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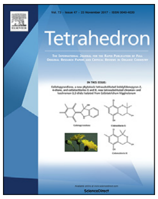

Dehydrosulfurative arylation with concomitant oxidative dehydrogenation for rapid access to pyrimidine derivatives

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ABSTRACT

This report describes a cascade reaction method for the synthesis of 2-arylpyrimidine derivatives via dehydrosulfurative carbon-carbon cross-coupling and concomitant oxidative dehydrogenation under a Pd/Cu catalytic system. It provides rapid and general access to a diverse range of 2-arylpyrimidines in a single step from a wide range of 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) and arylboronic acids.

1. Introduction

Organosulfur compounds are promising electrophilic partners and alternatives to the most common organohalides or related substrates in metal-catalyzed coupling reactions.[1] In 2000, Liebeskind and Srogl reported mechanistically unprecedented Pd-catalyzed/Cu-mediated cross-coupling of thioesters with boronic acids to generate ketones.[2] This desulfurative cross-coupling has extended the use of organosulfur compounds as electrophilic partners for coupling with diverse nucleophilic partners to produce unparalleled outcomes, which are unattainable by the traditional carbon-carbon bond formation.[3] A notable example is the direct dehydrosulfurative carbon-carbon cross-coupling of thioamide fragments, containing latent free-thiol functionalities with boronic acids under microwave conditions.[4] Applications of this reaction protocol to thioamide, thiourea, or thiourethane compounds with boronic acids, stannanes, siloxanes or terminal alkynes have been successful.[5,6] The results are unusual given that C–S cross-coupling is typically favored in traditional cross-coupling reactions with such substrates.[7]

Recently, we found that the oxidative dehydrogenation of 2-alkylthiodihydropyrimidines to produce 2-alkylthiopyrimidines proceeded well in the presence of a Cu catalyst with no additional reagents.[8] This reaction protocol was applied to 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) to produce 2-arylthiopyrimidines via Cu-catalyzed C–S cross-coupling and concomitant oxidative dehydrogenation.[9] Based on these results, we envisioned a cascade reaction combining dehydrosulfurative arylation of the DHPM (DHPM tautomer **I1**) with arylboronic acid and oxidative dehydrogenation using a Pd/Cu catalytic system (Scheme 1). This method could provide the means for rapid generation of fully substituted 2-arylpyrimidine derivatives in a single step.

The pyrimidine motifs are embedded as a privileged scaffold of many valuable drugs, such as the hypocholesterolemic agent rosuvastatin (Crestor) and potent anticancer drug imatinib (Gleevec).[10] Despite their prominent biological importance, the reported synthetic strategies toward various pyrimidine derivatives are not well developed particularly for rapid generation of useful diversity. Most synthetic approaches to fully substituted 2-arylpyrimidines rely on the arylation of pyrimidines containing halides or related leaving groups at the C2 position, which require multi-step

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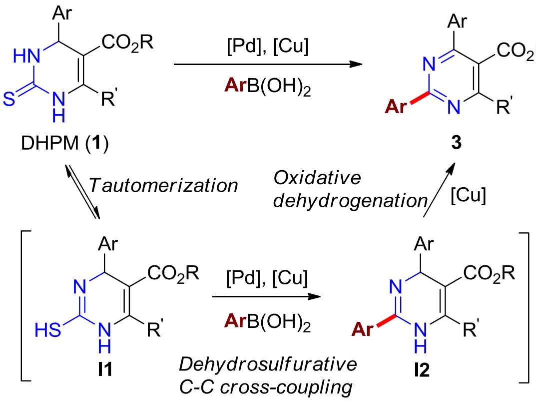
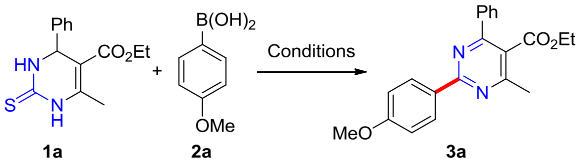


Scheme 1. Synthetic strategy for 2-arylpyrimidines.

Table 1
Optimization of reaction conditions.[a]



Entry	[Pd]	[Cu]	Base	Solvent	Yield (%)[b]
1	$Pd(PPh_3)_4$	CuTC	K_2CO_3	DMF	44
2	$Pd(PPh_3)_4$	CuTC	K_2CO_3	dioxane	46
3	$Pd(PPh_3)_4$	CuTC	K_2CO_3	NMP	52
4	$Pd(PPh_3)_4$	CuTC	K_2CO_3	DMA	50
5	$Pd(PPh_3)_4$	CuTC	K_2CO_3	PhMe	67
6	$Pd_2(dba)_3$	CuTC	K_2CO_3	PhMe	64
7	$Pd(dba)_2$	CuTC	K_2CO_3	PhMe	62
8	$Pd(OAc)_2/PPh_3$	CuTC	K_2CO_3	PhMe	45
9	$PdCl_2/PPh_3$	CuTC	K_2CO_3	PhMe	trace
10	$Pd(PPh_3)_4$	CuTC	–	PhMe	54
11	$Pd(PPh_3)_4$	CuTC	Cs_2CO_3	PhMe	40
12	$Pd(PPh_3)_4$	CuTC	^{t}BuOK	PhMe	70
13	$Pd(PPh_3)_4$	CuTC	K_3PO_4	PhMe	85
14	$Pd(PPh_3)_4$	CuI	K_3PO_4	PhMe	27
15	$Pd(PPh_3)_4$	CuBr	K_3PO_4	PhMe	21
16	$Pd(PPh_3)_4$	$Cu(OAc)_2$	K_3PO_4	PhMe	10
17	$Pd(PPh_3)_4$	CuTC	K_3PO_4	PhMe	63[c]
18	$Pd(PPh_3)_4$	CuTC	K_3PO_4	PhMe	40[d]
19	$Pd(PPh_3)_4$	CuTC	K_3PO_4	PhMe	64[e]
20	$Pd(PPh_3)_4$	CuTC	K_3PO_4	PhMe	73[f]
21	$Pd(PPh_3)_4$	CuTC	K_3PO_4	PhMe	trace[g]

[a] Reaction conditions: **1a** (0.14 mmol), **2a** (0.17 mmol), [Pd] (15 mol%), CuTC (3.0 equiv), base (2.0 equiv), and solvent (0.8 mL) at 100 °C for 16 h under Ar.
[b] Isolated yields.
[c] With 10 mol% of $Pd(PPh_3)_4$.
[d] With 1.5 equiv of CuTC.
[e] At 80 °C.
[f] At 120 °C.
[g] Under air.

synthesis of the pyrimidine coupling partners.[11,12] We report herein a one-step synthesis of fully substituted 2-arylaminopyrimidines from DHPMs using a Pd/Cu catalytic system, which offers very rapid diversification, given that the DHPMs possessing diverse substituents at C4-C6 (R^1-R^3 in Scheme 1) can be easily prepared by the Biginelli three component reaction, with versatile β-ketoesters, aldehydes, and thiourea.[13]

2. Results and discussion

The study commenced with an examination of the reaction with DHPM **1a** and $4\text{-}MeOC_6H_4B(OH)_2$ (**2a**) in the presence of $Pd(PPh_3)_4$ (15 mol%), Cu(I)-thiophene-2-carboxylate (CuTC, 3.0 equiv) and K_2CO_3 (2.0 equiv) in dimethylformamide (DMF) at 100 °C for 16 h under Ar. The reaction afforded the desired product **3a**[12a] in 44% yield, which enabled further optimization (Table 1).[14,15]

For further optimization of the reaction, we investigated the solvent effect and observed that PhMe was better than other solvents such as DMF, dioxane, *N*-methyl-2-pyrrolidone (NMP), or *N*,*N*-dimethylacetamide (DMA) (entries 1–5). With respect to the Pd source, $Pd(PPh_3)_4$ was superior to other Pd(0) or Pd(II) complexes, such as $Pd_2(dba)_3$ and $Pd(dba)_2$ or $Pd(OAc)_2$ and $PdCl_2$, respectively, (entries 6–9). In the absence of a base, the reaction also produced the desired product (entry 10); however, the base was shown to be an important factor with regards to increasing the reaction yield. The highest efficacy among the bases examined in the studies was found for K_3PO_4, which gave the product **3a**, with an 85% yield (entries 5 and 11–13). Lesser amount of either $Pd(PPh_3)_4$ or CuTC reduced the reaction yield (entries 17 and 18), and the variation of the reaction temperature did not improve the result (entries 19 and 20). When the reaction was performed under air, only a trace amount of the desired product was obtained (entry 21). In all cases, we did not observe the compounds **I2**.

Under optimal reaction conditions, we investigated the reaction with various DHPMs and arylboronic acids. With respect to arylboronic acid, the reaction method was compatible with a wide range of aryl- and heteroarylboronic acids (Table 2). When the electronic effect or the substituent position at the arylboronic acid was examined, the reaction did not vary due to either factor. Phenylboronic acid was also suitable as a reaction partner to produce **3b**[12a] in 89% yield. In addition to the initially tested 4-OMe group, the electron-donating 4- or 2-Me group also afforded good results (**3c**[12a] and **3d**,[12a] respectively), although steric hindrance might cause a lower reaction yield for the 2-Me group than for the 4-Me group. Halide groups, F, Cl, and Br at the para position, resulted in the corresponding products **3e,f**[12a] and **3g**, respectively, in 68–88% yields. Other electron-withdrawing substituents, such as NO_2 and CF_3, also yielded the desired products **3h** (74%) and **3i**[11c] (73%), respectively. The arylboronic acids substituted at the meta position afforded the corresponding products with moderate to good yields (**3j**[12b] and **3k-m**, 52–78%), and bicyclic naphthalenylboronic acid resulted in **3n** in 79% yield. Disubstituted arylboronic acids were also investigated as coupling partners, with desired products, **3o** (53%), **3p** (72%), and **3q** (57%) for 3,5-dichloro-, 3,4-dimethoxy-, and 3-fluoro-4-methoxyphenylboronic acid, respectively. When the reaction condition was applied to heteroarylboronic acids, the desired products **3r-t** were produced in 58–72% yields.

To determine the scope of the reaction with respect to the DHPM substrates, the reaction was carried out with various substituents at the C4-Ph group in the DHPMs **1** (Table 3). Halide groups, F and Br produced the desired products with similar yields, regardless of their positions at the C4-Ph group (**4aa**,[11c] **4ab-ac** and **4ad**,[12a] 71–79%). The electron-donating substituent OMe group at the para or meta position also provided the corresponding product **4ae**[11c] (72%) or **4af**[16] (85%), respectively. DHPMs possessing bicycle and heteroarenes at the C4 position, such as 2-naphthyl, 2-pyridinyl, and 2- and 3-thiophenyl groups, were also shown to be compatible for the reaction method (**4b, 4c**,[16] and **4d-e**). When the DHPMs containing the Ph group at the C6 position and Ar at the C4 position were treated with $C_6H_5B(OH)_2$ under the optimal reaction conditions the desired products **4fa**[17] and **4fb-fe** were produced in 63–87% yields. The cross-coupling reactions of DHPMs possessing various aryl groups at the C4 position with a range of arylboronic acids were also carried out to expand the scope of the reaction method. The reaction of DHPM having 3- or $4\text{-}MeOC_6H_4$ group at