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Copper-catalyzed aerobic oxidative dehydrogenation for conversion of 2-(alkylthio)-1,4-dihydropyrimidines to 2-(alkylthio)pyrimidines

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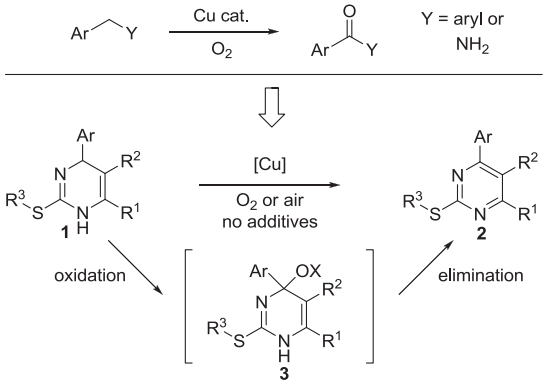
ABSTRACT

A simple and efficient aerobic oxidative dehydrogenation reaction method for the conversion of 2-(alkylthio)-1,4-dihydropyrimidines to 2-(alkylthio)pyrimidines using copper catalyst with no additives, such as an oxidant, acid, or base, has been developed. The reaction was successful with a wide range of 2-(alkylthio)-1,4-dihydropyrimidine substrates.

1. Introduction

Copper-catalyzed coupling reactions, recognized as a powerful tool in synthetic chemistry, have been used as key steps in the synthesis of heterocycles.[1] In addition, copper catalysis has recently been used in the oxidation of sp^3 carbons to carbonyl carbons. Maes[2] and Fu[3] reported that the methylene group of aryl(di)azinylmethanes and arylmethanamines, respectively, is oxidized to a carbonyl group under O_2. Based on these results, we envisioned a copper-catalyzed aerobic oxidative dehydrogenation reaction method for the conversion of dihydropyrimidyl thioether **1** to pyrimidyl thioether **2**. The 2° alcohol was reported as the minor product in the oxidation of 2-benzyl pyridine,[2] and the aminal was proposed as the intermediate in the oxidation of arylmethanamines;[3] thus, oxidation of **1** was expected to produce alcohol **3a** (X=H) or oxygenated species **3b** (X=O) as an intermediate. Further oxidation of the intermediate is not allowed; instead, the elimination is expected to produce aromatic pyrimidine **2** (Scheme 1).



Scheme 1. Copper-catalyzed aerobic oxidative dehydrogenation of **1**.

Because substrate **1** with diverse substituents at C4–C6 can be easily prepared via the Biginelli reaction[4] of thiourea, ketoesters, and aldehydes,[5] followed by simple alkylation, the pyrimidyl thioethers produced by the oxidative dehydrogenation can be intermediates for diverse pyrimidine-based drugs or drug candidates. For example, compound **2** (Ar=4-F–C_6H_4, R^1=Me, R^2=CO_2Me, R^3=*i*-Pr) has been used as an intermediate in the production of rosuvastatin.[6] In addition, cross-coupling reactions, such as the Liebeskind–Srogl reaction,[7] can transform compound **2** derivatives to diverse C4-aryl pyrimidines.[8]

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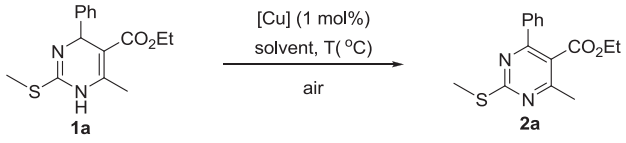
In contrast to the facile dehydrogenation of Hantzsch dihydropyridines, the reaction of dihydropyridines is known to be more difficult due to their greater stability.[9] Previously reported methods for the oxidative dehydrogenation of **1**, such as TBHP/$CuCl_2$/K_2CO_3,[10a] MnO_2/MW,[10b] $PhI(OAc)_2$,[10c] NHPI/$Co(OAc)_2$/O_2,[10d] and Re(I)/hν/K_2CO_3,[10e] give acceptable yields;[11] however, they require stoichiometric or excess oxidants or bases, or conditions such as μW or *hν* radiation. Herein, we report an efficient oxidative dehydrogenation reaction of dihydropyrimidyl thioether under air using only copper catalysts with no additional reagents.

2. Results and discussion

To optimize the reaction conditions, we reacted **1a** under various Cu catalysts, solvents, and temperatures. The results are summarized in Table 1.

Table 1
Optimization of reaction conditions for aerobic oxidative dehydrogenation[a]



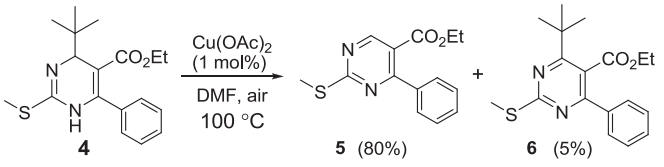
Entry	[Cu]	Solvent	*t* (h)/*T* (°C)	Conv. (%)[b]/yield (%)[c]
1	$Cu(OAc)_2$	THF	12/rt	Trace
2	$Cu(OAc)_2$	$PhCH_3$	12/rt	Trace
3	$Cu(OAc)_2$	Dioxane	12/rt	Trace
4	$Cu(OAc)_2$	DMF	12/rt	10
5	$Cu(OAc)_2$	NMP	12/rt	8
6	$Cu(OAc)_2$	$PhCH_3$	8/100	26
7	$Cu(OAc)_2$	Dioxane	8/100	35
8	$Cu(OAc)_2$	THF	8/reflux	21
9	$Cu(OAc)_2$	DMF	8/100	100/86
10	$Cu(OAc)_2$	NMP	8/100	80/67
11	$Cu(OAc)_2$	DMF	2.5/100	100/86
12	CuCl	DMF	2.5/100	>99/80
13	CuBr	DMF	2.5/100	74/60
14	CuI	DMF	2.5/100	65/57
15	$CuCl_2$	DMF	2.5/100	80/70
16	CuCl	NMP	8/100	75/57
17	CuBr	NMP	8/100	65/50
18	CuI	NMP	8/100	53/42
19	$CuCl_2$	NMP	8/100	72/60
20	$Cu(OAc)_2$	DMF	5/50	52/30
21	None	DMF	2.5/100	6
22	None	NMP	8/100	5

[a] Reaction conditions: substrate **1a** (0.2 mmol), catalyst (1.0 mol %) and solvent (1.0 mL) under air.
[b] Based on the ^1H NMR spectra.
[c] Isolated yield.

At room temperature, the reaction using $Cu(OAc)_2$ (1.0 mol %) in THF, toluene, or 1,4-dioxane for 12 h under air resulted in a trace amount of the desired product **2a** (entries 1–3). We optimized the reaction conditions by replacing the solvent with DMF or NMP at room temperature (entries 4 and 5), resulting in an appreciable amount of **2a**. When the reaction was carried out at 100 °C for 8 h in the presence $Cu(OAc)_2$, the conversion in all solvents increased. In the case of DMF and NMP, the conversions were 100% and 80%, respectively, while 21–35% conversion was obtained in the other three solvents (entries 6–10). Because DMF was the most effective solvent, further optimization was carried out in DMF. Further experiments showed that the reaction was complete within 2.5 h at 100 °C (entry 11). We found that both Cu(I) and Cu(II) catalysts have potential for aerobic dehydrogenation; among Cu sources, $Cu(OAc)_2$ was the best catalyst for the reaction compared with other catalysts such as CuCl, CuBr, CuI, and $CuCl_2$, in either DMF (entries 12–15) or NMP (entries 16–19). Notably, in the absence of a Cu catalyst, a detectable amount of **2a** was produced (entries 21 and 22).

Under optimal conditions, the reaction was performed with diversely substituted dihydropyrimidine substrates. First, we performed the reaction with a gradual increase in the bulkiness of R^3 to examine the effect of the sulfide group. The reaction yield was inversely proportional to bulkiness: 92% (MeS), 70% (EtS), 67% (*n*-PrS), and 65% (*i*-PrS) (entries 1–4). For R^2 of the alkoxycarbonyl, the Et group (entry 1) showed a higher yield than Me, *i*-Pr, or *t*-Bu groups (entries 5–7). When we carried out the reaction with various R^1 groups, the Ph and Me groups resulted in markedly higher yields compared to the Et, *n*-Pr, and *i*-Pr groups, which afforded the corresponding products in similar yields (entries 8–11). In contrast to the case of R^1 as the Me group, the steric effect of R^3 was not significant when R^1 was the Ph group (entries 12–14), which indicates that the electron conjugation of the core ring with the R^1 group plays a major role in the dehydrogenation reaction. With respect to Ar at C4, we investigated the effect of substituents at the aryl group, heterocycles, and the bicyclic aryl group. The reaction did not exhibit a preference toward either electronic or steric effects of the substituent of aryl groups. For the electron-donating methoxy group, no significant steric effect was observed when the substrates with 2- and 4-methoxyphenyl groups were reacted to produce **2o** and **2p**, respectively, in high yields (entries 15 and 16). The electron-withdrawing NO_2 and F groups also afforded the corresponding products in high yields. Based on these results and the similar yields of the 3- and 4-NO_2 groups (entries 17 and 18), the reaction did not involve the intermediates of the cationic or anionic ring system. Substrates possessing bicycles and heterocycles at C4, such as the 2-naphthyl, 2-pyridinyl, or 2-thiophenyl groups, were also suitable for this reaction method (entries 20 and 21). Overall, the reaction method was compatible with a wide range of functional groups at C2 and C4–C6.

After demonstrating that the reaction method is suitable for the oxidative dehydrogenation of various dihydropyrimidyl thioethers, we investigated the reaction mechanism. The electron conjugation of the ring with the R^1 group played an important role in the reaction, and neither cationic nor anionic intermediates were involved; thus, the reaction likely proceeded via a radical intermediate. To obtain further insight into the reaction mechanism, we reacted **4**, which possessed a *t*-Bu group instead of an aryl group at the C4 position (Scheme 2). Similar to previous studies on TBHP/$CuCl_2$/K_2CO_3[10a] and NHPI/$Co(OAc)_2$/O_2[10d] giving exclusively debutylated product **5** through a radical mechanism, we also obtained **5** as the major product (80%), along with **6** (5%). As well as the electronic effect of R^1, this result also supports the radical mechanism of the reaction.



Scheme 2. Aerobic oxidative dehydrogenation of dihydropyrimidyl thioether possessing *t*-Bu group at C4.

To determine whether both O_2 and H_2O are involved in the aerobic oxidative dehydrogenation, we performed the reaction under Ar, oxygen-free Ar with H_2O, and anhydrous O_2. The reaction proceeded much faster under anhydrous O_2 than under oxygen-free Ar with H_2O (Table 3). This result indicates that O_2 is primarily responsible for the reaction, although anhydrous O_2 gave a lower yield than air.

The Yamamoto group proposed two mechanisms for the oxidative dehydrogenation of **2** or DHPM using TBHP/$CuCl_2$/K_2CO_3.[10a]