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Aerobic copper-promoted oxidative dehydrosulfurative carbon–oxygen cross-coupling of 3,4-dihydropyrimidine-1*H*-2-thiones with alcohols†

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An aerobic Cu-promoted oxidative dehydrosulfurative carbon–oxygen cross-coupling of 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) with both aliphatic and aromatic alcohols is described. Together with the ready availability of DHPMs and both alcohols, the method furnishes facile access to biologically valuable 2-alkoxyxypyrimidines with rapid diversification.

Pyrimidine motifs have received great interest from organic and medicinal chemists owing to their intriguing biological profile as well as being parts of DNA and RNA.¹ Extensive research on this privileged scaffold has brought to the market dozens of drugs with highly potent activity against disease-causing microbes, viruses, and mycobacteria as well as cancer, inflammation, hypertension, and diabetes.² In particular, the 2-alkoxyxypyrimidine structure has been incorporated into commercial herbicides such as bispyribac-sodium³ and pyriminobac-methyl,⁴ and osteogenesis inducers including purmorphamine (Fig. 1).⁵ In addition, 2-alkoxyxypyrimidine compounds are known to be selective PDGFR α inhibitors which induce apoptosis and autophagy in carcinoma cells⁶ and potent NAD⁺-dependent DNA ligase (LigA) inhibitors as potential antibacterial agents.⁷

For the preparation of 2-alkoxyxypyrimidines, nucleophilic aromatic substitution⁸ or Pd-catalyzed C–O cross-coupling of 2-(pseudo)halopyrimidine compounds with alcohols has been commonly performed (Scheme 1A).⁹ In most cases, these strategies require tedious multistep synthesis of the densely substituted pyrimidine partners and, thus have limitation in preparing the diverse pyrimidine derivatives rapidly. In addition, competing β -hydride elimination reactions are an additional hurdle in metal-catalyzed C–O coupling of (pseudo)halides with aliphatic 1° or 2° alcohols.

For more efficient syntheses of pyrimidine derivatives with rapid diversification, we have employed 3,4-dihydropyrimidin-1*H*-2-thione (DHPM), which can be readily prepared by the well-

known Biginelli three-component reaction,¹⁰ as an alternative to the 2-(pseudo)halopyrimidine. We recently developed the Cu-mediated oxidative dehydrosulfurative C–O cross-coupling of DHPMs with trialkylborates to generate the corresponding 2-alkoxyxypyrimidines (Scheme 1B1).¹¹ The reaction method with triarylborates was also found to be applicable to the synthesis of 2-aryloxyxypyrimidines, but not practical due to non-commercial availability and non-trivial preparation of most of the triarylborates. We subsequently developed Libeskind–Srogle-type¹² Pd-catalyzed/Cu-mediated oxidative dehydrosulfurative C–O cross-coupling of DHPMs with readily available aryl alcohols for the synthesis of 2-aryloxyxypyrimidines (Scheme 1B2).¹³ Although both reaction methods offered the desired 2-alkoxyxypyrimidine products in moderate to good yields, their reaction conditions require large amounts of metals – 4.5 equivalents of Cu for borates and the mixture of 0.2 equivalents of Pd and 3 equivalents of Cu for aryl alcohols. The large amount of metals required for these reactions led us to pursue an alternative method that reduce the amount of Cu source and can be used

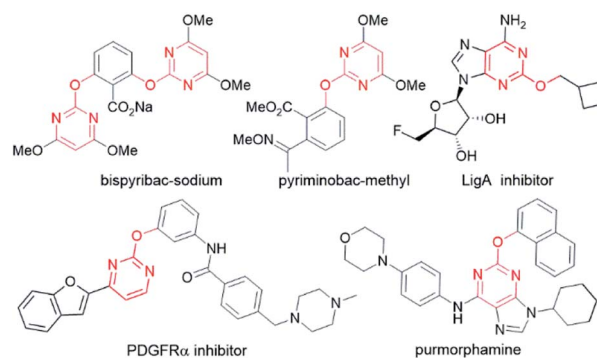


Fig. 1 Biologically valuable 2-alkoxyxypyrimidine derivatives.

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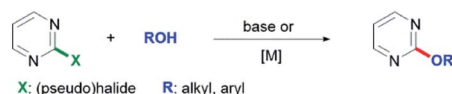
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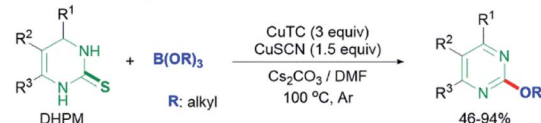
A. Conventional work

Nucleophilic substitution or [M]-catalyzed C-O cross-coupling

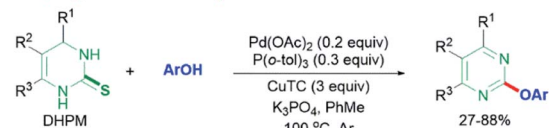


B. Our previous work

1) Cu-mediated oxidative dehydrosulfurative C-O cross-coupling of DHPM with trialkylborate

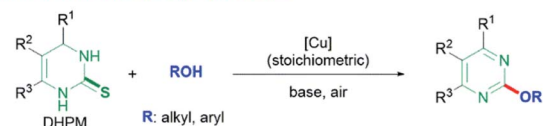


2) Pd-catalyzed/Cu-mediated oxidative dehydrosulfurative C-O cross-coupling of DHPM with aryl alcohol



C. This work

Aerobic Cu-promoted oxidative dehydrosulfurative C-O cross-coupling of DHPM with aromatic/aliphatic alcohol



Scheme 1 Synthetic strategy to 2-alkoxy pyrimidine derivatives. (A) Conventional synthesis, (B) our previous synthesis, (C) this work.

for both aromatic and aliphatic alcohols. We report herein a dehydrosulfurative C-O cross-coupling of DHPMs with both aliphatic and aromatic alcohols with concomitant oxidative dehydrogenation (aromatization), promoted by stoichiometric amount of Cu under air (Scheme 1C). Considering the ready availability of DHPMs and both alcohols, the method furnishes a highly efficient access to various 2-aryl(alkyl)oxy pyrimidine derivatives.

We commenced the studies with the reaction of DHPM **1a** and PhOH as coupling partners in the presence of Cu(i)-thiophene-2-carboxylate (CuTC, 2 equiv.) and Cs₂CO₃ (2 equiv.) in toluene at 100 °C for 18 h under Ar atmosphere. The reaction provided the desired 2-phenoxy pyrimidine **3a** in 23% yield (entry 1, Table 1), which led us to investigate the reaction by varying reaction parameters. When copper(i) 3-methylsalicylate (CuMeSal) was used instead of CuTC, the desired product was produced in 32% yield (entry 2). The reaction yield was increased to 69% when Cu(OAc)₂ was used (entry 3) while other Cu(i) or Cu(ii) sources, such as CuCl, CuI, CuBr, or CuBr₂, were not effective (entries 4–7). With respect to base, Ag₂CO₃, which gave the desired product in 91% yield, was superior to other bases examined in the studies, such as Cs₂CO₃, K₂CO₃, *t*-BuOK, CsF, and Na₂CO₃ (entries 8–12). Toluene was better than other solvents, such as *o*-xylene, 1,4-dioxane, *N,N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), or dimethylsulfoxide (DMSO) for the reaction (entries 13–17). With respect to the amount of Cu(OAc)₂, it was shown that 1.5 equivalents of

Table 1 Optimization studies^a

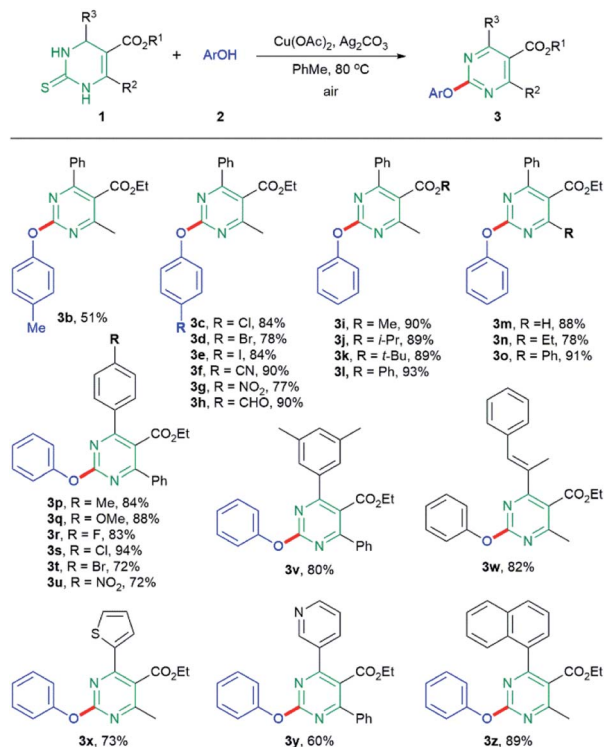
Entry	Cu (equiv.)	Base	Solvent	T (°C)	Yield (%)
1	CuTC (2)	Cs ₂ CO ₃	PhMe	100/Ar	23
2	CuMeSal (2)	Cs ₂ CO ₃	PhMe	100/Ar	32
3	Cu(OAc) ₂ (2)	Cs ₂ CO ₃	PhMe	100/Ar	69
4	CuCl (2)	Cs ₂ CO ₃	PhMe	100/Ar	0
5	CuBr (2)	Cs ₂ CO ₃	PhMe	100/Ar	0
6	CuI (2)	Cs ₂ CO ₃	PhMe	100/Ar	0
7	CuBr ₂ (2)	Cs ₂ CO ₃	PhMe	100/Ar	0
8	Cu(OAc) ₂ (2)	K ₂ CO ₃	PhMe	100/Ar	75
9	Cu(OAc) ₂ (2)	<i>t</i> -BuOK	PhMe	100/Ar	54
10	Cu(OAc) ₂ (2)	CsF	PhMe	100/Ar	51
11	Cu(OAc) ₂ (2)	Ag ₂ CO ₃	PhMe	100/Ar	91
12	Cu(OAc) ₂ (2)	Na ₂ CO ₃	PhMe	100/Ar	63
13	Cu(OAc) ₂ (2)	Ag ₂ CO ₃	<i>o</i> -Xylene	100/Ar	83
14	Cu(OAc) ₂ (2)	Ag ₂ CO ₃	Dioxane	100/Ar	55
15	Cu(OAc) ₂ (2)	Ag ₂ CO ₃	DMF	100/Ar	Trace
16	Cu(OAc) ₂ (2)	Ag ₂ CO ₃	NMP	100/Ar	Trace
17	Cu(OAc) ₂ (2)	Ag ₂ CO ₃	DMSO	100/Ar	Trace
18	Cu(OAc) ₂ (1.5)	Ag ₂ CO ₃	PhMe	100/air	91
19	Cu(OAc) ₂ (1.5)	Ag ₂ CO ₃	PhMe	100/air	90
20	Cu(OAc) ₂ (1.5)	Ag ₂ CO ₃	PhMe	80/air	90
21	Cu(OAc) ₂ (1.2)	Ag ₂ CO ₃	PhMe	80/air	89
22	Cu(OAc) ₂ (1)	Ag ₂ CO ₃	PhMe	80/air	88
23	Cu(OAc) ₂ (0.5)	Ag ₂ CO ₃	PhMe	80/air	74
24	Cu(OAc) ₂ (0.2)	Ag ₂ CO ₃	PhMe	80/air	55

^a Reaction conditions: DHPM **1a** (0.18 mmol), PhOH **2a** (0.20 mmol), base (0.36 mmol), and solvent (1.0 mL) for 18 h.

Cu(OAc)₂ was as effective as 2 equivalents of Cu(OAc)₂ in the production of the desired product (entry 18). We found that the reaction under air proceeded as efficiently as that under Ar atmosphere (entry 19), which means that oxygen is not likely to participate in the reaction process. There was no difference in the reaction yield between the reaction temperature at 80 °C and 100 °C (entry 20). Further investigation of the reaction exhibited that 1–1.5 equivalents of Cu(OAc)₂ with no other additives have almost the same effect on the production of the desired product under air (entries 19–22). Less than 1 equivalent of Cu(OAc)₂ provided lower yields of the desired product (entries 23 and 24).

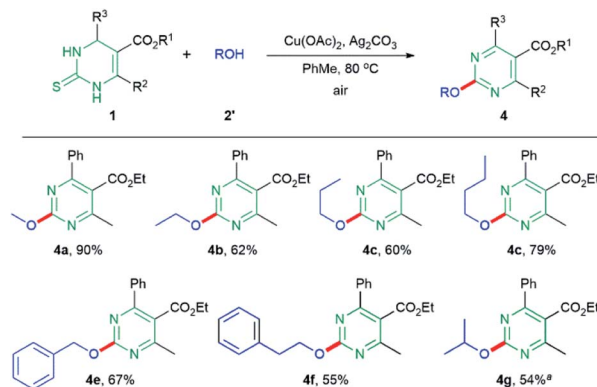
We assessed the scope of the reaction with various DHPM and aliphatic/aromatic alcohol coupling partners under optimal conditions using 1.1 equivalents of Cu(OAc)₂. With regard to aryl alcohols, various substituents at the *para* position of phenyl ring were investigated (Scheme 2). When *p*-cresol was reacted with DHPM **1a**, the desired aryloxy pyrimidine **3b** was generated in 51% yield.¹⁴ In the case of the aryl alcohols possessing electron-withdrawing group at the *para* position, the reaction with **1a** provided the desired products in higher yields, comparing to the case of *p*-cresol; halide group, Cl, Br, or I, and other electron-withdrawing groups such as CN or NO₂ afforded





Scheme 2 Scope of the reaction with respect to DHPMs and aromatic alcohols. Reaction conditions: DHPM **1** (0.18 mmol), aryl alcohol **2** (0.20 mmol), Cu(OAc)₂ (0.20 mmol), Ag₂CO₃ (0.36 mmol) in PhMe (1.0 mL) at 80 °C under air.

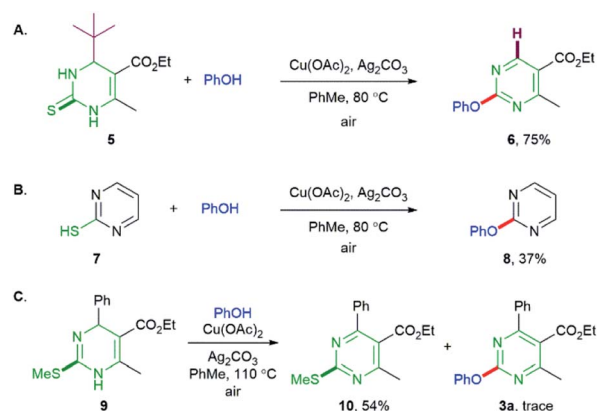
the corresponding products **3c–g** in 77–90% yields. In particular, formyl group, which provided **3h** in low yield (27%) in the previous Pd-catalyzed/Cu-mediated reaction, was also suitable functional group to produce **3h** in 90% yield. We next assessed the reaction scope regarding DHPM substrates possessing various substituents at C4–C6 positions. For R¹ at C5 position, both alkyl and aryl groups were compatible with the reaction; methyl, *i*-propyl, *t*-butyl, and phenyl groups afforded the corresponding products **3i–l** in similarly high yields. With respect to C6 substituents (R²), the reaction of DHPM containing no C6 substituent with phenol gave the desired product **3m** in 88% yields. Ethyl and phenyl groups at the C6 position also provided the desired products **3n** and **3o** in good yields. For the C4 substituent (R³), both electron-donating and -withdrawing groups at the *para* position of C4 aryl were adequate for the reaction; tolyl, anisyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, and 3,5-dimethylphenyl groups provided the corresponding products **3p–v** in 72–94% yields. Note that the presence of halide group in either alcohol or DHPM partner did not cause any potentially competitive C–O coupling on the halide-attached carbon. Instead of aryl group, styryl group at the C4 position yielding **3w** in 82% yield was also proven to be compatible under the reaction conditions. The DHPM with heterocyclic thiophenyl or pyridinyl group, or bicyclic naphthyl group at the C4 position was efficiently transformed to the corresponding products **3x–z** in 60–89% yields.



Scheme 3 Scope of the reaction with respect to DHPMs and aliphatic alcohols. Reaction conditions: DHPM **1** (0.18 mmol), aliphatic alcohol **2'** (0.20 mmol), Cu(OAc)₂ (0.20 mmol), Ag₂CO₃ (0.36 mmol) in PhMe (1.0 mL) at 80 °C under air.

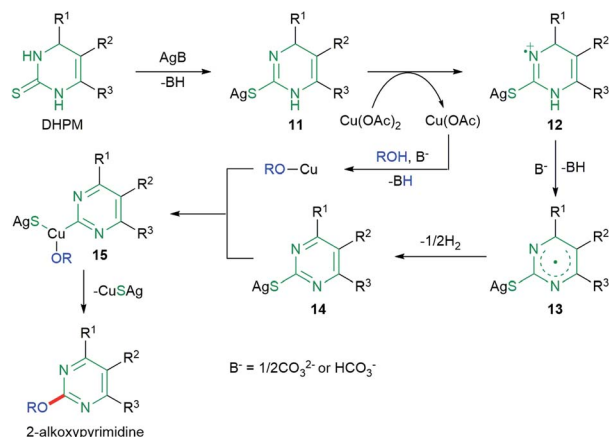
We also assessed the reaction scope with respect to aliphatic alcohols (Scheme 3). When the reactions of DHPM **1a** with 1° alcohols were performed, methoxy- (**4a**, 90%), ethoxy- (**4b**, 62%), *n*-propoxy- (**4c**, 60%), and *n*-butoxypyrimidine (**4d**, 79%) were obtained in moderate to good yields. Other aliphatic alcohols, such as benzyl- or phenethyl alcohol also provided the desired products **4e** and **4f** in 67% and 55% yields, respectively. The reaction with 2° alcohol *i*-PrOH produced the desired product **4g** in 10% yield. This unacceptably low yield increased to 54% in the presence of 1 equivalent of phenanthroline under the reaction conditions. The 3° alcohol, *t*-BuOH, did not appreciably provide the desired product. In these studies, we did not observe any possibly competitive β-hydride elimination side-reactions.

In order to understand the mode of the reaction, we performed the reaction of DHPM **5** containing *t*-butyl group at the C4 position and obtained the debutylated product **6** in 75% yield (Scheme 4A). This result supports that the oxidative dehydrogenation (aromatization) proceeds *via* a radical intermediate as described in the literatures published by others¹⁵ and us.^{11,13} The reaction of 2-mercaptopyrimidine **7** with phenol



Scheme 4 Control experiments. Reactions of phenol with (A) DHPM **5**, (B) 2-mercaptopyrimidine **7**, (C) dihydropyrimidinyl thioether **9**.





Scheme 5 A plausible mechanism.

provided the phenoxy pyrimidine **8** (Scheme 4B), which can agree with the proposition that the C–S single bond generated after deprotonation participates in the coupling of DHPM. We found that the reaction of dihydropyrimidinyl thioether **9** with PhOH yielded pyrimidinyl thioether **10** as the major product along with a trace amount of **3a**, which indicates that the oxidative dehydrogenation could proceed prior to the C–O coupling.

Based on the results, we propose a plausible reaction mechanism as depicted in Scheme 5. Due to no significant difference in reaction yields between air and Ar atmosphere (Table 1), oxygen is unlikely to participate in the reaction process. Deprotonation and complexation with Ag₂CO₃ could generate **11** containing C–S single bond, which is then oxidized to pyrimidine **14** likely *via* radical intermediate **13** formed from nitrogen radical cation **12**. The radical cation **12** could be produced from **11** by a single electron transfer.¹⁶ An oxidative addition of **14** to Cu(I)OR generated from the reaction of Cu(I) species with alcohol could provide Cu(III) complex **15**, which is then converted to 2-alkoxy pyrimidine by a reductive elimination.

In summary, we have developed an aerobic Cu-promoted oxidative dehydrosulfurative carbon–oxygen cross-coupling of DHPMs. The reaction proceeded efficiently with diverse DHPMs and both aromatic and aliphatic alcohols. A wide range of readily available DHPMs and alcohols makes the presented reaction an attractive method to access to biologically and pharmacologically valuable 2-alkoxy pyrimidine derivatives with rapid diversification.

Conflicts of interest

There are no conflicts to declare.

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