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Dehydrosulfurative C−N Cross-Coupling and Concomitant Oxidative Dehydrogenation for One-Step Synthesis of 2-Aryl(alkyl)aminopyrimidines from 3,4-Dihydropyrimidin-1*H*-2-thiones

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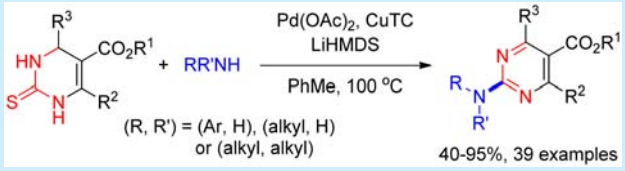
Supporting Information

ABSTRACT: A method for the synthesis of 2-aryl(alkyl)-aminopyrimidines from readily available 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) via dehydrosulfurative C−N cross-coupling and concomitant oxidative dehydrogenation under a Pd/Cu catalytic system is described. This reaction protocol provides unprecedented diversity of fully substituted 2-aryl-(alkyl)aminopyrimidines in a single step from a wide range of DHPMs and amine coupling partners.



The 2-aryl(alkyl)aminopyrimidine motifs are embedded as a privileged substructure and a key binding fragment toward targets in many important drugs, such as the hypocholesterolemic agent rosuvastatin (Crestor)[1] and the potent anticancer drug imatinib (Gleevec)[2] (Figure 1). They have also been proven

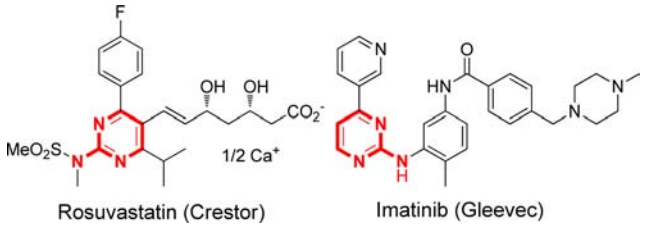


Figure 1. Structures of rosuvastatin and imatinib.

to trigger the inhibition of protein kinases or receptors in many development candidates.[3] Despite their biological importance, the synthetic strategy toward these compounds is limited in scope and generality, especially for the rapid generation of a diverse range of such compounds. Usually, the fully substituted 2-aryl(akyl)aminopyrimidines are obtained by nucleophilic aromatic substitution or metal-catalyzed C−N cross-coupling of pyrimidines containing halides or other leaving groups at the C2 position with amines, most of which require synthesis of pyrimidine partners in multiple steps from 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) or related starting materials.[4−6] Herein, we report a one-step synthesis of fully substituted 2-aryl(alkyl)aminopyrimidines from DHPMs via dehydrosulfurative C−N cross-coupling and concomitant oxidative dehydrogenation under a Pd/Cu catalytic system.

Organosulfur compounds have become increasingly important as promising electrophilic coupling partners in transition-metal-catalyzed C−C coupling reactions. In particular, Pd-catalyzed/Cu-mediated Liebeskind−Srogl dehydrosulfurative C−C cross-coupling of thioamide, thiourea, or thiourethane fragments containing latent free thiol functionalities with nucleophilic organometallic reagents or terminal alkynes has attracted much attention in synthetic organic chemistry.[7−9] The success of these reaction protocols led us to envision dehydrosulfurative C−N cross-coupling of DHPMs with aryl or alkylamines. To the best of our knowledge, no reports have been published describing the employment of a thiono (latent free thiol) group as a leaving group of the electrophilic coupling partner in C−N cross-coupling reactions.[10] Recently, we developed a Cu-catalyzed oxidative dehydrogenation reaction of 2-alkylthiodihydropyrimidines to produce 2-alkylthiopyrimidines,[11] which was applied to the cascade reaction for the conversion of DHPMs to 2-arylthiopyrimidines via C−S cross-coupling and oxidative dehydrogenation.[12] We envisaged a possible one-pot reaction method combining the dehydrosulfurative C−N cross-coupling of DHPM with amine and oxidative dehydrogenation using a Pd/Cu catalytic system. Since the oxidative dehydrogenation of 2-alkylthiopyrimidines worked best under air, we thought that the reaction of the dehydrosulfurative C−N cross-coupling of DHPM **1** with amine under argon, followed by oxidative dehydrogenation under air, could provide a one-pot synthesis of the target **2** (Scheme 1). Due to the simple preparation of DHPM substrates

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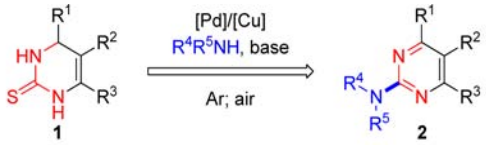
Scheme 1. Plan for the One-Pot Synthesis of Fully Substituted 2-Aryl(alkyl)aminopyrimidines from DHPMs

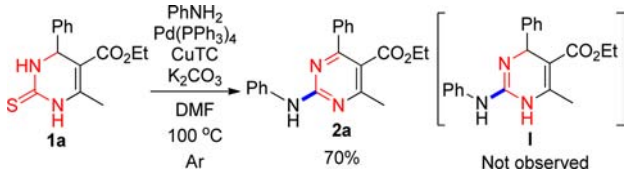


Dehydrosulfurative C-N cross-coupling of DHMP with amine under Ar, followed by oxidative dehydrogenation under air

possessing diverse substituents at C4−C6 using the Biginelli three-component reaction with versatile β-ketoesters, aldehydes, and thiourea,[13] the reaction method could provide a shortcut to diverse fully substituted 2-aryl(alkyl)aminopyrimidines.

The initial studies were carried out with DHPM **1a** (0.18 mmol) and aniline (2.0 equiv) in the presence of $Pd(PPh_3)_4$ (20 mol %), Cu(I)-thiophene-2-carboxylate (CuTC, 3.0 equiv), and K_2CO_3 (4.0 equiv) in DMF (2.0 mL) at 100 °C for 18 h under Ar to detect intermediate **I**. Interestingly, the reaction afforded only pyrimidine **2a**[4b] in 70% yield, without any observation of the expected product **I** under Ar (Scheme 2). The reaction

Scheme 2. Initial Result of the Reaction

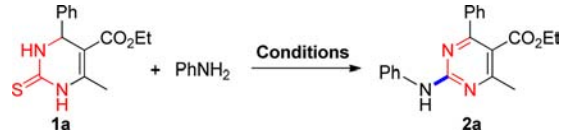


conditions under air produced messy results and provided **2a** in less than 10% yield. This led us to perform further optimization studies under argon without any consideration of the aerobic conditions for the oxidative dehydrogenation (Table 1).

With respect to the Cu source, CuTC was found to be superior to other Cu(I) or Cu(II) salts, such as CuI, CuBr, $Cu(OAc)_2$, or a mixture of CuI/CuTC (1:1) (entries 1−4). When $Pd(OAc)_2$ and $PdCl_2$ were used, yields similar to those with $Pd(PPh_3)_4$ were obtained (entries 5 and 6). Although $Pd(PPh_3)_4$ afforded a slightly higher yield, $Pd(OAc)_2$ was chosen for further optimization due to its higher stability, lower price, and easier isolation of the desired product. Regarding solvents, $PhCH_3$ was found to be more effective than other solvents such as DMF or dioxane (entries 6−8). With respect to the base, the desired product was also observed in the absence of a base (entry 9), but a base was shown to be an important factor for increasing the yield of the reaction. LiHMDS gave the product in 93% yield and was shown to be better than other bases such as K_2CO_3, Cs_2CO_3, Et_3N, and *t*-BuONa (entries 8 and 10−13). No desired product was obtained in the absence of either a Pd source or a Cu source (entries 14 and 15), and less $Pd(OAc)_2$ or CuTC reduced the yield of the reaction (entries 16−18). Varying the reaction temperature did not improve the reaction yield (entries 19 and 20).

Under optimal conditions, the reaction scope was subsequently explored with diverse DHPMs and amines. With respect to the arylamines, the reaction method was compatible with a wide range of functional groups (Figure 2). Electron-donating methyl and methoxy groups afforded the desired products **2b**[4h] and **2c**,[4b] respectively, in high yields. In the case of electron-withdrawing groups, the reaction also exhibited good

Table 1. Optimization of Reaction Conditions



entry	[Pd]	[Cu]	base	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$	CuI	K_2CO_3	DMF	22
2	$Pd(PPh_3)_4$	CuBr	K_2CO_3	DMF	20
3	$Pd(PPh_3)_4$	$Cu(OAc)_2$	K_2CO_3	DMF	trace
4	$Pd(PPh_3)_4$	CuI/CuTC	K_2CO_3	DMF	33
5	$PdCl_2$	CuTC	K_2CO_3	DMF	66
6	$Pd(OAc)_2$	CuTC	K_2CO_3	DMF	68
7	$Pd(OAc)_2$	CuTC	K_2CO_3	dioxane	70
8	$Pd(OAc)_2$	CuTC	K_2CO_3	$PhCH_3$	78
9	$Pd(OAc)_2$	CuTC		$PhCH_3$	55
10	$Pd(OAc)_2$	CuTC	Cs_2CO_3	$PhCH_3$	72
11	$Pd(OAc)_2$	CuTC	^{t}BuONa	$PhCH_3$	78
12	$Pd(OAc)_2$	CuTC	Et_3N	$PhCH_3$	53
13	$Pd(OAc)_2$	CuTC	LiHMDS	$PhCH_3$	93
14		CuTC	LiHMDS	$PhCH_3$	0
15	$Pd(OAc)_2$		LiHMDS	$PhCH_3$	0
16	$Pd(OAc)_2$	CuTC	LiHMDS	$PhCH_3$	58[c]
17	$Pd(OAc)_2$	CuTC	LiHMDS	$PhCH_3$	85[d]
18	$Pd(OAc)_2$	CuTC	LiHMDS	$PhCH_3$	35[e]
19	$Pd(OAc)_2$	CuTC	LiHMDS	$PhCH_3$	82[f]
20	$Pd(OAc)_2$	CuTC	LiHMDS	$PhCH_3$	90[g]

[a]Reaction conditions: **1a** (0.18 mmol), $PhNH_2$ (0.36 mmol), [Pd] (20 mol %), [Cu] (0.54 mmol), *t*-BuONa, LiHMDS (1.5 equiv) or other base (4.0 equiv), and solvent (2.0 mL) at 100 °C for 18 h under Ar. [b]Isolated yield. [c]With 5 mol % of $Pd(OAc)_2$. [d]With 10 mol % of $Pd(OAc)_2$. [e]With 1.5 equiv of CuTC. [f]At 80 °C [g]Reflux conditions.

results. Halide groups F, Cl, and I gave the desired products **2d**, **2e**,[4h] and **2f**,[4h] respectively, in 78−95% yields, and other electron-withdrawing groups such as nitro and cyano groups yielded **2g**[4h] (77%) and **2h**[4h] (94%), respectively. Heterobicyclic 8-aminoquinoline was also suitable as a reaction partner to produce **2i** in 58% yield. We observed that the steric hindrance of the functional group in an arylamine significantly affected the reaction under the optimal reaction conditions. For example, the reaction with sterically hindered *o*-methylaniline gave **2j**[4h] in only 16% yield. After examining literature precedents on desulfurative cross-couplings, we found that reaction conditions including TBSCl and $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ improved the reaction yield in the production of **2j** (65%).[14] When the reaction conditions were applied to bicyclic aminonaphthalenes and heterocyclic aminopyridine, the desired products **2k**−**m**[6a] were produced in 51−58% yields. Aliphatic amines were also investigated as the coupling partners and gave the desired products in 70−75% (**2n**,**o**[4e]) and 49% (**2p**[4e]) yields for 1° and 2° amines, respectively, when $PdCl_2$ and ligand P(*o*-toyl)$_3$ were used.

For the reaction scope with respect to the DHPM substrates, we performed the reaction with various substituents at C4−C6 in the DHPMs **1** (Figure 3). We observed that Et, *i*-Pr, and *t*-Bu for R^1 afforded the corresponding products in good yields (**3a**−**e**[15]). However, *t*-Bu exhibited the lowest yield, which might have been attributable to the decomposition of the $CO_2{}^tBu$ group under the reaction conditions. Regarding the substituents at C6 (R^2), both aliphatic and aromatic groups were compatible and resulted in good reaction yields regardless of their steric bulk. The effects of

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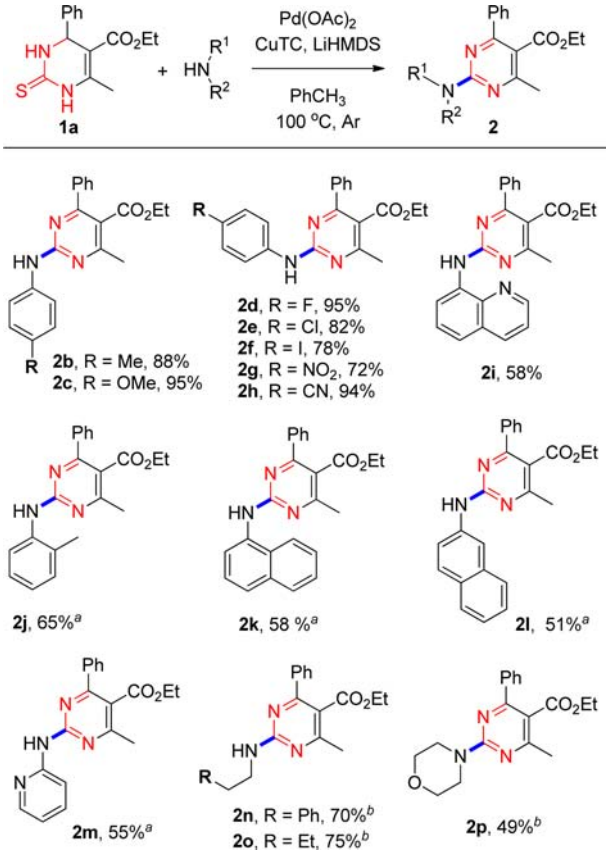


Figure 2. Scope of the reaction with respect to amine. Reaction conditions: **1a** (0.18 mmol), amine (0.36 mmol), $Pd(OAc)_2$ (20 mol %), CuTC (0.54 mmol), LiHMDS (0.27 mmol), and solvent (2.0 mL) at 100 °C under Ar. Yields are isolated yields. [a]$Pd(PPh_3)_4$ and TBSCl (1.0 equiv) were used. [b]$PdCl_2$ and P(*o*-toyl)$_3$ were used.

the substituents at C4 (Ar) were also investigated. Studies of the electronic effect by varying the para-substituent on the Ar moiety showed no distinct preference toward either electron-donating or -withdrawing groups. Electron-donating methyl or methoxy group delivered the corresponding product, **3f** or **3k**, respectively, in excellent yield. Halide groups F, Cl, Br, and I yielded the desired products (**3g**–**j**[4h,6a] and **3l**) in 62–90% yields, and we did not observe any evidence of the competing Buchwald–Hartwig amination reaction in these studies. The electron-withdrawing NO_2 group also delivered the desired product in high yield (**3m**). Substrates possessing bicycles and heterocycles at C4, such as 2-naphthyl, 3-pyridinyl, or 2-thiophenyl groups, were also suitable for the reaction method (**3n**,**o** and **3q**). Reactions of some of the above DHMP compounds with various amine compounds, such as aryl, heteroaryl, bicyclic amines, and aliphatic morpholine, were performed to expand the scope of the reaction method. As a result, all of the reactions produced the desired products in moderate to good yields (**3p** and **3r**–**v**).

Dehydrosulfurative C–N cross-coupling and Biginelli reaction offer diverse 2-amino groups and C4/C6 substituents, respectively, but diversification of the substituents at C5 is limited in light of the general synthesis of fully substituted 2-aminopyrimidine derivatives. For the diversification of C5 substituents, we attempted a decarboxylative arylation reaction[16] of the obtained pyrimidinyl ester compound. Hydrolysis of compound **2a** produced the corresponding acid, which was reacted with PhBr in the presence of $PdCl_2$, CuO, and PPh_3 in

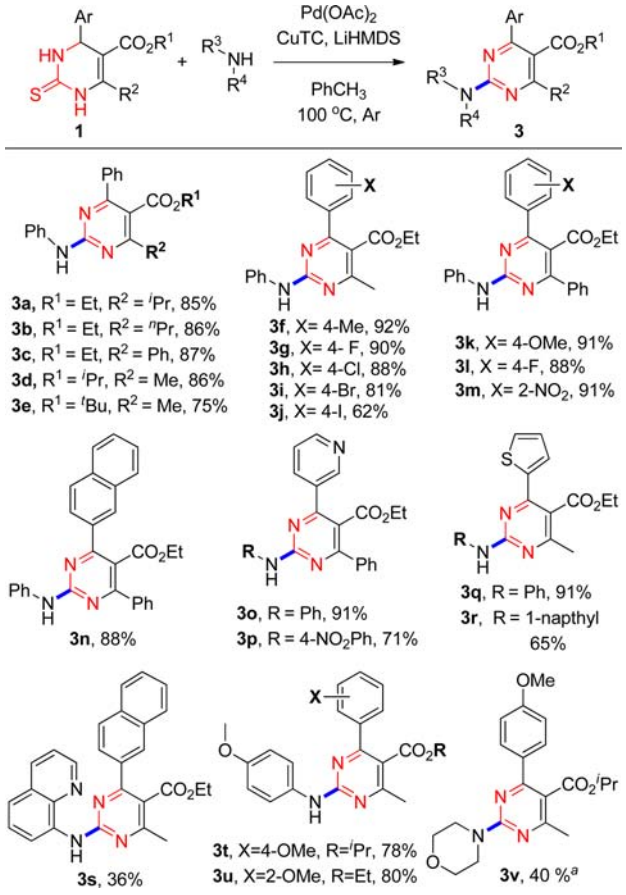
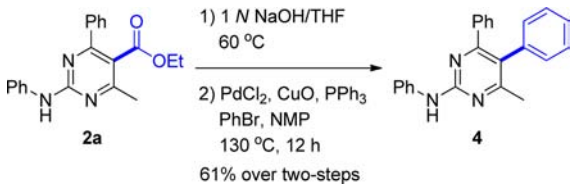


Figure 3. Scope of the reaction with respect to DHPM and amine. Reaction conditions: **1** (0.18 mmol), amine (0.36 mmol), $Pd(OAc)_2$ (20 mol %), CuTC (0.54 mmol), LiHMDS (0.27 mmol), and $PhCH_3$ (2.0 mL) at 100 °C under Ar. Yields are isolated yields. [a]$PdCl_2$ and P(*o*-toyl)$_3$ were used.

NMP at 130 °C for 12 h. As a result, we obtained the desired product **4** in 61% yield over two steps (Scheme 3).[17] Overall, we

Scheme 3. Decarboxylative Arylation at C5 of 2a



showed that the reaction sequence of the Biginelli three-component reaction followed by dehydrosulfurative C–N cross-coupling/oxidative dehydrogenation and then decarboxylative arylation is a highly efficient route for the general synthesis of fully substituted 2-aminopyrimidines.

In summary, we have developed a reaction method for the one-step synthesis of the fully substituted 2-aryl(alkyl)-aminopyrimidines from DHPMs via dehydrosulfurative C–N cross-coupling and oxidative dehydrogenation using a Pd/Cu catalytic system.[18] The reaction method proceeded efficiently with a wide range of DHPM and amine coupling partners. The reaction sequence of the Biginelli three-component reaction followed by dehydrosulfurative C–N cross-coupling/oxidative dehydrogenation and then decarboxylative arylation could offer

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simple preparation and diversification of 2-aryl(alkyl)-aminopyrimidines, which have been used as prominent substructures of drug molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02617.

Detailed experimental procedures and characterization data of compounds **2a−p**, **3a−v** and **4** and their ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(18) For a possible mechanism of the reaction, see the Supporting Information.

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