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

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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 hydrosulfonylation 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 hydrosulfonylation product.

Graphical Abstract

Keywords

Nagelamides; Azide synthesis; Natural products; Hydrosulfonylation; Cross-coupling

The nagelamide alkaloids¹ (e.g., **1–6**, Figure 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

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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 members⁵ 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 pyrrolicarboxamide 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 Rosen¹⁰ and subsequently expanded by Williams and co-workers,¹¹ including the detailed study of the reaction mechanism¹² 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 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 ideal 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

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 benzoic acid provided the corresponding benzamide **19** in good yield the structure of which was confirmed by X-ray crystallography (entry 7–8, Table 2). The benzyl-protected substrate **20** provided the expected amide **21** in good yield (entries 9–10, Table 2).

Reaction of the diazide **13** with thio acetic acid under neat conditions afforded a total of four different products that were isolated as two component mixtures (entry 11, Table 2). One of the mixtures contained the bis amide **22** along with a second product **23** in which acylation of the allylic azide occurred with concomitant reduction of the 2-azido group to the amine and hydrosulfenylation; this latter material was the major product in the mixture. The second two component mixture contained the C2-acetamide **24** and again a product **25** which had undergone reduction and hydrosulfenylation. Under solution conditions, a mixture of the same C2-monoacetamide **24** and addition product **25** were isolated favoring the C2-amide (entry 12, Table 2). When the same diazide **13** was reacted with thio benzoic acid rather than the benzamide the product from hydrosulfenylation in addition to reduction of 2-azido moiety **26** was obtained (entry 13, Table 2). The constitution of this product was firmly established through X-ray crystallography (Scheme 2).

When the 2-thiophenyl substituted derivative **14** was subjected to reaction with thio acetic acid under standard conditions the expected amide **27** was obtained in 58% yield (entry 14, Table 2). On the other hand, when the 2-oxo derivative **15** was reacted with thio acetic acid, the anticipated amide **28** was isolated in admixture with the addition product **29**, with the addition product being the major component (entry 15, Table 2). Encouragingly, the diazide substrate **16** lacking the imidazole protecting group underwent reaction very selectively and rapidly (2–3 min) delivering **30**, with no evidence of hydrosulfenylation (entry 16, Table 2). Interestingly, this reaction also proceeds equally rapidly in the absence of lutidine suggesting that the imidazole is acting as base (entry 17, Table 2).

To partially address the origin of these addition/reduction products, the reaction was performed in the presence of BHT (2 equiv.) as a radical scavenger. These results were somewhat ambiguous in that there appeared to be an induction period, but the formation of the reduction/addition product **26** was observed in comparable yield, suggesting that formation of **26** is not via a radical pathway.²² We did isolate and fully characterize **33** (R = Ph) which indicated that the thio acid served as the reductant.²³ A control reaction in which only the azide was absent from the reaction mixture demonstrated that **33** was not formed in the absence of the C2-azide. Presumably, reduction of the azide begins by nucleophilic attack of the thio acid on the terminal nitrogen to afford **31** after protonation (Scheme 2).^{11–12, 21,24} Cleavage of the N-S bond through attack of the thio acid sulfur produces the diacyl disulfide **33** and expels nitrogen, and upon protonation of **34** the reduction is completed.²⁵ Hydrosulfenylation proceeds via nucleophilic addition and subsequent protonation.

To probe this chemistry further, we prepared and evaluated advanced models en route to nagelamides A and C. The formation of the dimeric substrates **43** and **46** was accomplished through a Stille cross-coupling reaction between the iodoimidazole **38** and either of the known *E*- or *Z*-stannanes *E*-**39** and *Z*-**39** (Scheme 3) to deliver **40** and **44** respectively in good yields.^{6, 26} The Stille cross-coupling between **38** and *E*-**39** has been reported previously, however, the reaction conditions led to partial desilylation. Changing the solvent from DMF to THF minimized the loss of the TBS groups; presumably this is a function of the reduced solubility of the CsF additive and attenuated nucleophilicity of fluoride in this solvent. Reduction of the more substituted double bond in **40** by catalytic hydrogenation provided **41** containing the framework of nagelamide A (**2**).²⁷ Desilylation of the product with TBAF provide the diol **42** which was characterized by X-ray crystallography. This structure determination not only confirmed that reduction occurred at the more substituted double bond but also that the connectivity between the “oroidin” units was correct.²⁸ Treatment of diol **42** with DPPA and DBU resulted in the conversion of the allylic alcohol to the azide, but the primary alcohol stopped at the phosphate intermediate stage. Fortunately, addition of external azide in the form of tetrabutylammonium azide (TBAA) followed by heating at reflux delivered the required bis azide **43**. Desilylation of the bis vinylimidazole **44** with TBAF followed by reaction of the bis allylic alcohol **45** with DPPA and DBU provided the bis azide **46** in good yield. Both dimeric azides underwent acylation with thioacetic acid (16 equiv.) to give the bis acetamides **47** and **50** in good yields (entries 20 and 23, Table 2). Using lower equivalents of the thio acids resulted in the formation mono acetamides in modest yields in addition to the bis amides (entries 18–19 and 21–22, Table 2). Interestingly, in the case of the nagelamide C model, the less substituted allylic azide was more reactive leading to the formation of only one mono azide, the structure of which was easily assignable based on the ¹H NMR data.

In summary, we have investigated the coupling reaction between thio acids and azides on an imidazole framework. While simple allylic azide systems provide amides efficiently, the reaction of 2-azido derivatives is complicated by hydrosulfenylation and reduction of the 2-azido group to an amine. However, the free imidazole substrate appears to undergo C2-amide formation only. Reaction of the C2-azide in preference to the allylic azide can be

understood based on the rate studies performed by Williams and coworkers which indicate that electron deficient azides react faster than electron rich azides.¹² This fact may be behind the observation that the free 2-azidoimidazole forms the amide so rapidly as it may be protonated at N3 and thus the azide highly electron deficient. The presence of a thiophenyl group at C2 is tolerated and leads to the expected product. Dimeric systems, provide the required bis amides in good yields although a large excess of the thio acid was necessary for good conversions. Further studies in this area and application to the total synthesis of several oroidin dimers are currently underway and will be reported in due course.

Acknowledgments

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27. This outcome was not by design, but was rather a fortuitous observation that permitted us to access the nagelamide A framework.
28. In our reported synthesis of nagelamide D we found significant differences in the NMR data for synthetic and sponge-derived materials. This X-ray data confirm the structure of the synthetic material and add further weight to either issues with the structural assignment of the natural product or the data.

- First examination of thio acid/azide click reaction in imidazole containing substrates.
- Unusual azide reduction/hydrosulfenylation processes observed.
- Free imidazoles viable substrates.

Figure 1.
Representative examples of the nagelamide alkaloids

Scheme 1.
Preparation of monomeric azide substrates

Scheme 2.

Putative mechanism for formation of reduction/addition product (X-ray structure of reduction-addition product **26**)

Scheme 3.

Preparation of dimeric nagelamide A and nagelamide C models (X-ray crystal structure of semi-reduced diol **42**)

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)

Table 2

Products from reactions of imidazole-containing azides with thio acids.

Entry	Substrate	Conditions ^a	Product (%)	Product (%)
	9		17 (85)	18 (6)
1		Neat MeCOSH (4 equiv.), 1 h	17 (85)	18 (6)
2		Neat, MeCOSH (4 equiv.), lut., 1 h	17 (81)	-
3		MeCOSH, lut., 3 h	17 (68)	-
4		MeCOSH., lut, 55 °C, 3 h	17 (63)	-
5		MeCOSH, lut., 0 °C, 4.5 h ^b	17 (55)	-
6		MeCOSH, 3 h	17 (38)	10
			19 (46)	X-ray structure of compound 19
7		PhCOSH, lut., O/N	19 (46)	
8		PhCOSH (4 equiv.), lut., O/N	19 (96)
	20		21 (51)	
9		MeCOSH, lut., 20 h	21 (51)	
10		MeCOSH (4 equiv.) , lut., 20 h	21 (67)	

Entry	Substrate	Conditions ^a	Product (%)	Product (%)
	13		22	24
			23	25
11	13	Neat MeCOSH, lut., 2.5 h	(39; 22:23 = 1:3)	(37; 24:25 = 1:2)
	13		24	25
12	13	MeCOSH, lut., 4.5 h	(54; 24:25 = 5:2)	
	13		26	
13	14	PhCOSH, lut., 4 h	26 (32)	
	14		27	
14	15	MeCOSH, lut., 20 h	27 (58)	
	15		28	29
15		MeCOSH (4 equiv.), lut., 20 h	(40; 28:29 = 1:3)	

Entry	Substrate	Conditions ^a	Product (%)	Product (%)
	16		30 (63)	
16		MeCOSH, lut., <5 min	30 (63)	
17		MeCOSH, <5 min	30 (63)
	43		47	48
				49
18		MeCOSH (4 equiv.), lut., O/N	28	10/10
19		MeCOSH (8 equiv.), lut., O/N	51	20/9
20		MeCOSH (16 equiv.), lut., O/N	75	-
	46		50	51
21		MeCOSH (4 equiv.), lut., O/N	58	36
22		MeCOSH (8 equiv.), lut., O/N	61	16
23		MeCOSH (16 equiv.), lut., O/N	69	-

^a. Reactions were conducted with 2 equiv. of thio acid, 2 equiv. of lutidine in MeOH (0.26 M) at room temperature unless indicated otherwise; where increased equivalents of thio acid were used the corresponding amount of lutidine was used.

^b. This reaction was conducted at 0.94 M.