noted that ideally in the 2-azido substituted derivative, chemoselective reaction of the allylic azide would be optimal for this chemistry to be useful. Introduction of substituents at C2 can be accomplished readily by deprotonation of the known silyl ether **8**[13] with *n*-BuLi and then exposure to a suitable electrophile. In the case of azides the use of a sulfonyl azide delivers the required product **10** in good yield (Scheme 1, entry 1, Table 1).[18] The thioether **11** can be accessed also in good yield by treatment of the deprotonated imidazole with phenyl disulfide. Reaction of the deprotonated imidazole with $(TMSO)_2$ provided the 2-oxo derivative **12** in low but usable yield.[19] Desilylation of each of these derivatives was accomplished with TBAF and introduction of the allylic azide was performed as before with DPPA and DBU providing the corresponding allylic azides **13**–**15** (Table 1). In the case of the 2-azido derivative **13**, the DMAS group was removed by acid-catalyzed methanolysis to give the free imidazole **16** in excellent yield and mild conditions (Scheme 1).[20] The benzyl protected derivative **20** was obtained via a similar process from the known allylic alcohol (not shown).[13]



Scheme 1. Preparation of monomeric azide substrates.

In an initial experiment, the parent substrate **9** was reacted with neat thio acetic acid according to Rosen's report,[10] which delivered the expected acetamide **17** in good yield along with a small amount of the corresponding thioamide **18** (entry 1, Table 2).[21] Solution conditions (MeOH) were also effective for the preparation of the amide resulting in similar efficiencies (entries 3–6, Table 2), although heating of the reaction mixture to reflux did not lead to increase in yield (entry 4). As expected, when this reaction was conducted in the absence of lutidine, the yield of the amide dropped (entry 6, Table 2). Similarly, reaction with thio

Table 1
Yields for preparation of C2-functionalized allylic azides.

X	C2-Functionalization (%)	ROH (%)	Azide (%)
N_3	**10** (63)	60	**13** (80)
SPh	**11** (57)	89	**14** (58)
OH	**12** (19)	85	**15** (64)