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Cu(II)-Catalyzed Acylation by Thiol Esters Under Neutral Conditions: Tandem Acylation-Wittig Reaction Leading to a One-Pot Synthesis of Butenolides

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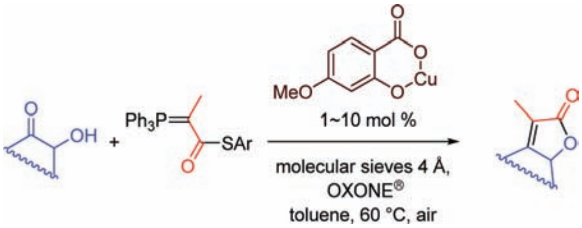
ABSTRACT



The first catalytic acylation of alcohols with a thiol ester present in Wittig reagents under neutral conditions catalyzed by the Cu(II) salt through a push−pull mechanism is reported. Furthermore, a new methodology for the one-pot lactonization of acyloins by a copper catalyst is developed. The synthetic utility of this method for the synthesis of natural products is shown.

Thiol esters are among the most important easily handled, stable acylating agents of alcohols in organic syntheses and biological systems.[1] Generally, acylations using a thiol ester are carried out under basic conditions to activate the alcohols. Although there have been several reports on *O*-acylations using thiol esters mediated by stoichiometric or substoichiometric amounts of soft metal salts such as Hg(II), Ag(I), Cu(I), and Cu(II),[2] no catalytic reactions under neutral conditions have been reported because the thiolates eliminated by the acylation would deactivate the metal salts. Previously, we found a tandem acylation Wittig-lactonization reaction of acyloins with the Wittig reagent containing an ester in the syntheses of sundiversifolide.[3] In this reaction, an excess of the Wittig reagent and high temperatures were required to complete the reaction. Since the reaction with the Wittig reagent having a trifluoroethyl ester proceeded faster, the acylation would be the rate-determining step. If a catalytic reaction under mild and neutral conditions could be developed, it would become a useful synthetic method for butenolides,[4] an important unit of bioactive natural

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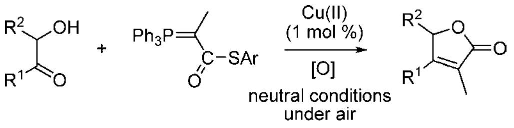
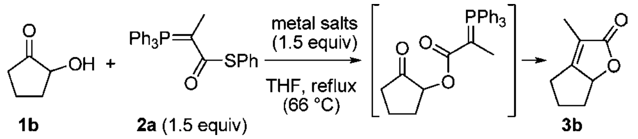
products. Herein, we describe the first acylation of alcohols by thiol esters catalyzed by copper(II) salts under neutral conditions followed by the intramolecular Wittig reaction providing butenolides in one pot (Scheme 1).

Scheme 1



First, we examined the soft metal salt-mediated Wittig lactonization of 2-hydroxycyclopentanone (**1b**), where the acylation of acyloins, with the Wittig reagent **2a** having a thiol ester, would be selectively accelerated by the metal salts even in the presence of acyloins. Although the reaction did not proceed under reflux in THF in the absence of metal salts (entry 1) or in the presence of a hard metal salt (entry 2), the desired lactone **3b** was obtained in the presence of 150 mol % of soft metal salts (entries 4−9), with $Cu(OAc)_2$ providing the product in 80% yield within 30 min (entry 6), as shown in Table 1. In contrast, the reaction was not or little accelerated by the other Cu(II) catalysts (entries 10−13).

Table 1. Acceleration of Acylation by Metal Salts



entry	metal salt	time (h)	yield (%)
1	–	3.5	no reaction
2	$Mg(OAc)_2$	3.5	trace
3	$Mn(OAc)_2$	2.5	no reaction
4	$Fe(OAc)_2$	3.5	11
5	$Co(OAc)_2$	3.5	26
6	$Cu(OAc)_2$	0.5	80
7	$Zn(OAc)_2$	3.5	61
8	$[Rh(OAc)_2]_2$	3.5	55
9	$Ag(OAc)_2$	3.5	51
10	$Cu(OTf)_2$	2.0	no reaction
11	$Cu(ClO_4)_2$	2.0	no reaction
12	$CuCl_2$	2.0	no reaction
13	$Cu(acac)_2$	3.5	38

During the course of this study, a small amount of diphenyl disulfide was isolated as a side product. It would be generated by oxidation of the thiolate eliminated by the acylation along with reduction of Cu(II) to Cu(I). We thought that if the thiolate could be converted entirely into the disulfide, which is expected to be a much poorer ligand for Cu(II), and the resulting Cu(I) oxidized to Cu(II), then the active catalyst Cu(II) would be regenerated (Figure 1);[5] thus, the Cu(II) catalyst would play a double role, namely activation of the C−S bond and removal of the thiolate.

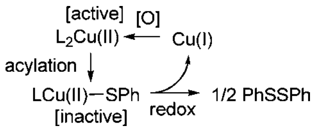
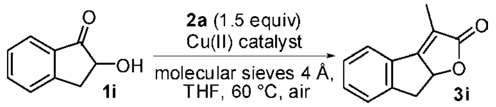


Figure 1. Cu(II)-catalyzed oxidation of thiolate.

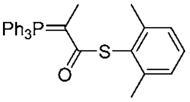
On the basis of this concept, we attempted the Cu(II)-catalyzed Wittig lactonization of 2-hydroxyindanone (**1i**) in air as an oxidant (Table 2). As expected, the $Cu(OAc)_2$ catalyzed reaction furnished the lactone **3i** in 82% yield at 60 °C in 6 h (entry 1). The fact that the reaction resulted in

Table 2. Optimization of Cu(II)-Catalyzed Acylation-Wittig Lactonization

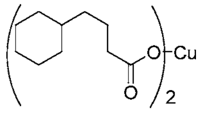


entry	Cu(II) catalysts	mol %	additive	time (h)	yield (%)
1	$Cu(OAc)_2$	10	–	6	82
2	$Cu(OAc)_2$	10	(under Ar)	6	28
3	$Cu(OCOCF_3)_2$	10	–	5	94
4	**4**	10	–	6	58
5	$Cu(OCOPh)_2$	10	–	5	60
6	**5**	10	–	5	91
7	**6**	10	–	5	97
8	**6**	10	$NaIO_4$[a]	4.5	98
9	**6**	10	OXONE[b]	2	92
10	**6**	2	OXONE[b]	5	76
11[c]	**6**	2	OXONE[b]	4	91

[a] One and a half equivalents. [b] Three equivalents. [c] **2b** was used as the Wittig reagent.



2b



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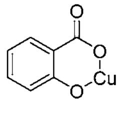

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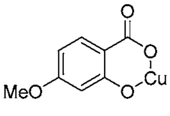

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28% yield under Ar suggested that oxidants are essential for catalytic turnover (entry 2). Encouraged by these results, we next screened Cu(II) salts as possible catalysts. Among the "monodentate-type" carboxylate salts (entries 1−5), Cu(OCOCF$_3$)$_2$ gave the best yield (entry 3). Although the benzoate salts resulted in a moderate yield (entry 5), the bidentate-type salicylate salts (**5** and **6**)[6] provided **3i** in higher yields. In place of air as an oxidant, NaIO$_4$ could be used and OXONE was found to accelerate considerably the catalytic reaction to provide **3i** in 2 h in high yield (entry 9). Even using 2 mol % of the catalyst, **3i** was obtained in good yield (entry 10). From these results, the rate determining step would be reoxidation of Cu(I) to Cu(II) in this catalytic system. Finally, the Wittig reagent **2b** having 2,6-dimethylphenylthioester was found to provide **3i** in excellent yield using only 2 mol % of the catalyst, probably because the sterically more congested Cu(II)SAr complex (see Figure 3) might be more easily converted into disulfide and Cu(I).

To establish the generality of this catalytic lactonization, various kinds of acyloins were reacted with **2b** using **6** as a catalyst in toluene.[7] As shown in Figure 2, several cyclic and acyclic acyloins were transformed into the desired lactones in high yields. The α-hydroxyl lactone (**1h**), the sterically congested acyloin (**1j**), the key intermediates (**1k**, **1l**) for the syntheses of the bioactive natural products, sundiversifolide[8] and heritonin,[9] respectively, also afforded the corresponding lactones. Compared to the low yield (1.4%) by the intramolecular Horner-Emmons-lactonization,[9a] our method gave the product in much higher yield.

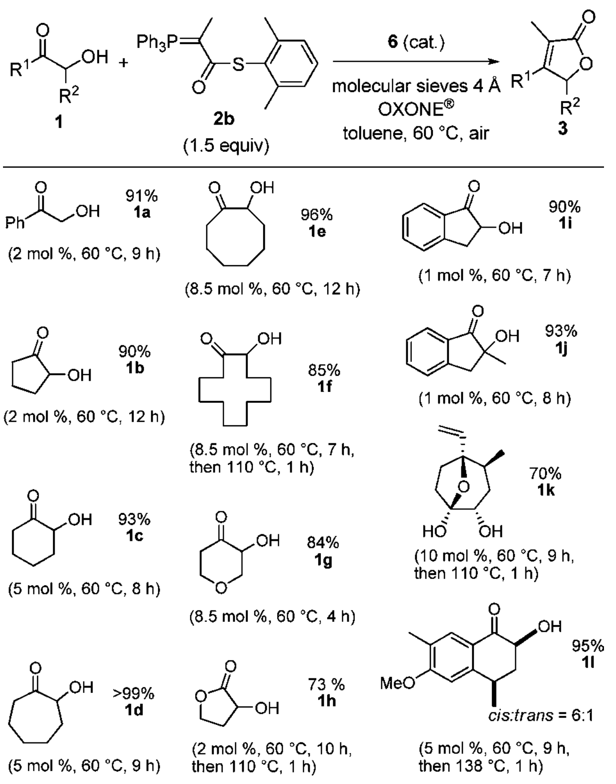

Figure 2. Tandem acylation-Wittig lactonization of acyloins.

A plausible mechanism for this catalytic reaction is shown in Figure 3. The thiol ester would be activated by Cu(II) catalyst as Masamune proposed.[2a,b] In this catalytic system, the phosphorus ylide on the α position would be an essential substituent, because simple thiol esters without a phosphorus ylide were not converted into the corresponding *O*-ester by this catalyst. Therefore, we estimated that the ketene-like intermediate, as illustrated in **7**, would be generated by a push−pull mechanism, which involves the double activation of the C−S bond by both the soft Lewis acidic Cu (II) (pull) and the electron-donating phosphorus ylide (push). The ketene intermediate **7** would undergo rapid acylation, followed by the intramolecular Wittig reaction, to provide the lactone **3**. A redox reaction of the thiolate complex **8** would afford a thiyl radical **10**, which would be converted into the disulfide, and the Cu(I) salt **9**, which would be oxidized to regenerate the catalyst **6**.

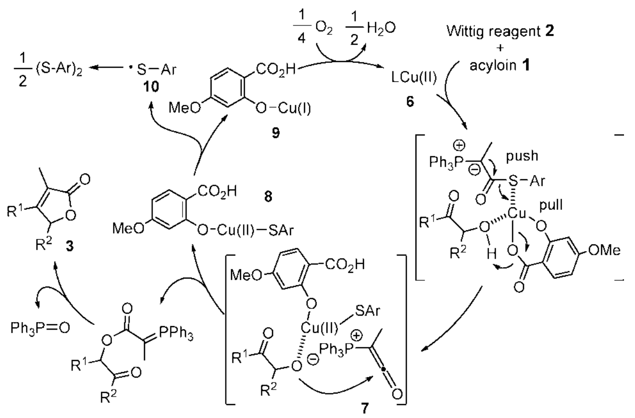

Figure 3. Proposed mechanism.

In conclusion, we have found the catalytic acylation of alcohols with a thiol ester present in Wittig reagents under neutral conditions catalyzed by the Cu(II) salt by a push−pull mechanism. Furthermore, we have developed a new methodology for the one-pot lactonization of acyloins by a copper catalyst. Further investigations to elucidate the detailed mechanism of this reaction are now in progress.

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(6) For X-ray crystal structure analysis of **6**, see Supporting Information.

(7) Toluene is safer than THF under oxidative conditions. Furthermore, the catalyst turnover number in toluene was fairly better than in THF.

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Supporting Information Available: General procedures, characterization data of new compounds, ^{1}H- and ^{13}C NMR spectra of new compounds. X-ray data for the catalyst **6** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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