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Thio acid-mediated conversion of azides to amides – Investigation of 2-azidotetrahydobenzimidazoles and derivatives

Lawton A. Seal II, Olatunji S. Ojo, Delphine Gout, Carl J. Lovely *

Department of Chemistry and Biochemistry, 700 Planetarium Place, University of Texas at Arlington, TX 76019, USA

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ABSTRACT

An investigation of the thio acid-azide coupling reaction to afford amides is reported employing 2-azidotetrahydrobenzimidazoles and the corresponding spiro fused 2-azidoimidazolones. The tetrahydrobenzimidazole derivatives react as expected to produce the analogous amides, whereas the imidazolones result in the formation of the thiohydantoin derivatives. The thiohydantoins appear to result from an addition elimination pathway.

Azides serve as a key functional group in synthetic chemistry, in particular, they play a central role in the preparation of primary amines and their derivatives, in addition to serving as 1,3-dipoles in what has become a textbook example of [3+2] cycloadditions [1–4]. Several effective methods exist for azidation through classical substitution pathways. As well, they are relatively robust functional groups which allows them to serve as masked amino groups [5,6]. In the context of a number of active total synthesis projects of nitrogen rich alkaloids of the oroidin (e.g., **1** [7–9] and **2,** [10–12] Fig. 1) [13,14] and *Leucetta* families of sponge metabolites [15,16], azide intermediates were in hand wherein classical reductions were either not feasible or in some cases undesirable, because of chemoselectivity considerations. Furthermore, many of the target alkaloids contained amides and thus we sought to identify a process where reduction and acylation could be accomplished either simultaneously or sequentially, potentially telescoping the syntheses. One particularly attractive possibility emerged to accomplish this; specifically the reaction of azides and thio acids to provide amides [17]. This transformation was observed initially by Just [18] and Rosen [19] and subsequently investigated systematically by Williams and co-workers [20,21]. In prior work, we investigated predominantly vinyl imidazole derivatives of varying complexity and discovered this transformation gave amides in generally good yields with thio acetic acid, and some examples with thio benzoic acid [17]. Examination of limited examples of

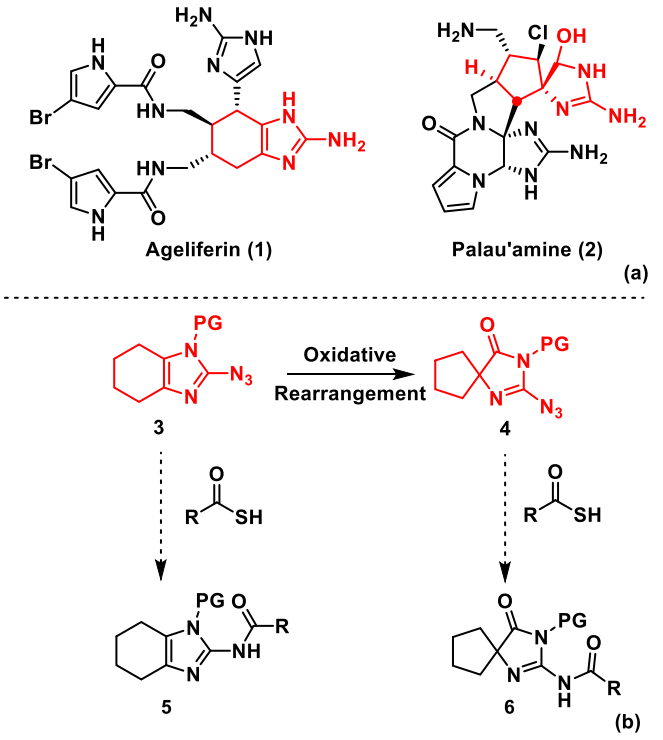

Figure 1. (a) Oroidin alkaloids ageliferin and palau'amine. (b) systems investigated in this report.

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

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C2-substituted azides revealed chemoselectivity for reaction of the C2-azide in the presence of an allylic azide, and that even unprotected imidazoles participate in this chemistry [17]. However, several targets of interest contained tetrahydrobenzimidazole moieties **3** or could be accessed via their rearrangement **3** → **4**; specifically ageliferin (**1**) and palau'amine (**2**). Accordingly, in the

Table 1
Products from reactions of 2-azidotetrahydrobenzimidazole and imidazolotetrazolones with thio acids.

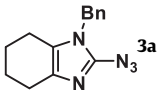
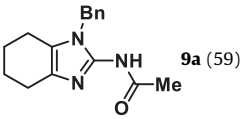
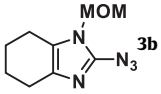
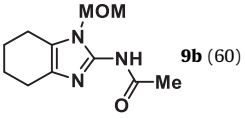
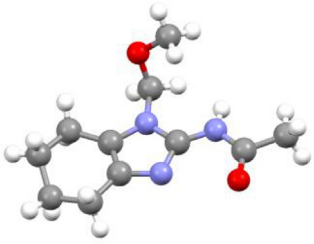
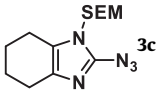
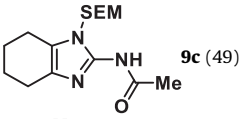
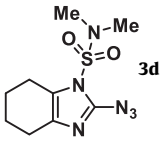
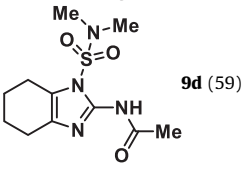
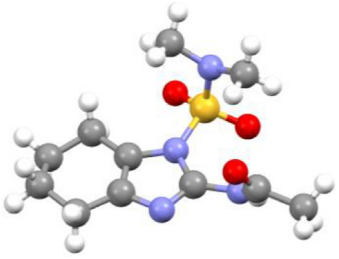
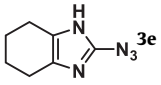
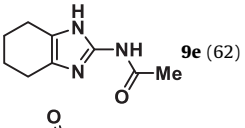
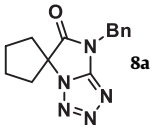
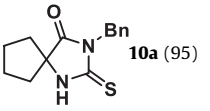
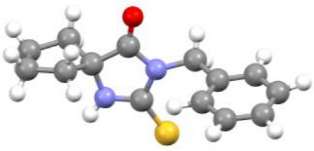
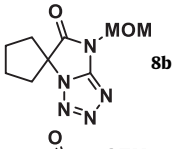
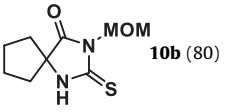
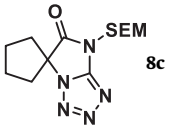
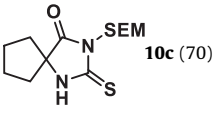
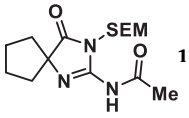
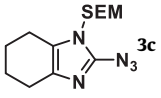
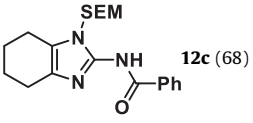
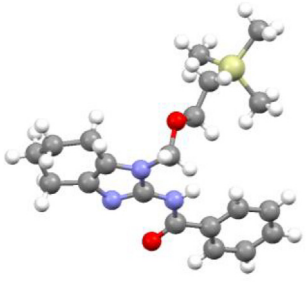
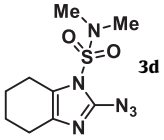
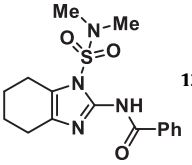
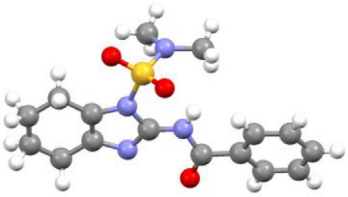
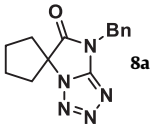
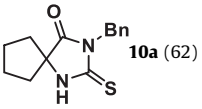
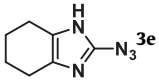
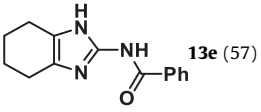
Entry	Substrate	Thio acid[a]	Product (%)	Product (%)
1	 **3a**	AcSH	 **9a** (59)	
2	 **3b**	AcSH	 **9b** (60)	 X-ray structure of **9b**
3	 **3c**	AcSH	 **9c** (49)	
4	 **3d**	AcSH	 **9d** (59)	 X-ray structure of **9d**
5	 **3e**	AcSH[b]	 **9e** (62)	
6	 **8a**	AcSH	 **10a** (95)	 X-ray structure of **10a**
7	 **8b**	AcSH	 **10b** (80)	
8	 **8c**	AcSH	 **10c** (70)	 **11c** (7)
9	 **3c**	BzSH	 **12c** (68)	 X-ray structure of compound **12c**

Table 1 (*continued*)

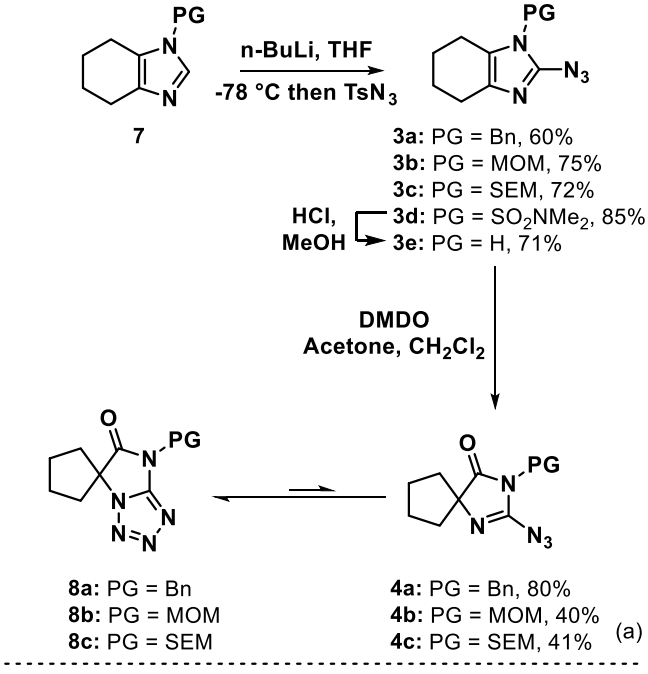
Entry	Substrate	Thio acid[a]	Product (%)	Product (%)
10	 **3d**	BzSH	 **12d** (54)	 X-ray structure of compound **12d**
11	 **8a**	BzSH	 **10a** (62)	
12	 **3e**	BzSH[b]	 **13e** (57)	

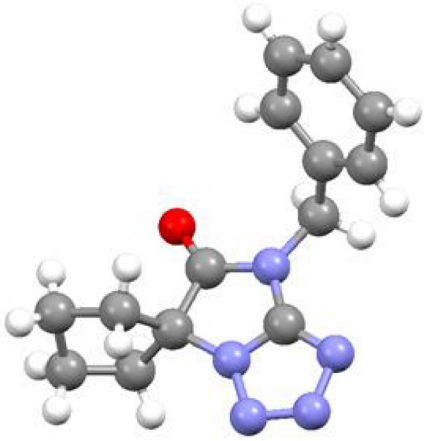
[a]Reactions were conducted with 2 equiv. of thio acid, 2 equiv. of 2,6-lutidine in MeOH (0.26 M) at room temperature unless indicated otherwise.
[b]No 2,6-lutidine was used in this case.

present manuscript, we report the application of this chemistry to 2-azido tetrahydrobenzimidazoles **3** → **5** and the corresponding 2-azido spiroimidazolone derivatives **4** → **6** (Table 1).

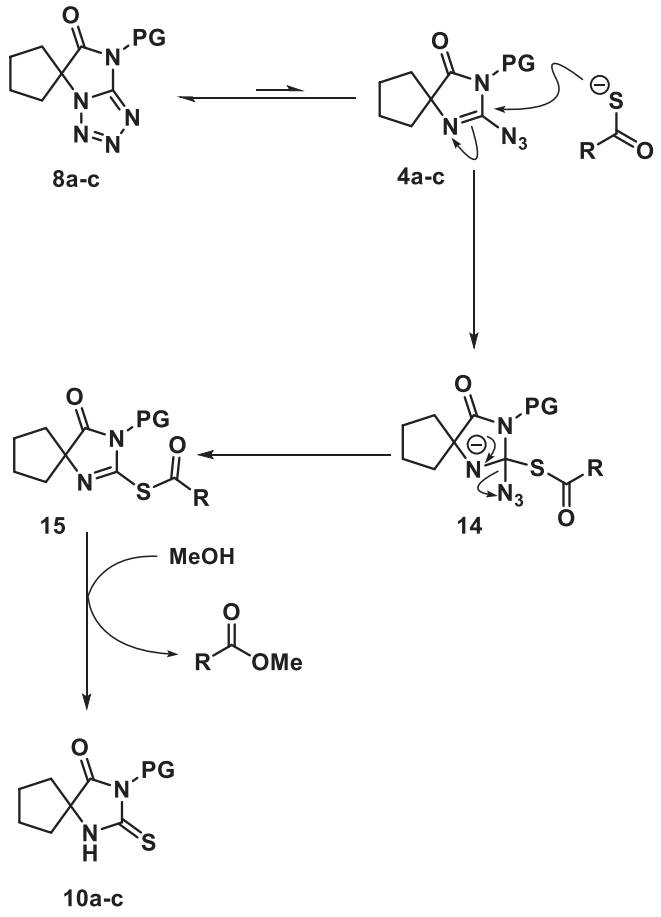
The substrates were readily prepared from benzimidazole by partial hydrogenation and *N*-substitution [22,23]. Four different protecting groups were evaluated that provided options for subsequent deprotection and in three cases increase the acidity of the C2-position, facilitating introduction of the azide. Accordingly, each of the protected tetrahydobenzimidazoles was treated with *n*-BuLi and then reacted with tosyl azide [24] providing 2-azidoimidazoles in good yields (Scheme 1) [22,23]. Oxidative rearrangement of these *N*-substituted intermediates with dimethyldioxirane (DMDO), with the exception of the DMAS-protected derivative, affords the corresponding imidazolones in good yields [22,23]. One interesting observation that was overlooked in our initial report of **4a** [25], was that it exists as the tetrazole valence tautomer rather than the azido form [26,27]. This was evident in the IR data where the stretching frequency corresponding to the azide was absent and a subsequent X-ray structure of **8a** clearly shows the bicyclic imidazolotetrazole system (Scheme 1b). Closer examination of the spectroscopic data of the other imidazolones revealed they too were isolated as the tetrazole tautomer [28–33]. One additional substrate was prepared from the DMAS-protected derivative on methanolysis with acidic methanol delivered the parent 2-azido derivative **3e** [17,34–35].

With the five azides **3a-e** in hand, their reactivity with thioacetic acid in methanol with 2,6-lutidine as base was evaluated [17,20,21]. Each of the substrates delivered the corresponding amide **9a-e** in moderate yield, although no attempt was made to optimize these yields. Two derivatives were subjected to X-ray crystallography which clearly revealed the formation of the acetamide. This transformation affords a chemoselective approach to the preparation of 2-amido imidazole derivatives [36]. Surprisingly, and in contrast to the tetrahydrobenzimidazoles, the spiro 2-azidoimidazolones **4a-c** undergo reaction with thio acetic acid to afford the 2-thiohydantoin derivatives. This was confirmed both through mass spectrometry and through an X-ray crystal structure of the Bn-protected congener. In addition to the thiones **10a-c**, small quantities of the expected amide were obtained in the case of **11c**. Several substrates were reacted with thio benzoic acid, including a tetrazole. In the cases of the tetrahydrobenzimidazoles the corresponding benzamides **12c-d** were obtained. The spiroimidazolones again delivered the thiohydantoin derivatives.




(b)

Scheme 1. (a) Preparation 2-azide substrates. (b) X-ray crystal structure of tetrazole 8a.



Scheme 2. Putative mechanism for the formation of the thiones.

In order to account for the formation of the thiohydantoins, our assumption is that the azido-azomethine tautomer **4a-c** behaves more like an imidate undergoing an addition–elimination reaction with the thio acid serving as the nucleophile (**4a-c** → **14** → **15**, Scheme 2). Methanolysis of the mixed anhydride **15** produces the thione **10a-c** after tautomerization.

In summary, we have extended the coupling reaction between thio acids and azides to the tetrahydrobenzimidazole framework. These reactions proceed efficiently to deliver the corresponding amides with a variety of *N*-protecting groups. Attempts to apply this transformation to the corresponding spiro 2-azidoimidazolones resulted in the formation of spiro thiohydantoins rather than the anticipated amide. Of note is that this chemistry effectively enables the chemoselective acylation of a 2-aminoimidazoles. 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.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152484.

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