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Molecular iodine-mediated S–N and C–N cross-coupling and oxidative aromatization of 3,4-dihydropyrimidin-2(1*H*)-thiones with secondary amines

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ABSTRACT

A domino S–N and C–N coupling/oxidative aromatization process to synthesize 2-aminothio-phenylpyrimidines and 2-amino-phenylpyrimidines by S–N and C–N cross-coupling reactions is described. This methodology couples 3,4-dihydropyrimidine-2-thiones and secondary amines catalyzed by molecular iodine. Remarkably the C–N coupled product was obtained via a desulfitative coupling-aromatization reaction in one-pot reaction.

Introduction

Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs)[1] are central subunits in a broad range of medicinal agents which display interesting pharmacological and biological properties such as calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors, and hepatitis B virus replication inhibitors.[2] The DHPM core is also found in several marine derived natural products such as Crambine, Batzelladine B, (potent HIV gp-120CD4 inhibitors) and Ptilomycalin alkaloids.[3] Additionally, the DHPMs are important building blocks in the synthesis of multifunctionalized pyrimidines. Although much effort has been made on the development of methods for the synthesis of the pyrimidine derivatives,[4] few methodologies are available toward efficient synthesis of *C2*-substituted pyrimidines from DHPMs. In general, *C2*-substituted pyrimidines were obtained from DHPMs by a four-step strategy involving sequential dehydrogenation, tautomerization, activation, and coupling with a nucleophile.[5,6] It was not until 2005 that a more efficient approach was achieved via PyBroP-mediated coupling reaction of 1,4-dihydropyrimidine with nucleophiles.[7] Recently, our group realized the synthesis of *C2*-substituted pyrimidines by cross-coupling reaction of pyrimidin-2-ylsulfonates or 2-hydroxypyrimidine with nucleophiles at room temperature.[8] Kappe and our groups have developed an efficient desulfitative carbon–carbon coupling reaction between 3,4-dihydropyrimidin-2-thiones and boronic acids[9] or alkynes[10] under modified Liebeskind-Srogl Pd-catalyzed and Cu(I)-mediated conditions. Dehydrogenation of the DHPMs is also a well known difficult process leading to low yield, when oxidizing agents such as SeO_2, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), or HNO_3 were used.[11] The dehydrogenation of DHPMs using *tert*-butylhydroperoxide (TBHP) has been introduced by Yamamoto et al.,[12] which can be applied on a large scale. (Diacetoxyiodo)benzene, ceric ammonium nitrate (CAN), $Mn(OAc)_3$, and MnO_2 have been employed in the oxidative aromatization of 1,4-dihydropyrimidine.[13]

To date, a simple S–N or C–N cross-coupling and oxidative-aromatization of 3,4-dihydropyrimidine-2(1*H*)-thione with an amine have never been used for the direct synthesis of 2-aminothio-phenylpyrimidine and 2-amino-phenylpyrimidine derivatives. Herein we present the first I_2-catalyzed S–N and C–N coupling/oxidative aromatization process for the synthesis of *C2*-substituted pyrimidine derivatives from 3,4-dihydropyrimidine-2(1*H*)-thione and amines (Scheme 1). This direct method from 3,4-dihydropyrimidine-2(1*H*)-thione does not need any additives and proceeds with high selectivity at different temperatures, which selectively forms 2-aminothio-phenylpyrimidines and 2-amino-phenylpyrimidines at rt and 140 °C, respectively.

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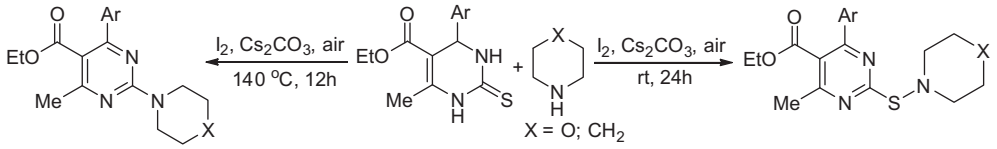


Scheme 1. Direct coupling/aromatization of 3,4-dihydropyrimidin-2-thiones with amines.

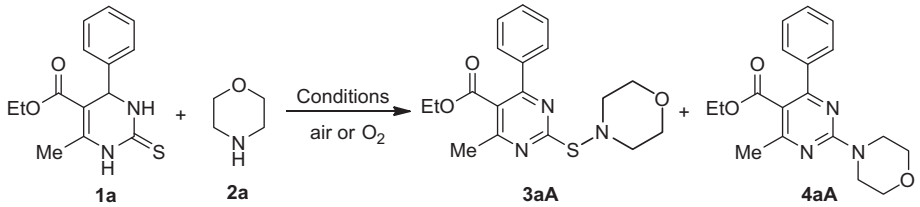
Results and discussion

As a starting point in our investigations, we examined the reaction between model substrate 3,4-dihydropyrimidine-2(1*H*)-thione (**1a**, 0.5 mmol) and morpholine (**2a**, 1.0 mmol, 2.0 equiv). To our delight, when the reaction was performed using molecular iodine (0.2 equiv) as the catalyst under air atmosphere in dichloromethane (DCM) at room temperature for 24 h, a S–N cross-coupling and aromatization product **3aA** was obtained, albeit with a low yield (56%) together with the isolation of a C–N coupling-aromatization product **4aA** (12%) (Table 1, entry 1). Similar reaction yield and selectivity were also observed when combining 0.2 equiv of I_2 with 1.0 equiv of CAN or DDQ as the catalysts, which provided product **3aA** in yield of 42% and 40%, respectively (entries 2 and 3). Good reaction yield and selectivity were observed when using 2.0 equiv of I_2 as the catalyst, which provided the S–N coupling product **3aA** in good yield of 74% (entry 4). When the reaction was performed under an oxygen atmosphere at rt, the yield of **4aA** was increased to 75% within 12 h (entry 5). These results are in agreement with the observation that compound **1a** can be coupled to give the functionalized bis(2-pyrimidyl) disulfide under air atmosphere catalyzed by Cu(II),[14] which indicated that O_2 plays a role in the oxidative stage. It was confirmed when **1a** was treated with **2a** under a nitrogen atmosphere, no coupling reaction was observed to take place as determined by TLC and ^{1}H NMR spectroscopy (entry 6). Other solvents, such as toluene, THF, MeCN, xylene, and DMF, provided worse results (entries 7–11). PEG-400 also exhibited good results yielding **3aA** in 73% yield with a small amount of **4aA** (entry 12). Reducing the amount of I_2 led to the formation of **3aA** in a lower yield (entry 13). Prolonged reaction times gave a lower yield of **3aA** with a slightly higher yield of **4aA** (entry 14). Improving the reaction temperature led to the increase of **4aA** yield and the best yield of **4aA** in 65% was obtained at 140 °C for 12 h using PEG-400 as the solvent (entries 15 and 16).

Based on these results and reported procedure,[14] we proposed the mechanism of the formation of S–N and C–N coupling products as shown in Scheme 2. The formation of disulfide **D** was performed catalyzed by air and I_2, then S–N and C–N coupling of **D** with morpholine **2a** occurred respectively at rt and 140 °C. The formation of the intermediate **D** and **3aA** with **4aA** was detected in the reaction of **1a** with **2a** at 100 °C by LC–MS. The alternative mechanism is also plausible. That is, the C–N coupling reaction may be completed by the substitution of **3aA** with morpholine **2a**. This was confirmed by the reaction of **3aA** with morpholine **2a** in PEG-400 at 140 °C for 5 h to give the C–N product **4aA**. We propose that iodine serves not only as the catalyst but also as the oxidant. We speculate that iodine is probably transformed into some hypervalent iodine species in the presence of oxygen from the air and of Cs_2CO_3. This could thus explain why the reaction needs an excess amount of I_2.

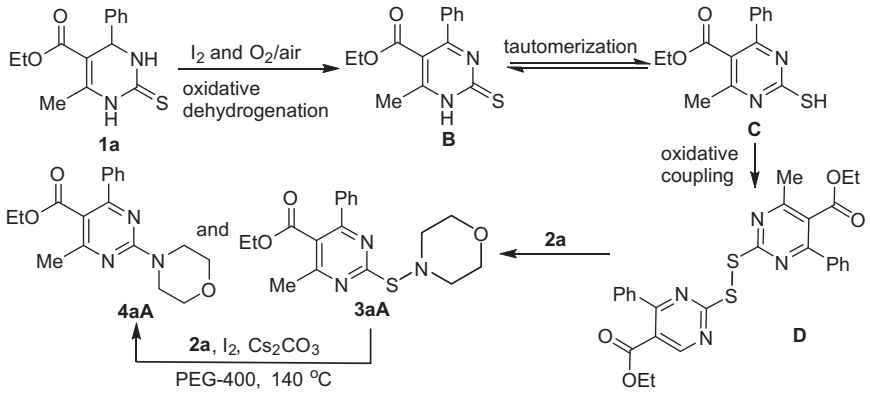
With the optimized conditions in hand, we then examined the scope of 3,4-dihydropyrimidine-2(1*H*)-thione substrates by varying the substituents on the aromatic ring to explore the generality

Table 1
Optimization conditions for S–N coupling[a]



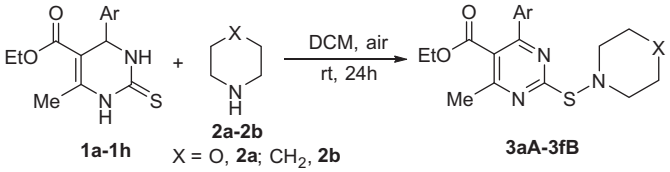
Entry	Catalyst (equiv)	Solvent	Temp (°C)	**3aA**[b]	**4aA**[b]	Time (h)
1	I_2 (0.2)	DCM	rt	56	12	24
2	I_2 (0.2)/CAN(1.0)	DCM	rt	42	10	24
3	I_2 (0.2)/DDQ(1.0)	DCM	rt	40	10	24
4	I_2 (2.0)	DCM	rt	74	10	24
5[c]	I_2 (2.0)	DCM	rt	75	12	12
6[d]	I_2 (2.0)	DCM	rt	—	—	24
7	I_2 (2.0)	Toluene	rt	60	11	24
8	I_2 (2.0)	Xylene	rt	60	12	24
9	I_2 (2.0)	THF	rt	54	10	24
10	I_2 (2.0)	MeCN	rt	45	12	24
11	I_2 (2.0)	DMF	rt	20	5	24
12	I_2 (2.0)	PEG-400	rt	73	5	12
13	I_2 (1.0)	PEG-400	rt	45	5	12
14	I_2 (2.0)	DCM	rt	69	17	36
15	I_2 (2.0)	PEG-400	100	25	55	12
16	I_2 (2.0)	PEG-400	140	5	65	12

[a] Reaction conditions: **1a** (0.5 mmol) and **2a** (1.0 mmol, 2.0 equiv), I_2 (1.0 mmol, 2.0 equiv), Cs_2CO_3 (0.5 mmol, 1.0 equiv) in solvent (3 mL) under air atmosphere.
[b] Isolated yield.
[c] The reaction was carried out under an O_2 atmosphere.
[d] The reaction was carried out under a N_2 atmosphere.



Scheme 2. A proposed mechanism for the S–N and C–N coupling reactions.

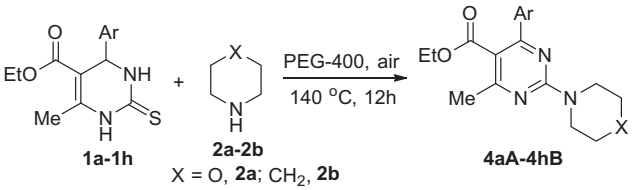
Table 2
S–N coupling of 3,4-dihydropyrimidine-2(1*H*)-thiones **1** with amines **2**[a]



Ar (**1**)	Amine **2**	Product (yield[b], %)	Ar (**1**)	Amine **2**	Product (yield[b], %)
C_6H_5 (**1a**)	**2a**	**3aA** (74)	4-ClC_6H_4 (**1h**)	**2a**	**3hA** (74)
4-MeC_6H_4 (**1b**)	**2a**	**3bA** (80)	C_6H_5 (**1a**)	**2b**	**3aB** (72)
4-$MeOC_6H_4$ (**1c**)	**2a**	**3cA** (81)	4-MeC_6H_4 (**1b**)	**2b**	**3bB** (78)
4-BrC_6H_4 (**1d**)	**2a**	**3dA** (72)	4-$MeOC_6H_4$ (**1c**)	**2b**	**3cB** (78)
4-$NO_2C_6H_4$ (**1e**)	**2a**	**3eA** (73)	4-BrC_6H_4 (**1d**)	**2b**	**3dB** (69)
3-$NO_2C_6H_4$ (**1f**)	**2a**	**3fA** (70)	4-$NO_2C_6H_4$ (**1e**)	**2b**	**3eB** (70)
4-FC_6H_4 (**1g**)	**2a**	**3gA** (72)	3-$NO_2C_6H_4$ (**1f**)	**2b**	**3fB** (72)

[a] Reaction conditions: **1** (1.0 mmol) and **2** (2.0 mmol, 2.0 equiv), I_2 (2.0 mmol, 2.0 equiv), Cs_2CO_3 (1.0 mmol, 1.0 equiv) in DCM (3 mL) under air atmosphere at rt for 24 h.
[b] Isolated yield.

Table 3
C–N coupling of 3,4-dihydropyrimidine-2(1*H*)-thiones **1** with amines **2**[a]



Ar (**1**)	Amine **2**	Product (yield[b], %)	Ar (**1**)	Amine **2**	Product (yield[b], %)
C_6H_5 (**1a**)	**2a**	**4aA** (65)	C_6H_5 (**1a**)	**2b**	**4aB** (61)
4-MeC_6H_4 (**1b**)	**2a**	**4bA** (68)	4-MeC_6H_4 (**1b**)	**2b**	**4bB** (55)
4-$MeOC_6H_4$ (**1c**)	**2a**	**4cA** (70)	4-$MeOC_6H_4$ (**1c**)	**2b**	**4cB** (63)
4-BrC_6H_4 (**1d**)	**2a**	**4dA** (58)	4-BrC_6H_4 (**1d**)	**2b**	**4dB** (58)
4-FC_6H_4 (**1g**)	**2a**	**4gA** (62)	4-FC_6H_4 (**1g**)	**2b**	**4gB** (60)
4-ClC_6H_4 (**1h**)	**2a**	**4hA** (61)	4-ClC_6H_4 (**1h**)	**2b**	**4hB** (59)

[a] Reaction conditions: **1** (1.0 mmol) and **2** (2.0 mmol, 2.0 equiv), I_2 (2.0 mmol, 2.0 equiv), Cs_2CO_3 (1.0 mmol, 1.0 equiv) in PEG-400 (3 mL) under air atmosphere at 140 °C for 12 h.
[b] Isolated yield.

of these S–N and C–N coupling reactions. The reaction tolerated a variety of dihydropyrimidin-2-thiones giving a series of pyrimidine derivatives via S–N (Table 2) and C–N cross-coupling (Table 3). No matter what substituent groups are on the aromatic rings of 3,4-dihydropyrimidine-2(1*H*)-thione, the reactions proceeded smoothly, and the cross-coupling products were isolated in moderate to good yields. In terms of the effect of structural features, introducing electron donating groups (Table 3, substrates **1b** and **1c**) to the aromatic ring is proved favorable to the reaction, with the desired products being isolated in slightly higher yields than those with electron withdrawing groups (Table 3, substrates **1d**–**h**). The structures of the S–N coupling products were confirmed

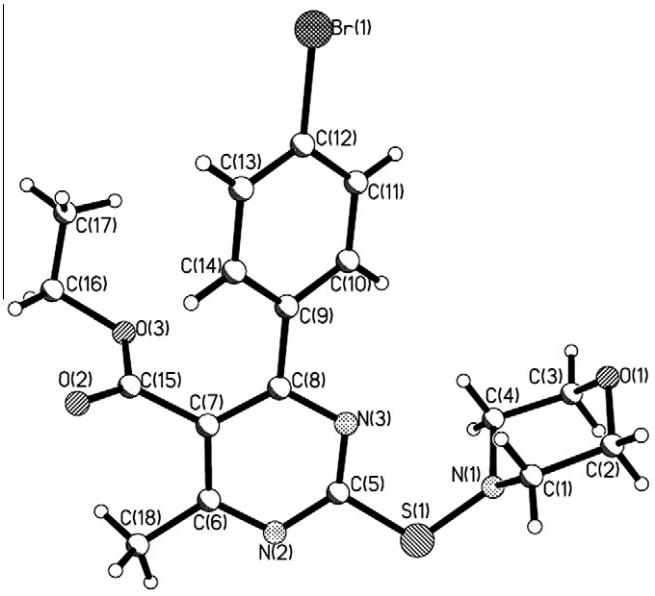


Figure 1. ORTEP diagram of compound **3dA**.

by example of X-ray diffractometry of **3dA** (Fig. 1).[15] Cyclic secondary amines piperidine and morpholine are most successful in this process; however, acyclic amines did not give promising results.

It is noteworthy that the study reported above, to our best knowledge, is the first general exploration of cross-coupling reaction of 3,4-dihydropyrimidine-2(1*H*)-thiones with amines to selectively give S–N and C–N coupled product under mild reaction conditions. This cross-coupling reaction, in which only one step is needed for directly using 3,4-dihydropyrimidine-2(1*H*)-thiones as starting material, is superior to other reported processes. Remarkably the C–N coupled product was obtained via a desulfitative coupling-aromatization reaction in one-pot reaction.

Conclusions

In summary, we have developed a novel and efficient synthetic method to prepare S–N and C–N functionalized pyrimidines by the I_2-catalyzed S–N and C–N coupling/oxidative aromatization process between 3,4-dihydropyrimidine-2(1*H*)-thiones and amines. Compared to previously known approaches, the simplicity (only one-step is needed for using 3,4-dihydropyrimidine-2(1*H*)-thiones as starting material) and higher efficiency make this method particularly attractive.

Acknowledgments

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Supplementary data

Supplementary data (details of experimental procedures and characterization data (copies of ^{1}H NMR, ^{13}C NMR for all new compounds)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.113. These data include MOL files and InChiKeys of the most important compounds described in this article.

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15. CCDC No. CCDC 817452 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.