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Copper-Catalyzed One-pot Synthesis of Pyrimidines from Amides, *N*,*N*′-dimethylformamide dimethylacetal, and Enamines

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Abstract. A versatile copper catalyzed one-pot synthesis of diversely substituted pyrimidines directly from amides, *N*,*N*′-dimethylformamide dimethylacetal (DMF–DMA) and enamines has been established. The reaction involved the two C–N bonds and one C–C bond formation by formal [2+1+3] annulation approach to pyrimidines. This protocol is based on the use of readily available primary amides, DMF–DMA and enamines to install di- and tri-substituted pyrimidine structure with diverse functionality in one-pot manner, which makes this strategy to be appealing for the medicinal chemistry.

Keywords: Pyrimidine; DMF–DMA; Enamine; Copper

Pyrimidines are one of the biologically important heterocycles, which are present in various natural products,[1] synthetic intermediates,[2] pharmaceuticals[3] (Figure 1) and other materials of interest.[4] Recently, pyrimidines are also used as directing groups for the study of C–H activation reactions.[5] In view of the importance of pyrimidines in the diverse fields, various synthetic methods have been developed for the concise and efficient synthesis of substituted pyrimidines. One of the common approaches is Pinner's pyrimidine synthesis (Eq 1, Scheme 1a),[6] which involves the reaction of amidines (N–C–N) with 1,3-dicarbonyl compounds (C–C–C). Synthetic variants of the 1,3-dicarbonyl compounds have also been employed for the synthesis of pyrimidines, for example the Morita-Baylis-Hillman reaction.[7] A second interesting approach involves the conversion of *N*-vinyl or *N*-aryl amides with nitriles to the subsequent pyrimidine or quinazoline[8] (Eq 2, Scheme 1a). Nevertheless, the availability of numerous methods,[9] the long-lasting interest and utility of the pyrimidine scaffold has led further interest in the development of new synthetic routes, particularly more efficient, versatile and straightforward approaches using various catalysts for the synthesis of structurally diverse pyrimidines from readily available materials.

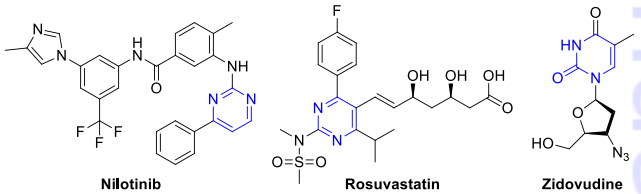

Figure 1. Selected Examples Containing Pyrimidine Core

Over the past few years, novel methodologies utilizing copper-catalyzed transformations have been developed.[10a-b] Such methods provide significant benefits to the synthesis of variety of heterocycles, because copper salts are inexpensive environmentally-benign and possess low toxicity[10c-f] and therefore are widely used in organic synthesis. In addition, many amide building blocks are available[11] and their use in the construction of various heterocycles is common. To the best of our knowledge, the use of primary amides for the construction of pyrimidine using a formal [2+1+3] annulation approach (Scheme 1b) has not been reported to date. Continuing our efforts in the application of enamines to the synthesis of various heterocycles,[12] we report in this update a copper-catalyzed, one-pot synthesis of pyrimidines directly from primary amides, *N*,*N*′-dimethyl formamide dimethylacetal (DMF–DMA) and enamines. The reaction involves the formation of an *N*-acylamidine

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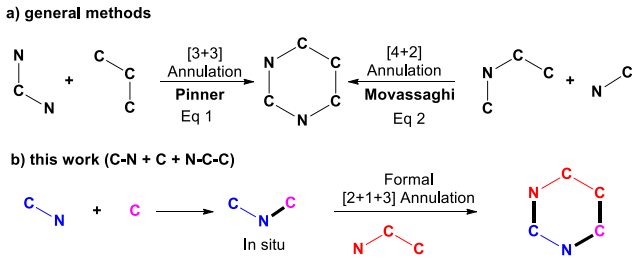
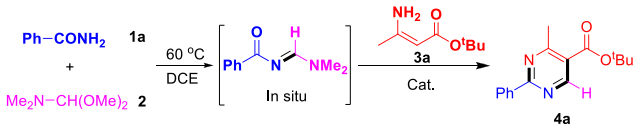


Scheme 1. Structural Fragment-based Pyrimidine Synthesis

followed by a copper-catalyzed cyclization of this *N*-acylamidine with enamine, producing pyrimidines.

Table 1. Optimization of Reaction Conditions[a]

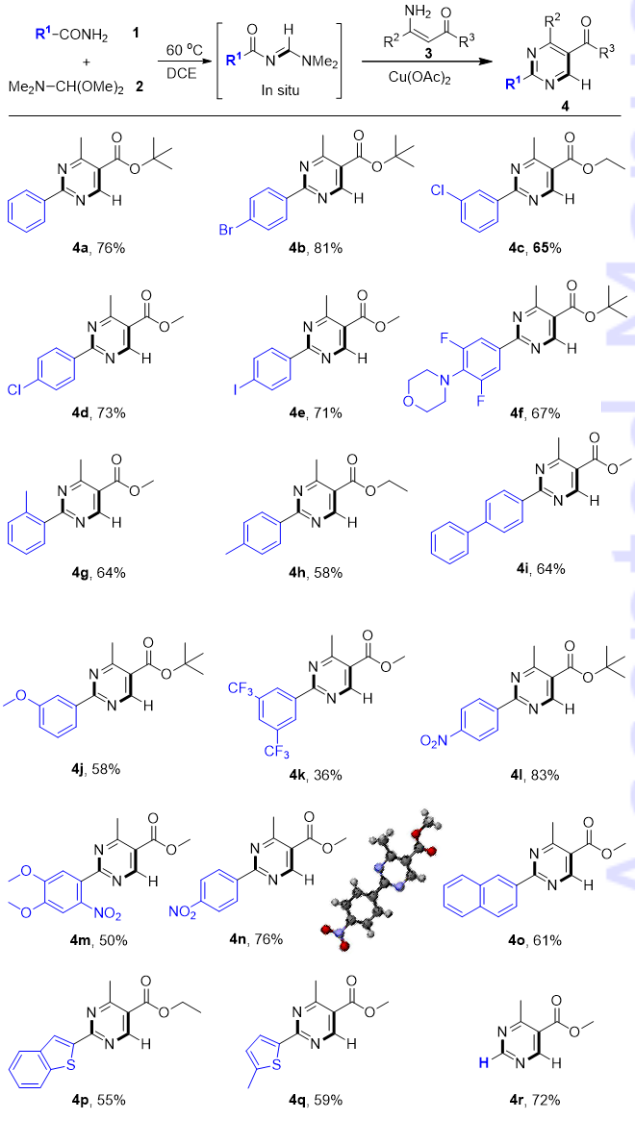


entry	Catalyst (20 mol %)	temp (°C)	solvent	yield[b] (%)
1	No Catalyst	120	DCE	23
2	CuI	120	DCE	51
3	$CuBr_2$	120	DCE	39
4	CuCl	120	DCE	42
5	$CuCl_2$	120	DCE	35
6	LiBr	120	DCE	trace
7	$FeCl_2$	120	DCE	trace
8	$FeCl_3$	120	DCE	trace
9	$InCl_3$	120	DCE	trace
10	$NiCl_2.6H_2O$	120	DCE	26
11	$Zn(OAc)_2.2H_2O$	120	DCE	31
12	**$Cu(OAc)_2$**	**100**	**DCE**	***82 (76[c])***
13	$Cu(OTf)_2$	100	DCE	75 (70[c])
14	TsOH	100	DCE	21

[a]**1a** (0.2 mmol), **2** (0.24 mmol) and **3a** (0.3 mmol) in 2 ml solvent and 4Å molecular sieve (250 mg) for 6 h. [b]Conversion based on crude ^{1}H NMR. [c] Isolated yield.

DMF-DMA is known as an electrophilic one carbon synthon. When it reacts with amide functionality, it gives *N*-acylamidine. The formation of *N*-acylamidine[13-15] requires excess DMF-DMA (3-4 equv.) and high reaction temperatures (100-120°C). In order to simplify the pyrimidine synthesis, first we optimized the *N*-acylamidine reaction conditions. We observed that the reaction of benzamide with 1.2 equivalents of DMF-DMA at 60 °C for 2-3 hours (Table 1) could proceed quantitatively, as determined by ^{1}H NMR. Once the optimization of the synthesis of the *N*-acylamidine was successfully achieved, we commenced our study for the synthesis of pyrimidines by subjecting benzamide (**1a**), DMF-DMA (**2**), and *t*-butyl-3-amino crotonate (**3a**) in the presence of various catalysts and solvents in one-pot reaction (Table 1 and Supporting Information). In our first attempt the reaction was carried out without any catalyst, and the expected pyrimidine product **4a** was formed in 23% yield as assessed by ^{1}H NMR (Table 1, entry 1). We then began the optimization of reaction conditions for this one-pot reaction. Considering the valuable contributions of various metal catalysts in the synthesis of heterocyclic systems, we carried out the reaction of the enamine (**3a**) and *N*-acylamidine prepared in situ with the copper catalysts as shown in Table 1, including copper iodide, copper bromide, copper (I) chloride, copper (II) chloride, copper acetate and copper trifluoroacetate. Among them, copper acetate (20 mol%) was found to be the best, delivering 82% conversion based on ^{1}H NMR (Table 1,entry 12). Lithium bromide, ferric dichloride, ferric trichloride and indium trichloride all failed to produce pyrimidines. The reaction catalyzed by hydrated catalysts such as nickel chloride, zinc acetate and *p*-toluene sulfonic acid afforded pyrimidines with low yields.

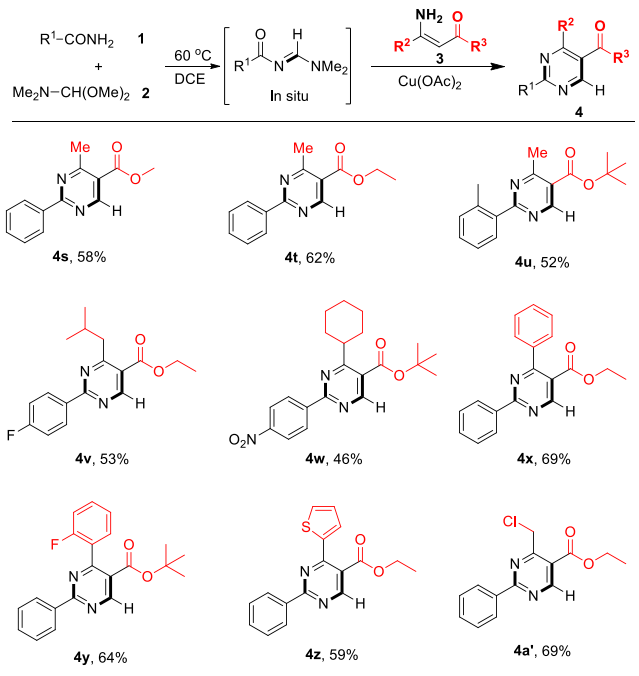
Table 2. Substrate Scope for Amides[a,b]



[a]**1** (0.2 mmol), **2** (0.24 mmol), **3** (0.3 mmol) and $Cu(OAc)_2$ (0.04 mmol) in 2 mL solvent and 4 Å molecular sieve (250 mg). [b]Isolated yield.

Having established the optimal reaction conditions in hand, various mono, di and tri substituted aromatic amides were subjected to the copper-catalyzed cyclization reaction in order to examine the electronic and steric effects of the substituents on the aryl amides (**1**) (Table 2). The results indicated that reaction of amides incorporating different halogen group, such as –Cl, –Br, –I and –F proceeded with good yields (**4b-f**). The reaction of aryl amides with electron-donating groups, such as phenyl, methoxy, amino and methyl group on the aryl ring, gave moderate yields (**4g-j**). Electron-withdrawing groups, such as CF_3, NO_2 group containing benzamide resulted in moderate to good yield (**4k-n**). In addition to various benzamides, 2-naphthamide gave the corresponding pyrimidine derivative **4o** with 61% yield. Moreover, the thiophene derivates **4p** and **4q** were obtained in reasonable yield when benzo[b]thiophene-2-carboxamideand5-methyl thiophene-2-carboxamidewere used as the substrates. Interestingly, when we used formamide, instead of aromatic amide, the present procedure successfully gave the methyl 4-methylpyrimidine-5-carboxylate **4r** with 72% yield, a di-substituted pyrimidine compound, thus demonstrating the diversity of the present procedure.

Table 3. Substrate Scope for Enamines[a,b]



[a]**1** (0.2 mmol), **2** (0.24 mmol), **3** (0.3 mmol) and $Cu(OAc)_2$ (0.04 mmol) in 2 mL solvent and 4Å molecular sieve (250 mg). [b]Isolated yield.

Encouraged by the good tolerance of amide groups in this reaction, we subjected different enamines to this one-pot reaction and found that the enamines were successfully converted into the corresponding pyrimidines in moderate to good yields under the optimized reaction conditions (Table 3). Alkyl-3-aminobut-2-enoate containing different alkyloxy groups such as methyl, ethyl and *t*-butyl provided the corresponding 2-aryl-4-alkyl-pyrimidines with good yields (**4s-4u**). When enamine substrates having isobutyl, cyclohexyl, phenyl, and 2-fluorophenyl group used in this study, the corresponding products were formed with moderate yields (**4v-4y**). With the heterocyclic substrate ethyl (*Z*)-3-amino-3-(thiophen-2-yl) acrylate, the pyrimidine (**4z**) was obtained in 59% yield. The present method provides a simple and easy preparation of ethyl 4-(chloromethyl)-2-phenyl pyrimidine-5-carboxylate (**4a′**) in 69% yield. The method failed, however, to generate pyrimidines from enamines, such as 4-amino-*2H*-chromen-2-one and 1-(t-butyl)-5-ethyl-3-aminopent-2-enedioate. It was also observed that DMF-DMA was useful for the pyrimidine synthesis while other acetal such as DMA-DMA (*N,N′*-dimethylacetamide dimethylacetal) were not successful, probably due to steric hindrance.

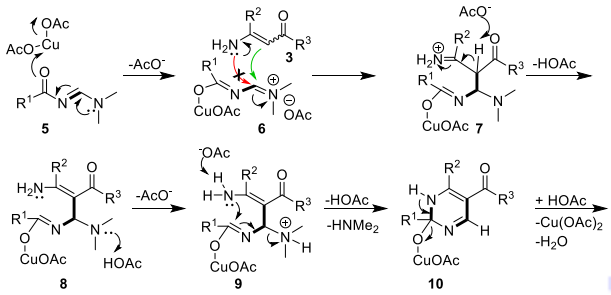


Figure 2. The Possible Reaction Pathway

The possible reaction mechanism pathway has been described in Figure 2. Initially, the nucleophilic substitution reaction of amide with DMF-DMA will result into the formation of *N*-acylamidine **5**.[16] Considering the characteristics of enamines, which can mostly react as C-nucleophile[17] the reaction pathway is regarded as nucleophilic reaction of double bond of enamine with the *N*-acylamidine. The lone pair of electron of nitrogen of *N,N′*-dimethylamine group possibly assisting the oxygen of carbonyl of *N*-acylamidine **5** to coordinate with copper acetate to form **6**. The double bond of enamine **3** attacks the highly electrophilic amidines carbon attached to the electron pulling quaternary nitrogen of **6** and forms **7** which further led to **8** with the formation of AcOH. Further protonation of the nitrogen of *N,N'*-dimethyl amine and make it again quaternary nitrogen to form the **9**, which then cyclized to **10** with the removal of *N,N′*-dimethyl amine and AcOH. This further aromatized to afford the pyrimidine **4**. This pathway is regioselective and led to predominantly 2-arylpyrimidine confirmed by X-ray single crystal structure[18] of **4n**. Here the possibility of the attack of amino group of enamine **3** on the quaternary nitrogen of **6** is ruled out by the fact that if it would have happened, then it may form 6-arylpyrimidine.

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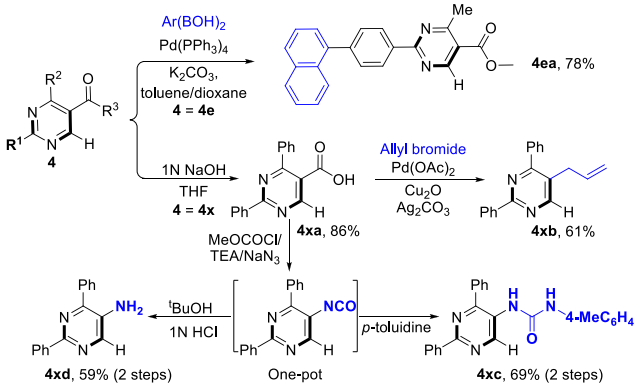
With pyrimidine core in hand, we were interested to explore the functional transformation reactions of this newly synthesized pyrimidine scaffold (Scheme 2). The reaction of pyrimidine **4e** with naphthalen-1-boronic acid under the standard Suzuki cross coupling reaction conditions gave the pyrimidine **4ea** with 78% yield, appended with a bulky naphthalene core at the 4th position of the phenyl directly attached to the pyrimidine ring (Scheme 2). Although the transition metal-catalyzed decarboxylative carbon–carbon bond formation reactions of aromatic carboxylic acid are well established,[19-20] there are few reports on the decarboxylative carbon–carbon bond formation reactions of hetero-aromatic systems mainly for activated systems such as thiophene, furan and especially for highly privilege scaffold such as pyrimidine are very few.[20] The palladium catalyzed decarboxylative C-5 allylation of **4xa** with ally bromide was achieved to form the allyl pyrimidine, **4xb** with 61% yield. Such pyrimidine bearing allyl group could be useful for further functionalization. Furthermore, the carboxylic acid **4xa** can be converted to isocyanate intermediate via Curtis rearrangement of acyl azides. The resulting isocyanate intermediate can serve as the precursor for various useful amino compounds, such as urea (**4xc**) and arylamine (**4xd**). The follow up chemistry/application was found to be interesting as substituting C5 of pyrimidine is still limited.



Scheme 2. Follow-up Chemistry

In conclusion, a novel and versatile one-pot synthesis of biologically interesting functionalized pyrimidines has been developed *via* the copper-catalyzed reaction of readily available primary amides as building blocks with *N*,*N*-dimethylformamide dimethylacetal and enamines. This protocol provides regioselective access to functionally diverse pyrimidines involving C–N + C + N–C–C fragments and leads to [2+1+3] formal cyclization in just one operationally friendly step.

Experimental Section

To an oven dried Schlenk tube was charged with amide (0.2 mmol), DMF-DMA (0.24 mmol) and DCE (2.0 mL). The tube was closed with Teflon cap and placed in a preheated oil bath at 60 ℃. After consumption of the starting material (approx. 2-4 hours, monitored by TLC) 4Å molecular sieve (250 mg), $Cu(OAc)_2$ (0.04 mmol) and enamine (0.3 mmol) were charged and the reaction was heated at 100 ℃ for 6-18 hours. After completion of reaction (monitored by TLC PE/EA10:1), the mixture was filtered through celite and washed with DCM. Organic layer was then concentrated and the resulting residues were purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford the pure product.

Acknowledgements

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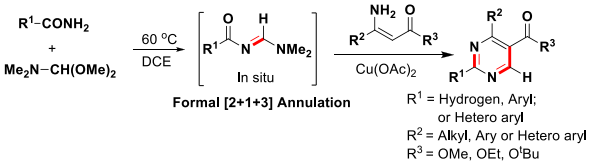

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