Copper-catalyzed oxidative desulfurization–oxygenation of thiocarbonyl compounds using molecular oxygen: an efficient method for the preparation of oxygen isotopically labeled carbonyl compounds†

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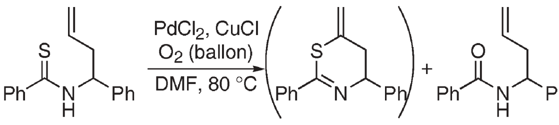
A novel copper-catalyzed oxidative desulfurization reaction of thiocarbonyl compounds, using molecular oxygen as an oxidant and leading to formation of carbonyl compounds, has been developed, and the utility of the process is demonstrated by its application to the preparation of a carbonyl-^{18}O labeled sialic acid derivative.

Stable and unstable isotopically labeled bioactive compounds have served as key components in studies aimed at uncovering the *in vivo* or *in vitro* behavior of biomolecules.[1,2] Because most physiologically interesting substances contain carbonyl groups, methods for the introduction of oxygen isotopes into this grouping are particularly attractive and, as a result, are in high demand.[2] However, no general procedures for accomplishing this task are available. Consequently, the development of a versatile method for direct oxygen isotope labeling that uses readily available water and/or molecular oxygen as oxygen isotope sources, is highly significant.

It is well known that thiocarbonyl compounds undergo desulfurization to generate the corresponding carbonyl compounds when treated with stoichiometric oxidants.[3] As such, this reaction has the potential of serving as a selective technique for introduction of oxygen isotopes into carbonyl groups. However, a thiocarbonyl desulfurization reaction involving molecular oxygen has not been explored. One exception is the process described by Gano and Atik that takes place under photo-irradiation conditions.[3a]

During our studies of transformations of thioamides,[4] we observed that an attempted metal-catalyzed Wacker-type cyclization[5] reaction of allylated thioamide **1** failed to give the desired thiazine **2**. Instead, the amide **3**, in which the sulfur atom of the thioamide is replaced by oxygen, formed quantitatively (eqn (1)). This observation led to an investigation in which we uncovered a general copper-catalyzed thermal oxidative desulfurization-oxygenation of thiocarbonyl compounds using molecular oxygen as an oxidant. Below, we describe the results of this effort along with an application of this process to the introduction of a carbonyl-^{18}O label into a biologically interesting sialic acid derivative by using $^{18}O_2$ gas.

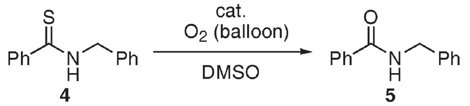


1 **2**: not observed **3**: quant. (1)

In our initial studies, reactions of *N*-benzyl-benzenecarbothioamide (**4**) and a catalytic amount of metal salts in DMSO under an oxygen atmosphere at 80 °C were explored in order to assess the catalytic activity of several metal salts (eqn (2), Table 1). We observed that the reaction promoted by copper(I) chloride gave the corresponding amide **5** quantitatively within a 15 min time period (entry 1). In contrast, palladium(II) chloride was completely inactive as a catalyst for this process (entry 2). Iron(III) chloride and silver(I) acetate also promote the desulfurization reaction of **4** but these salts display low catalytic activities (entries 3, 4). No reactions were observed to occur when nickel(II) or cobalt(II) chloride are used or when metal salts are absent (entries 5–7).

Importantly, an oxygen atmosphere is necessary for the progress of this reaction (entry 8). Studies of the CuCl promoted reaction of **4** demonstrated that the use of polar solvents, such as DMSO and DMF (entry 9), are optimal. In contrast, only trace amounts of product are formed when less polar solvents are employed

Table 1 Desulfurization–oxygenation of thioamide **4**[a]



4 **5** (2)

Entry	Cat. (mol%)	Solvent	Time/h	Conv. (%)[b]
1	CuCl (20)	DMSO	1/4	100 (98)[c]
2	$PdCl_2$ (20)	DMSO	16	0
3	$FeCl_3$ (20)	DMSO	25	100
4	AgOAc (20)	DMSO	20	11
5	$NiCl_2$ (20)	DMSO	6	0
6	$CoCl_2$ (20)	DMSO	6	0
7	—	DMSO	16	0
8[d]	CuCl (20)	DMSO	1	0
9	CuCl (20)	DMF	3	100
10	CuCl (20)	Toluene	6	Trace
11	CuCl (20)	$(CHCl_2)_2$	6	Trace
12	CuCl (5)	DMSO	7	34
13	CuCl (1)	DMSO	16	0

[a] Reactions were carried out with thioamide **4** in the presence of catalytic amount of metal salt under an oxygen atmosphere at 80 °C. [b] Conversions were determined by ^{1}H NMR. [c] Isolated yields of **5** are given in the parenthesis. [d] The reaction was carried out under Ar atmosphere.

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† Electronic supplementary information (ESI) available: Experimental details, characterization of all new compounds, and mass spectrum charts of co-product and elemental sulfur. See DOI: 10.1039/b701048f

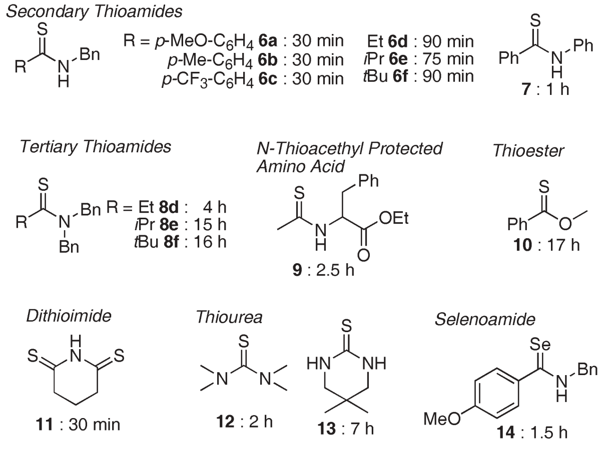


Fig. 1 Scope of substrates.

(entries 10, 11). The amount of CuCl significantly influences the reaction rate. When 5 mol% of CuCl is used, reaction takes place slowly and only a 34% yield of amide **4** is obtained after a 7 h time period (entry 12). In addition, no reaction occurs after 16 h when 1 mol% of CuCl is employed (entry 13).

Having developed optimized conditions for this process, we next explored the substrate scope of the desulfurization process. Each reaction was carried out in DMSO at 80 °C in the presence of 20 mol% of CuCl. The substrates and times required for their complete conversion to the corresponding carbonyl compounds are shown in Fig. 1.[6] Although the rates of the catalytic reactions were highly sensitive to the structures of the thioamide starting materials, simple variations in reaction times enabled each process to reach completion. The results of this effort show that chalcogenocarbonyl compounds, such as *N*-thioacetyl protected amino acid **9**, thioester **10**, dithioimide **11**, thiourea **12**, **13**, and selenoamide **14**, serve as competent substrates for this reaction.

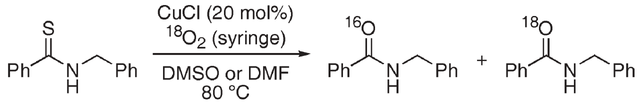
Carbonyl oxygen isotope labeling of thioamide **4** by using $^{18}O_2$ gas was examined next (eqn (3)). The extent of ^{18}O introduction into the amide product **5** was determined by using mass spectrometric analysis (Table 2 and 3). When DMSO is used as the solvent, ^{16}O atom is preferentially introduced into the amide at initial stages of the reaction (2–5 min) and the $^{16}O : ^{18}O$ ratio after complete reaction is *ca.* 48 : 52. In contrast, the reaction of **4** carried out in DMF, although taking place slowly, gives **5** with a $^{16}O : ^{18}O$ ratio of *ca.* 16 : 84. These observations suggest that DMSO can serve as a competitive oxidant for the catalytic process[7] and that oxygen gas is an efficient oxygen source for the reaction in DMF. In addition, the $^{16}O : ^{18}O$ ratio in **5** remains unchanged after aqueous work up and purification of the product by silica gel column chromatography (Table 2 and 3). Furthermore, the $^{16}O : ^{18}O$ ratio does not change when partially labeled amide **5** ($^{16}O : ^{18}O$ = 15 : 85) is treated with $^{16}O_2$ gas in the presence of CuCl in DMSO.[8] Therefore, carbonyl oxygen exchange between **5** and H_2O, DMSO or O_2 gas does not occur under the conditions used.

Table 2 The labeling reaction in DMSO

Time	2 min	5 min	45 min (completion)	After work up
$^{16}O : ^{18}O$	100 : 0	93 : 7	51 : 49	48 : 52

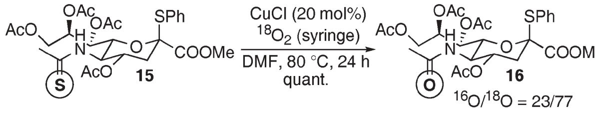
Table 3 The labeling reaction in DMF

Time	5 min	4 h (completion)	After work up
$^{16}O : ^{18}O$	Trace	16 : 84	15 : 85



(3)

To demonstrate the power of this novel oxygen isotope labeling method, we explored its use in the preparation of the ^{18}O-labeled sialic acid derivative **16**, which is a key building block of glycoproteins and sugar chain (eqn (4)).[9–11] The thioacylated sialic acid **15**, which serve as the substrate for this process, is formed quantitatively by the reaction of **16** with Lawesson's reagent. Introduction of the ^{18}O-label was performed by reacting **15** in DMF at 80 °C for 24 h under an $^{18}O_2$ atmosphere. This process yields the ^{18}O labeled sialic acid derivative **16** in quantitative yield and a $^{16}O : ^{18}O$ ratio of 23 : 77.



(4)

A pale yellow, low polarity solid byproduct is generated in each desulfurization reaction. The mass spectrum of this substance contains a molecular ion peak at *m/z* 256 and fragment peaks that are separated by 32 mass units. This fragmentation pattern is exactly the same as that of elemental sulfur.[12] This result clearly suggests that elemental sulfur (S_8) is the co-product. In addition, the amount of elemental sulfur produced in each case is nearly stoichiometrically equivalent to the amount of amide formed. These observations suggest that the thiocarbonyl sulfur (oxidation number = −2) is formally oxidized and eliminated from starting thiocarbonyl compound as elemental sulfur (oxidation number = 0). Importantly, the generated elemental sulfur does not poison the copper catalyst. Further, co-products of sulfur compounds bearing oxygen atoms, such as sulfur dioxide, were not observed, and it is suggested that the thiocarbonyl sulfur did not directly contact the oxygen under the reaction pathway.

Although the intermediates involved in the desulfurization reaction have not yet been identified, it is possible to envisage a plausible mechanism for this process (Fig. 2). The initial event in the proposed pathway involves stepwise two-electron oxidation of the thiocarbonyl sulfur in **I** by *in situ* generated copper(II) to give intermediate **II**. The reduced copper(I) species is then re-oxidized to copper(II) by molecular oxygen. A reduced nucleophilic O(−II)

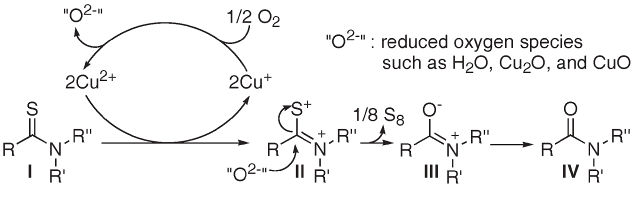


Fig. 2 Tentative reaction pathway.

species (probably water and/or copper complexes) is formed in this step in a manner similar to that observed in the catalytic cycle of the Wacker oxidation.[13] The generated nucleophilic oxygen species adds to **II** and elemental sulfur is eliminated to give the corresponding amide **IV**.

Earlier, Portella *et al.* described a photo-induced single-electron-transfer oxidation–activation of thiocarbonyl compounds by oxygen gas.[14] In contrast to the photochemical counterpart, the present catalytic reaction proceeds without loss of efficiency under dark conditions. In addition, the reaction does not take place in the absence of the copper catalyst or oxygen gas (Table 1, entries 7 and 8). Although demonstrating its unique features, these observations do not rule out a possible mechanism for the copper-catalyzed reaction involving electron transfer from thiocarbonyl sulfur to activated molecular oxygen promoted by an active copper species (*eg.*, oxo-complex).[14,15]

In conclusion, we have uncovered a new transition-metal-catalyzed oxidative desulfurization–oxygenation reaction of thiocarbonyl compounds that uses molecular oxygen as a stoichiometric oxidant. In addition, we have shown how this process can be used to introduce oxygen isotope labels into biologically important substances.

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7 The activation pathway of DMSO with oxygen gas and a copper catalyst is not clear. However, in this context, Mikolajczyk and coworker reported a similar desulfurization–oxygenation reaction, which is promoted by a catalytic amount of an electrophile such as sulfuric acid, boron trifluoride or iodine in DMSO. This reaction gives the corresponding carbonyl compound, and dimethyl sulfide and elemental sulfur as side products, see: (*a*) M. Mikolajczyk and J. Luczak, *Synthesis*, 1974, 491; (*b*) M. Mikolajczyk and J. Luczak, *Synthesis*, 1975, 114.

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