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Facile Amide Formation via *S*-Nitrosothioacids

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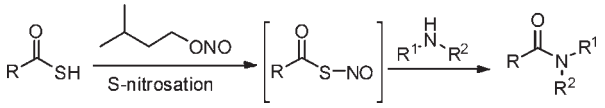
ABSTRACT



Here we report a novel amide bond formation strategy from simple thioacid and amine starting materials. The reaction is mediated by unstable but very reactive *S*-nitrosothioacid intermediates. This fast reaction under mild conditions should be useful in synthesis.

Due to the importance in biology and drug discovery, amide or peptide bond formation is an active area in organic chemistry. In the past decade, a number of new strategies for the construction of amide bonds have been discovered.[1] In particular, thioacid or thioester derivatives are attractive starting materials. Recent studies have revealed some unique reactivity of these sulfur-based compounds and demonstrated some advantages of them compared to carboxylic acid derivatives in amide and peptide bond forming sequences.[2] In our recent efforts to study new chemistry of thiol *S*-nitrosation,[3] we envisioned that if thioacids were subjected to nitrosation (Scheme 1), the corresponding *S*-nitrosothioacids (NTA) could be formed. Such a sulfur-nitrosation process may activate thioacids and lead to a facile acylation with certain nucleophiles. Herein, we report a very efficient amide bond formation mediated by NTA.

It is known that *S*-nitrosothiols are unstable moieties. Their chemistry, especially synthetically useful reactions, has not been well studied.[4] NTA type molecules have never been clearly identified, although such compounds may be involved in some thiyl radical formation processes.[5] In our study, we first tested the preparation of NTA. One example using thiobenzoic acid **1** is shown in Scheme 2. Compound **1** was treated with organonitrite (RONO) or $HCl/NaNO_2$ in organic solutions at rt or 0 °C. The resulted species, presumably NTA **2**, showed a deep green color (UV spectra of **2** were shown in the Supporting Information), which is the characteristic color of tertiary *S*-nitrosothiols. The NTA **2** appeared to be unstable as the green color readily faded when we attempted to isolate compound **2**. The final isolated product was disulfide **3**, which is the

(1) For selected reviews, see: (a) Bode, J. W. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765. (b) Han, S.; Kim, Y. *Tetrahedron* **2004**, *60*, 2447. (c) Nilsson, B. L.; Soellner, M. B.; Raines, R. T. *Annu. Rev. Biophys. Biomol. Struct.* **2005**, *34*, 91. (d) Kimmerlin, T.; Seebach, D. *J. Peptide Res.* **2005**, *65*, 229.

(2) For selected examples, see: (a) Bao, Y.; Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12924. (b) Wang, P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 17045. (c) Crich, D.; Sasaki, K. *Org. Lett.* **2009**, *11*, 3514. (d) Crich, D.; Sharma, I. *Angew. Chem., Int. Ed.* **2009**, *48*, 2355. (e) Crich, D.; Sharma, I. *Angew. Chem., Int. Ed.* **2009**, *48*, 7591. (f) Crich, D.; Sana, K.; Guo, S. *Org. Lett.* **2007**, *9*, 4423. (g) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. H. *Science* **1994**, *266*, 776. (h) Dawson, P. E.; Churchill, M. J.; Ghadiri, M. R.; Kent, S. B. H. *J. Am. Chem. Soc.* **1997**, *119*, 4325. (i) Liu, R.; Orgel, L. E. *Nature* **1997**, *389*, 52. (j) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754. (k) Sheehan, J. C.; Johnson, D. A. *J. Am. Chem. Soc.* **1952**, *74*, 4726.

(3) (a) Wang, H.; Xian, M. *Angew Chem., Int. Ed.* **2008**, *47*, 6598. (b) Zhang, J.; Wang, H.; Xian, M. *J. Am. Chem. Soc.* **2009**, *131*, 3854. (c) Wang, H.; Xian, M. *J. Am. Chem. Soc.* **2009**, *131*, 13238. (d) Zhang, J.; Li, S.; Zhang, D.; Wang, H.; Whorton, A. R.; Xian, M. *Org. Lett.* **2010**, *12*, 4208. (e) Zhang, D.; Devarie-Baez, N. O.; Pan, J.; Wang, H.; Xian, M. *Org. Lett.* **2010**, *12*, 5674. (f) Devarie-Baez, N. O.; Xian, M. *Org. Lett.* **2010**, *12*, 752.

(4) For selected reviews on *S*-nitrosothiols, see: (a) Williams, D. L. H. *Acc. Chem. Res.* **1999**, *32*, 869. (b) Szacilowski, K.; Stasicka, Z. *Prog. React. Kinet. Mech.* **2001**, *26*, 1. (c) Al-Sadoni, H. H.; Ferro, A. *Curr. Med. Chem.* **2004**, *11*, 2679. (d) Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. *Chem. Rev.* **2002**, *102*, 1091.

(5) Potapenko, D. I.; Bagryanskaya, E. G.; Tsentalovich, Y. P.; Reznikov, V. A.; Clanton, T. L.; Khramtsov, V. V. *J. Phys. Chem. B* **2004**, *108*, 9315.

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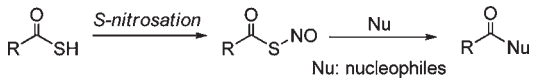
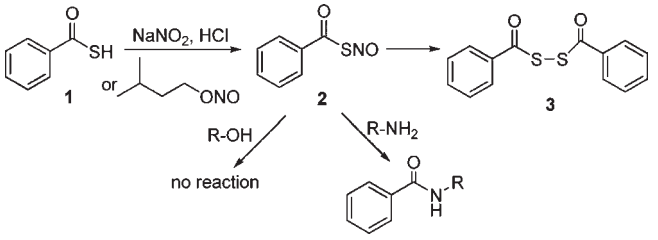
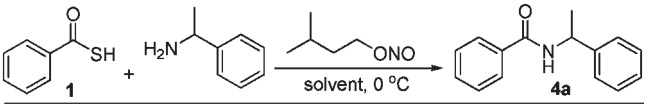
Scheme 1. Proposed NTA Coupling



Scheme 2. Formation of NTA and the Reaction of NTA



Scheme 3. Solvent Effects of NTA Mediated Amide Formation

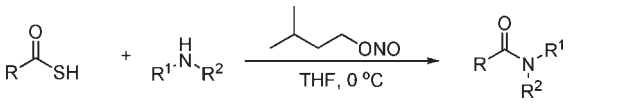


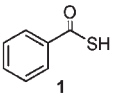
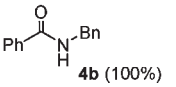
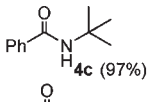
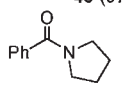
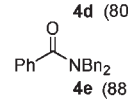
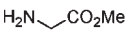
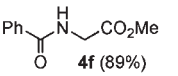
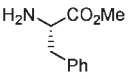
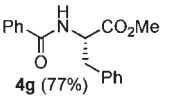
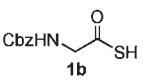
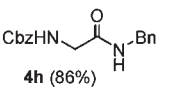
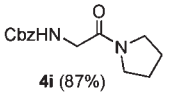
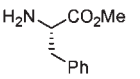
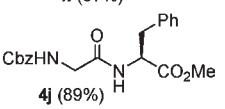
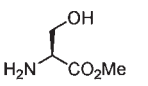
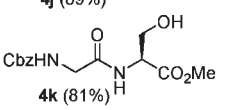
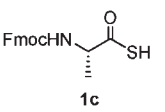
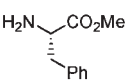
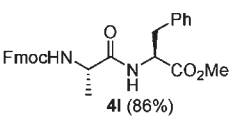
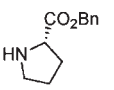
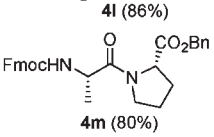
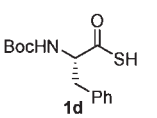
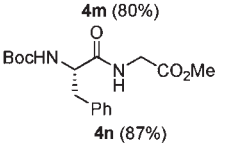
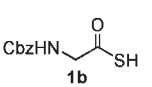
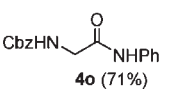
entry	solvent	reaction time	yield of **4a**
1	THF	5 min	96%
2	DCM	10 min	82%
3	DMF	10 min	75%
4	CH_3CN	5 min	94%
5	THF/PBS buffer (3/1)	10 min	95%
6	DMF/PBS buffer (1/1)	20 min	71%

expected decomposition product from *S*-nitrosothiols. Although NTA **2** was unstable, we tested the idea to trap NTA in situ with some nucleophiles. Amines proved to be excellent substrates, and the formation of amide bonds was achieved in a very effective way (see table 1 below). It was also remarkable that NTA, unlike other activated carboxylic acid derivatives, did not show any reactivity toward hydroxyl groups (such as benzyl alcohol, phenol, and *N*-hydroxysuccinimide). This is promising for further study of selective *N*-acylation.

We then optimized the conditions for this NTA mediated coupling between thioacids and amines. The best procedure was to mix the thioacid (1.0 equiv) and the amine (1.1 equiv) at 0 °C. Commercially available amyl nitrite (2.0 equiv) was then added dropwise into the solution. In this process, no additional base was needed. The formation of the desired amide product was observed immediately and in high yields (monitored by TLC). As shown in Scheme 3 (entries 1−4), this reaction worked nicely in a number of common solvents including THF, DCM, DMF, and CH_3CN. Water seemed to have little effect on the coupling as the reaction gave similar results in buffer containing

Table 1. NTA Mediated Amide Coupling

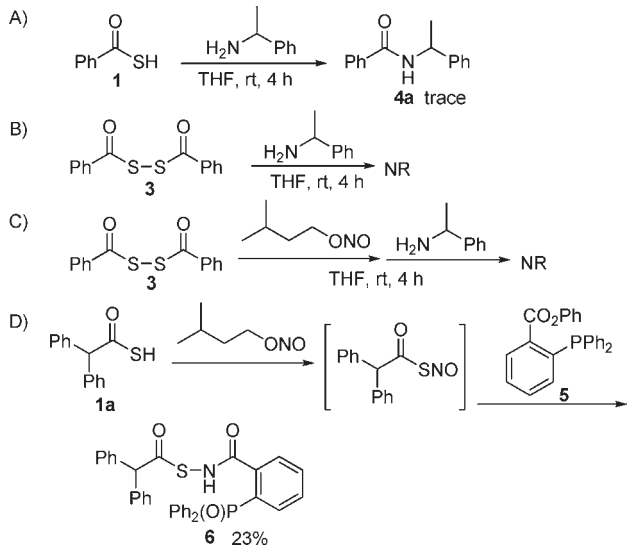


entry	thioacid	amine	product/yield
1	 **1**	$BnNH_2$	 **4b** (100%)
2			 **4c** (97%)
3			 **4d** (80%)
4		Bn_2NH	 **4e** (88%)
5			 **4f** (89%)
6			 **4g** (77%)
7	 **1b**	$BnNH_2$	 **4h** (86%)
8			 **4i** (87%)
9			 **4j** (89%)
10			 **4k** (81%)
11	 **1c**		 **4l** (86%)
12			 **4m** (80%)
13	 **1d**		 **4n** (87%)
14	 **1b**	$PhNH_2$	 **4o** (71%)

systems (entries 5 and 6). This process proved to be a very fast process, as in all the solvents the reaction completed within minutes at 0 °C.

To prove the reaction was indeed involving NTA, we carried out several control experiments (Scheme 4). The reaction between thioacid **1** and α-methyl-benzylamine

Scheme 4. Control Experiments



only led to the formation of amide **4a** in trace amounts at rt, even when the amine was used in large excess (10 equiv). A previous report by Orgel et al. also suggested that thioacids should not directly react with amines to form amides.[2i] As NTA are unstable species and could easily decompose to form disulfides, we then tested the reaction between disufide **3** and α-methyl benzylamine. Again, we did not observe the formation of the amide product (Scheme 4B). The addition of amyl nitrite into disulfide **3** did not lead to any amide formation either (Scheme 4C). Finally, we tried to capture the unstable NTA intermediates using the reductive ligation,[3a] which is a specific reaction of SNO groups. After several attempts, we were able to obtain the desired ligation product **6** using substrate **1a** (Scheme 4D). Although the yield of **6** was only 23%, the formation of this sulfenamide product strongly supported the presence of an NTA intermediate in the reaction.

The results shown above suggested that NTA act as an effective activating group to facilitate amide formation. To test the generality of this reaction, a series of thioacids and amines were employed under the optimized conditions (Table 1). The reaction proved to be very efficient with not only primary amines but also sterically hindered secondary amines (entries 1−8). We also tested several amino acid substrates. As expected, the corresponding dipeptide products were obtained in good yields in all substrates (entries 9−14). As shown in entry 10, a free hydroxyl group did not interfere with the reaction, which was consistent with our previous selectivity results. In all the cases, the reaction was able to be complete within 10 min at 0 °C.

In summary, we presented here a novel amide bond formation strategy from simple thioacids and amines. This process was mediated by reactive NTA intermediates. It revealed nitrosation as a novel strategy for thioacid activation. Compared to other amide formation methods, this reaction only utilized readily available organonitrite as the activation reagent. It took place under very mild reaction conditions, and the reaction rate was extremely fast. The chemistry is easily executed. It also showed excellent selectivity toward amines over hydroxyls. In our opinion, this method should be promising for peptide coupling/ligation and selective *N*-acylation. Further studies on the detailed reaction mechanism, the application of this method in synthesis and biology, and the exploration of new chemistry of NTA are currently ongoing in our laboratory.

Acknowledgment. This work is supported in part by NIH (R01GM088226) and a CAREER award from the NSF (0844931).

Supporting Information Available. Spectroscopic and analytical data and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org