Copper-catalyzed Oxidative Desulfurization-promoted Intramolecular Cyclization of Thioamides Using Molecular Oxygen as an Oxidant: An Efficient Route to Five- to Seven-membered Nitrogen-containing Heterocycles

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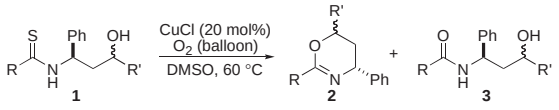
Copper-catalyzed oxidative desulfurization-promoted intramolecular cyclization reactions of thioamides take place under neutral and mild conditions by using molecular oxygen as an oxidant. The process yields a wide variety of nitrogen-containing heterocycles with high efficiency.

The generation of an electrophilic species via the oxidative activation of organosulfur compounds is of great interest.[1] Thiocarbonyl compounds, such as dithioic acid esters and thioamides, readily participate in these types of oxidant-initiated reactions.[1b,2c] Oxidants used for this purpose thus far include halonium species, such as NIS, NBS, and I_2. In these cases, the reactions are often accompanied by halogenation of aromatic moieties in the substrates and they produce hazardous by-products. Therefore, the development of environmentally benign oxidants that promote these processes under mild conditions is a worthy goal. On the other hand, we previously reported an alkylation-promoted desulfurization–cyclization of *N*-thioacyl-1,3-amino alcohols, but the reaction could be applied to limited substrates due to the low desulfurization activity.[2b] Therefore, we continuously investigated a widely applicable alternative desulfurization procedure. Below, we report the results of an investigation of a new copper-catalyzed oxidative desulfurization-promoted cyclization reaction of thioamides that uses molecular oxygen as a stoichiometric oxidant and that is widely applicable to the synthesis of nitrogen-containing heterocycles.

During recent studies,[2] we observed that simple thioamides readily yield the corresponding amides when treated with a copper catalyst under an oxygen atmosphere.[2d] We expected that this catalytic process, which takes place via oxidative activation of the C=S group, could be utilized for oxidative desulfurization-promoted substitution reactions. Initial experiments designed to probe this proposal were carried out using the cyclization of **1a**.[2b] Reaction of *anti*-**1a** with a catalytic amount of copper(I) chloride (20 mol %) at 60 °C in DMSO under an oxygen atmosphere leads to formation of dihydro-1,3-oxazine *cis*-**2a** in quantitative yield (Table 1, Run 1).[3–6] Fortunately, the syn diastereomer **1a** also undergoes efficient cyclization when treated under the same conditions (Run 2).[7] In each case, stereochemistry of the amino alcohol moiety is retained, indicating that the reaction formally proceeds via intramolecular nucleophilic addition of the hydroxy group to the activated thiocarbonyl without epimerization.[6] Importantly, the cyclization reaction occurs at room temperature (*anti*-**1a**: 93% NMR yield for 24 h, *syn*-**1a**: 84% NMR yield for 24 h) and it can be applied to gram-scale synthesis without loss of efficiency.[6] In addition, the cyclization reactions do not take place in the absence of either oxygen or CuCl, and they afford elemental sulfur as the sole co-product.[2d,5,6] These results clearly show that CuCl serves as a catalyst for the process and that oxygen is the stoichiometric oxidant. Exploration of the scope of the reaction reveals that cyclization of *syn*-**1b**, which contains a bulky *t*-butyl group α to the hydroxy nucleophile, takes place to give **2b** in high yield (Run 3). The chlorine atom-containing substrate **1c** also participates in this process with chlorine remaining intact under the reaction conditions (Runs 4 and 5). Also, **1d** and **1e**, in which the electrophilicity of the thiocarbonyl carbon is reduced by the presence of electron-donating groups, undergo cyclization without appreciable loss of efficiency (Runs 6–9). In contrast to reactions of the alkyl-substituted thioamides *anti*-**1f** and *anti*-**1g** that lead to formation of complex mixtures (Runs 11 and 13), the diastereomeric substrates *syn*-**1f** and *syn*-**1g** afford the respective products **2f** and **2g** in good yields (Runs 10 and 12). It may be partly due to the different stability of the diastereomers of 2-alkyldihydro-1,3-oxazines. Lastly, the tetrasubstituted dihydro-1,3-oxazines **5** can be prepared starting with the thioacyl amino alcohols **4** (Scheme 1) by using this methodology. Each of the stereoisomers **4a**–**4d** undergoes smooth cyclization to produce the corresponding dihydro-1,3-oxazines **5a**–**5d** in excellent yields.

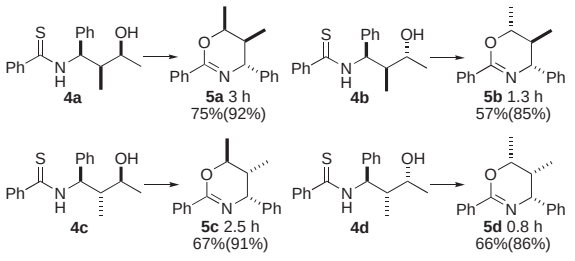
Table 1. Copper-catalyzed oxidative desulfurization–cyclization of *N*-thioacyl-1,3-amino alcohols[a]



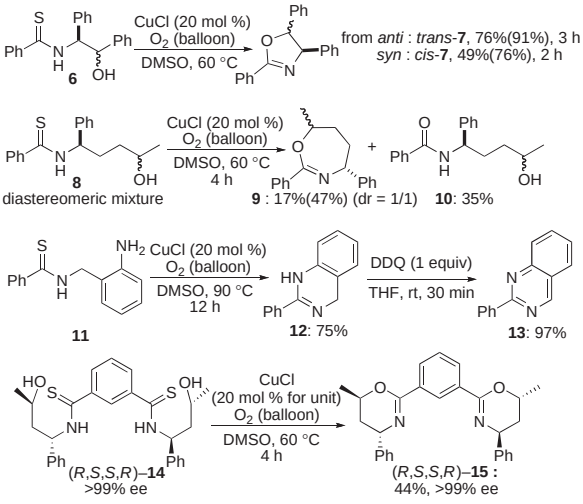
Run	Substrate		Time /h	Yield[b]/% 2	Yield[b]/% 3
1	**1a** R = Ph, R′ = Me	anti	4	71 (>99)	—
2		syn	3	71 (92)	—
3	**1b** R = Ph, R′ = *t*-Bu	syn	2.5	67 (81)	18 (19)
4	**1c** R = Ph, R′ = CH_2Cl	syn	3	53 (70)	— (30)
5		anti	4	43 (59)	20 (16)
6	**1d** R = 4-$MeOC_6H_4$-, R′ = Me	syn	4	76 (98)	trace
7		anti	2	76 (99)	trace
8	**1e** R = 2-$MeOC_6H_4$-, R′ = Me	syn	7	61 (93)	— (6)
9		anti	9	63 (88)	— (6)
10	**1f** R = *t*-Bu, R′ = Me	syn	24	66 (84)	— (3)
11		anti	22	— (13)	—
12	**1g** R = *i*-Pr, R′ = Me	syn	3	44 (84)	— (7)
13		anti	7	— (35)	—

[a]Reactions were performed in DMSO at 60 °C in the presence of CuCl (20 mol %) under oxygen atmosphere with vigorous stirring. [b]The isolated yields. NMR yields are shown in parentheses.

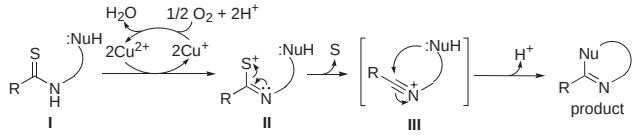
The versatility of the oxidative desulfurization–cyclization procedure was demonstrated by its application to the synthesis of a variety of five- to seven-membered nitrogen-containing heterocycles (Scheme 2). The reactions of *N*-thioacyl-1,2- or 1,4-



Scheme 1. Synthesis of tetrasubstituted dihydro-1,3-oxazines **5** at 80 °C.[6] NMR yields are shown in parentheses.



Scheme 2. Syntheses of a variety of nitrogen-containing heterocycles via oxidative desulfurization–cyclization.[6] NMR yields are shown in parentheses.



Scheme 3. Possible reaction pathway.

amino alcohol **6** and **8** give the corresponding heterocycles in moderate to high yields.[8,9] The reaction of *N*-(2-aminophenyl) thioamide **11**, although requiring a longer reaction time, proceeds to give dihydroquinazoline **12** which can be readily converted to quinazoline **13** by using oxidation.[10] Finally, reaction of optically pure bis(thioacylamino alcohol) (*R*, *S*, *S*, *R*)-**14**, derived from isophthalaldehyde and optically pure propylene oxide by using a two-step procedure,[7] affords optically pure bis-1,3-oxazine **15** in moderate yield. The three-step route used to prepare the chiral NCN pincer ligand **15** should be applicable to the preparation of a wide variety of chiral 1,3-bisoxazine ligands[11] due to the ready availability of enantiomerically pure epoxides.

A possible reaction pathway for the oxidative cyclization process is shown in Scheme 3. The initial event in the pathway involves oxidation of the thioamide sulfur **I** by in situ generated copper(II) to give a sulfenylium intermediate **II**.[1b,2c,2d] Because the corresponding alkylation-promoted S_N2-type cyclizations of sterically hindered *syn*-**1** do not take place at all,[2b] elemental sulfur may be then spontaneously eliminated to give nitrilium ion **III** which participates in nucleophilic addition of the internal alcohol to give the corresponding heterocyclic product.[12]

In conclusion, the above studies have led to the development of a novel and efficient copper-catalyzed intramolecular cyclization reaction of thioamides. The process uses molecular oxygen as the oxidant and can be carried out under neutral and mild conditions. Also, the reaction affords less hazardous elemental sulfur as the sole co-product. Further studies aimed at the discovery of new reactions based on metal-catalyzed oxidative desulfurization are underway.

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References and Notes

1 For selected examples of oxidative desulfurization reactions: a) Glycosidation via oxidative activation of a thioether, see review: K. C. Nicolaou, H. J. Mitchell, *Angew. Chem., Int. Ed.* **2001**, *40*, 1576. b) Oxidative desulfurization–fluorination, see review: M. Shimizu, T. Hiyama, *Angew. Chem., Int. Ed.* **2005**, *44*, 214.

2 a) T. Murai, H. Niwa, T. Kimura, F. Shibahara, *Chem. Lett.* **2004**, *33*, 508. b) T. Murai, H. Sano, H. Kawai, H. Aso, F. Shibahara, *J. Org. Chem.* **2005**, *70*, 8148. c) F. Shibahara, A. Kitagawa, E. Yamaguchi, T. Murai, *Org. Lett.* **2006**, *8*, 5621. d) F. Shibahara, A. Suenami, A. Yoshida, T. Murai, *Chem. Commun.* **2007**, 2354.

3 For examples of the synthesis of 1,3-oxazines, see: a) M. Sainsbury, in *Comprehensive Heterocyclic Chemistry II*, ed. by A. J. Boulton, Elsevier, Oxford, UK, **1996**, Vol. 6, Chap. 5, p. 301. b) M. K. Tse, S. Bhor, M. Klawonn, G. Anikumar, H. Jiao, C. Döbler, A. Spannenberg, W. Mägerlein, H. Hugl, M. Beller, *Chem.—Eur. J.* **2006**, *12*, 1855, and other examples were cited in ref 2b.

4 Because most 1,3-oxazines, 2-oxazolines, and 1,3-oxazepines are readily hydrolyzed under weakly acidic conditions therefore the ^{1}H NMR yields before purification by column chromatography on silica gel were also reported.

5 The crude material was determined by using ^{1}H NMR to be analytically pure (>98%), whereas ca. 8 wt % of elemental sulfur contaminated the sample as a ^{1}H NMR silent impurity (i.e. ca. 72 atom % of sulfur was recovered, and the isolated yield was 65%), which was detected by the elemental analysis and mass spectroscopy.

6 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/.

7 Alkylation-promoted desulfurization–cyclization of *syn*-**1** did not take place due to steric hindrance. See ref 2b.

8 For recent examples of synthesis of 2-oxazolines, see: A. Sakakura, S. Umemura, R. Kondo, K. Ishihara, *Adv. Synth. Catal.* **2007**, *349*, 551.

9 For a recent example of the synthesis of 1,3-oxazepine, see: C. Ma, S.-J. Liu, L. Xin, J. R. Falck, D.-S. Shin, *Tetrahedron* **2006**, *62*, 9002, and references cited therein.

10 For recent example of the synthesis of quinazoline, see: S. Ferrini, F. Ponticelli, M. Taddei, *Org. Lett.* **2007**, *9*, 69, and references cited therein.

11 For an asymmetric epoxidation using a chiral bis-1,3-oxazinea as a ligand, see ref 3b. And also see: M. K. Tse, S. Bhor, M. Klawonn, G. Anikumar, H. Jiao, A. Spannenberg, C. Döbler, W. Mägerlein, H. Hugl, M. Beller, *Chem.—Eur. J.* **2006**, *12*, 1875.

12 Further discussions of the reaction pathway are described in Supporting Information.

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