Synthesis of Arylthiopyrimidines by Copper-catalyzed Aerobic Oxidative C–S Cross-coupling

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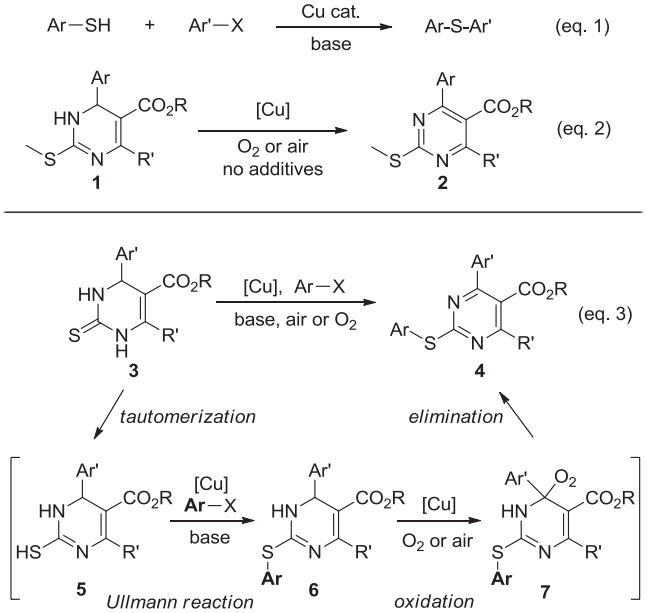
Copper-catalyzed C–S cross-coupling reactions have been considered as powerful tools in synthetic chemistry and utilized for diverse heterocycle syntheses (Equation 1, Scheme 1).[1] In the reactions, the aspects of no need of ligands has been particular advantage over other metal catalysis.[2] Recently, an interesting feature of copper catalysis has been revealed, in which sp^3 carbons are oxidized to carbonyl carbons using oxygen as an only oxidant.[3] As its further extension, we previously reported the copper-catalyzed aerobic oxidative dehydrogenation reaction of dihydropyrimidyl thioether **1** to (alkylthio)pyrimidine **2** with no additives, such as an oxidant, acid, or base (Equation 2).[4] Hinted by relative insensitivity of the C–S cross-coupling to O_2 or air we envisioned a copper-catalyzed cascade reaction, which combines the C–S cross-coupling (Equation 1) with concomitant oxidative dehydrogenation (Equation 2) as shown in Scheme 1. Herein, we report the synthesis of fully substituted arylthiopyrimidines **4** from 3,4-dihydropyrimidine-2(1H)-thiones (DHPMs) and aryl iodides under air, presumably via tautomerization, C–S cross-coupling, and oxidative dehydrogenation (oxidation followed by elimination) (Equation 3).[5]



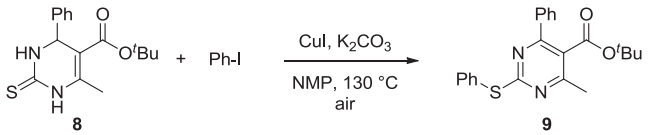
Scheme 1. Copper-catalyzed aerobic cascade reaction for the synthesis of arylthiopyrimidines.

DHPM substrates **3** can be easily synthesized by Biginelli three component reaction with aryl aldehyde, β-ketoester and thiourea.[6] They could be transformed to 2-arylthiopyrimidines **4** with providing various C4–C6 substituents by the proposed cascade reaction. The expected product **4** could be utilized in the production of diversely C-2 aryl-substituted compounds by cross-coupling reactions such as the Liebeskind–Srogl reaction.[7] Thus, implementation of this cascade reaction could allow facile access and diversification of novel pyrimidine compounds, which are embedded as an important substructures of many valuable drug candidates or intermediate of drugs, as evidenced by the well-known rosuvastatin and imatinib (Gleevec).[8]

Initially, we examined the cascade reaction of DHPM **8** (0.2 mmol) with iodobenzene (2.0 equiv) in the presence of CuI (20 mol %), K_2CO_3 (1.0 equiv) and solvent (0.2 mL) for 8 h under air (Table 1). At ≤ 70 °C, the reaction in $PhCH_3$, THF, or dioxane did not proceed (entries 1–3). However, the detection of a trace amount of the desired product **9**[5] in the case of DMF or NMP solvent (entries 4 and 5) led us to optimize the reaction conditions. Since higher temperature (100 °C) increased the reaction yield, we carried out the reaction with further elevation of temperature. We observed that the reaction yield increased accordingly up to 130 °C and that NMP was better solvent than DMF (entries 6–11). The reaction under O_2 resulted in lower reaction yield with decomposition than that under air (entry 12). Less amount of CuI (entries 13 and 14), or other bases such as Cs_2CO_3, *t*-BuOK, *i*-Pr_2NEt, and NEt_3 did not enhance the reaction yield (entries 15–18). Other Cu(I) or Cu(II) catalysts such as CuBr, CuCl, or $Cu(OAc)_2$ showed lower efficacy than CuI (entries 18–21). In the case that biphenyliodonium triflate was used as an arylating agent, the reaction exhibited lower yield than that with PhI (entry 22).

Under optimal conditions, the reaction scope was subsequently studied with diverse aryl iodide and DHPM

Table 1. Optimization of the cascade reaction of **8** with iodobenzene.[a,b]



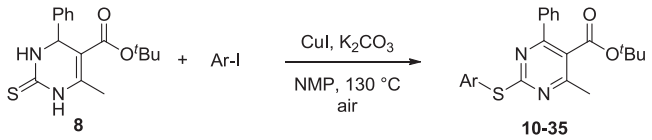
Entry	[Cu]	Base	Solvent	T (°C)	Yield
1	CuI	K_2CO_3	$PhCH_3$	70	0
2	CuI	K_2CO_3	THF	70	0
3	CuI	K_2CO_3	Dioxane	70	0
4	CuI	K_2CO_3	DMF	70	Trace
5	CuI	K_2CO_3	NMP	70	Trace
6	CuI	K_2CO_3	DMF	100	21
7	CuI	K_2CO_3	NMP	100	28
8	CuI	K_2CO_3	NMP	110	45
9	CuI	K_2CO_3	DMF	130	48
10	CuI	K_2CO_3	NMP	130	85
11	CuI	K_2CO_3	NMP	150	79
12	CuI	K_2CO_3	NMP	130	61[c]
13	CuI	K_2CO_3	NMP	130	45[d]
14	CuI	K_2CO_3	NMP	130	59[e]
15	CuI	Et_3N	NMP	130	38
16	CuI	*i*-Pr_2NEt	NMP	130	23
17	CuI	*t*-BuOK	NMP	130	62
18	CuI	Cs_2CO_3	NMP	130	47
19	CuCl	K_2CO_3	NMP	130	23
20	CuBr	K_2CO_3	NMP	130	62
21	$Cu(OAc)_2$	K_2CO_3	NMP	130	59
22	CuI	K_2CO_3	NMP	130	59[f]

[a] Reaction conditions: substrate **8** (0.2 mmol), PhI (0.4 mmol), base (0.2 mmol), catalyst (20 mol%), and solvent (0.2 mL) for 8 h under air.
[b] Isolated yields.
[c] Reaction was accomplished under O_2.
[d] 5 mol%.
[e] 10 mol% CuI were used.
[f] $Ph_2I^+OTf^-$ instead of PhI was used.

substrates. With respect to aryl iodide substrate, the reaction method was suitable for a wide range of functional groups and heterocyclic aryl iodides (Table 2). When the electronic effect or the position of substituent at the aryl iodide was investigated the reaction did not exhibit distinct variations depending on either of them. For electron-donating substituent, the order of the reaction yield was ortho- (74%) > meta- (59%) > para-position (53%) in the case of OMe, while meta- (62%) > ortho- (60%) > para-position (52%) in the case of Me (entries 1–6). For electron-withdrawing substituent, NO_2 or CF_3 group, best result was obtained with para-position followed by ortho- and then meta-position (entries 7–12). For halide substituted aryl iodides the reaction exhibited completely different substrate preference. For each halide, maximum yield was obtained with the substrate, meta-F (90%), para-Br (81%), and ortho-Cl (72%) (entries 13–21). Heterocyclic aryl iodides, iodopyrdine and iodothiophene were also compatible with the reaction. With respect to the position of the heteroatom, 2-iodopyridine resulted in a higher yield than 3-iodopyridine, while similar yields were shown for 2- and 3-iodothiophene (entries 22–25). Bicyclic 1-iodonaphthalene was also shown to be suitable substrate for the cascade reaction (entry 26).

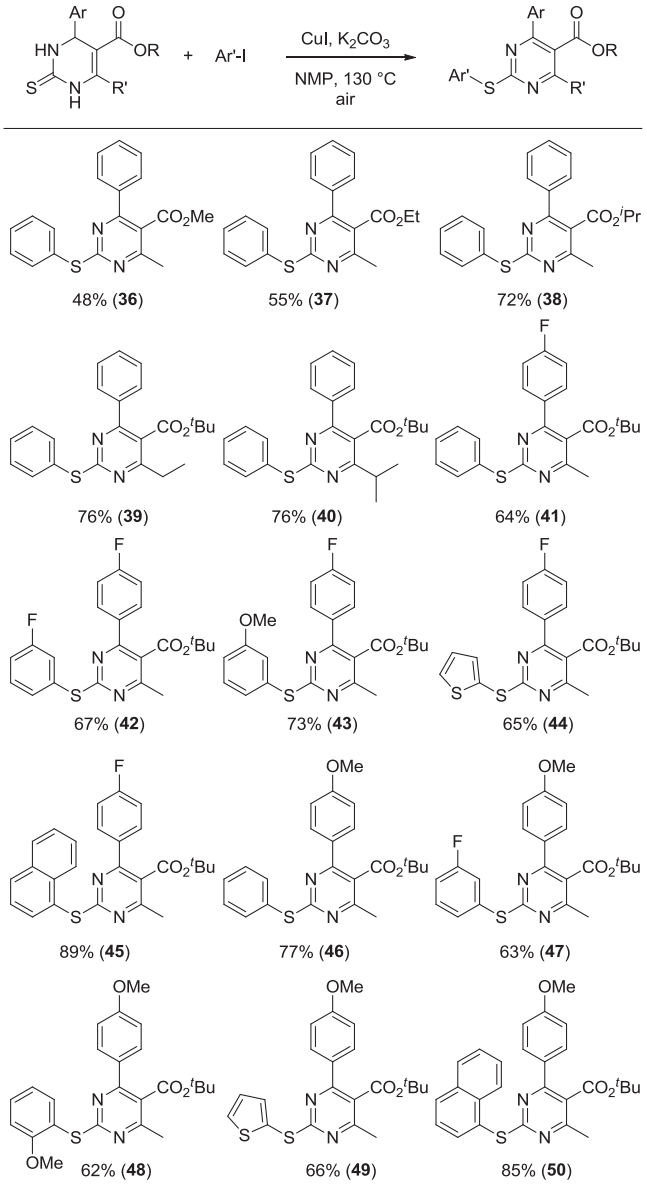
Next, we explored the scope of the reaction with respect to the DHPM substrate. At first, the steric effect of the alkoxy carbonyl group at C5 and alkyl group at C6 was investigated (Scheme 2). For the alkoxy carbonyl group, reaction yields decreased as its steric bulk increased- an order of *t*-Bu (**9**) > *i*-Pr (**38**) > Et (**37**[9]) > Me (**36**[10]). Regarding the substituent at C6, Et and *i*-Pr group afforded **39** and **40**, respectively, in same yield (76%), which are lower than that in the Me group case (**9**, 85%). To examine the substituent effect of C4 aryl group, the reactions of DHPM substrates possessing electron-withdrawing and donating substituents, para-F and para-OMe group were carried out. We observed that both substituents were suitable for the reaction with aryl iodides. In the

Table 2. Reaction scope with respect to aryl iodide.[a,b]



Entry	Ar	Product	Yield (%)
1	2-MeOC$_6$H$_4$	**10**	84
2	3-MeOC$_6$H$_4$	**11**	69
3	4-MeOC$_6$H$_4$	**12**	63
4	2-NO$_2$C$_6$H$_4$	**13**	74
5	3-NO$_2$C$_6$H$_4$	**14**	72
6	4-NO$_2$C$_6$H$_4$	**15**	80
7	2-FC$_6$H$_4$	**16**	70
8	3-FC$_6$H$_4$	**17**	95
9	4-FC$_6$H$_4$	**18**	77
10	2-BrC$_6$H$_4$	**19**	58
11	3-BrC$_6$H$_4$	**20**	66
12	4-BrC$_6$H$_4$	**21**	81
13	2-ClC$_6$H$_4$	**22**	72
14	3-ClC$_6$H$_4$	**23**	59
15	4-ClC$_6$H$_4$	**24**	58
16	2-CH$_3$C$_6$H$_4$	**25**	70
17	3-CH$_3$C$_6$H$_4$	**26**	72
18	4-CH$_3$C$_6$H$_4$	**27**	62
19	2-CF$_3$C$_6$H$_4$	**28**	70
20	3-CF$_3$C$_6$H$_4$	**29**	53
21	4-CF$_3$C$_6$H$_4$	**30**	77
22	2-pyridinyl	**31**	55
23	3-pyridinyl	**32**	46
24	2-thiophenyl	**33**	66
25	3-thiophenyl	**34**	64
26	1-naphthyl	**35**	88

[a] Reaction conditions; DHPM substrate (0.2–0.3 mmol), ArI (2.0 equiv), K_2CO_3 (1.0 equiv), CuI (20 mol%) and NMP (0.2–0.3 mL, 1.0 M) for 8–12 h under air.
[b] Isolated yields.



Scheme 2. Reaction scope with respect DHPM and aryl iodide. [a]Reaction conditions; DHPM substrate (0.2–0.3 mmol), ArI (2.0 equiv), K_2CO_3 (1.0 equiv), CuI (20 mol%), and NMP (0.2–0.3 mL, 1.0 M) for 8–12 h under air. [b]Isolated yields.

case of para-F substituent, the reaction with meta-MeO-PhI, 2-iodothiophene, 1-iodonaphthalene, PhI, or meta-F-PhI produced the corresponding product in similar yield (**41–45**). For para-OMe substituent, the reaction with PhI or ortho-MeO-PhI showed slightly lower reaction yield (**46** and **48**) compared with meta-F-PhI, 2-iodothiophene or 1-iodonaphthalene (**47**, **49**, and **50**).

In summary, we have developed a Cu-catalyzed cascade reaction for the synthesis of fully substituted 2-arylthiopyrimidines from 3,4-dihydropyrimidine-2(1*H*)-thiones (DHPMs) under aerobic conditions. This cascade reaction of DHPM with aryl iodide proceeds presumably via sequential tautomerization, C–S cross-coupling, and oxidative dehydrogenation (oxidation followed by elimination). Considering that DHPM substrates were easily synthesized by Biginelli three component coupling reaction of aryl aldehyde, β-ketoester, and thiourea, the present method provides a direct access toward diverse 2-arylthiopyrimidines which have been used as a prominent substructure of drug molecules.

Experimental

General. Common solvents were purified before use. Toluene ($PhCH_3$) and tetrahydrofuran (THF) were purified by distillation from calcium hydride and sodium-benzophenone, respectively. *N*-methyl-2-pyrrolidone (NMP, Aldrich Sure/Seal), *N*,*N*-dimethylformamide (AcroSeal), and 1,4-dioxane (Aldrich Sure/Seal) were used as received. All reagents were

reagent grade and purified when necessary. "Water" refers to distilled water. Reactions were monitored by thin layer chromatography (TLC) using Whatmann precoated silica gel plates. Flash column chromatography was performed over ultra pure silica gel (230–400 mesh) from Merck (Darmstadt, Germany). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 (300 MHz) spectrometer (Rheinstetten, Germany) using residual solvent peaks as an internal standard ($CHCl_3$: δ 7.24 ppm for proton and δ 77.0 ppm for carbon). Multiplicities for ^{1}H NMR are designated as: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of dd, dt = doublet of triplets, t = triplet, td = triplet of doublets, m = multiplet. Infrared spectra (IR) were recorded on JASCO FT/IR-4100 spectrometer (Rheinstetten, Germany) and are reported in reciprocal centimeter (cm^{-1}). High resolution mass spectra (HRMS) were obtained on BrukermicroTOF-Q (Rheinstetten, Germany).

General Procedure for Cu-catalyzed Aerobic Cascade Reaction. To a solution of DHPM (0.2–0.3 mmol) in NMP (1.0 M) were added ArI (2.0 equiv), CuI (20 mol %), and K_2CO_3 (1.0 equiv), and the resulting mixture was allowed to stir at 130 °C for 5–12 h under air. After cooling to room temperature, saturated NH_4Cl was added. The mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered through silica gel pad, and concentrated under reduced pressure. The crude product was purified by column chromatography to give the desired pyrimidine compound.

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Supporting Information. ^{1}H and ^{13}C NMR spectra of all new compounds.

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