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KO^{t}Bu-Promoted Synthesis of Multi-substituted 4-Aminopyrimidines from Benzonitriles and Aliphatic Amides

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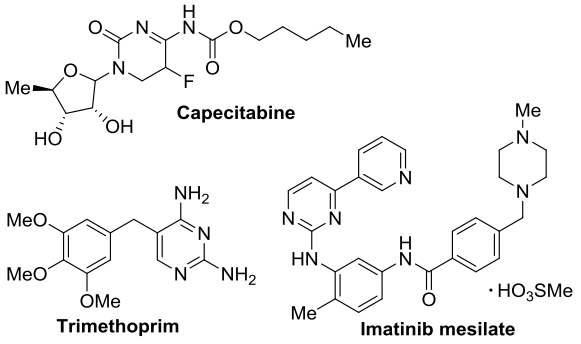
Multi-substituted 4-aminopyrimidines have been prepared from commercially available benzonitriles and aliphatic amides under transition-metal free conditions. With KO^{t}Bu as the only promoter, the desired pyrimidines were isolated in moderate to excellent yields.

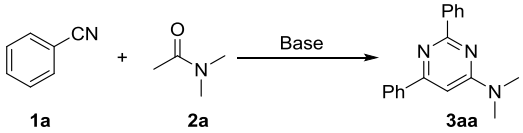
Pyrimidine and its derivatives are ubiquitous in natural products, functional materials and etc.[1] Various biological activities included anticonvulsant,[2] antitumor,[3] anticancer,[4] antiflammatory[5] and antimicrobial actives[6] have been reported. Representative examples of pharmaceuticals such as Trimethoprim,[7] Capecitabine[8] and Imatinib[9] containing pyrimidine moiety as the core structure (Scheme 1).



Scheme 1. Selected examples of pharmaceuticals containing pyrimidine core.

Considering the importance of pyrimidines, a variety of elegant approaches have been developed.[10] Examples of transition metal catalyst based procedures are gold-catalyzed cycloadditions of ynamides with two nitriles;[11] iron-catalyzed construction of 2-aminopyrimidines from alkynenitriles and cyanamides;[12] iridium-catalyzed multi-component synthesis of pyrimidines from amidines and alcohols;[13] niobium-catalyzed cycloaddition of alkynes and nitriles.[14] Transition metal-free procedures have also been developed.[15] Among these methodologies, the using of Tf_2O as promotor to prepare pyrimidines form nitriles and methyl ketones were established and applied. Here, we wish to report a new reaction pathway for the synthesis of pyrimidines from nitriles and amides. In our new procedure, KO^{t}Bu is been applied as the promotor. Various 4-aminopyrimidines were isolated in moderate to excellent yields.

Table 1. Optimization condition for the synthesis of *N,N*-dimethyl-2,6-diphenylpyrimidin-4-amine[a]



1a 2a 3aa

Entry	Base (equiv.)	T (℃)	Yield (%)[b]
1	KO^{t}Bu (2)	100	68
2	NaO^{t}Bu (2)	100	0
3	K_2CO_3 (2)	100	0
4	K_3PO_4 (2)	100	0
5	KOH (2)	100	0
6	NaOMe (2)	100	5
7	KOAc (2)	100	0
8	KO^{t}Bu (1)	100	27
9	KO^{t}Bu (3)	100	60
10	KO^{t}Bu (2)	80	19
11	KO^{t}Bu (2)	110	86(84)[c]

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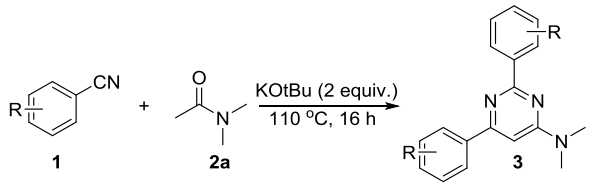
Electronic Supplementary Information (ESI) available: [general procedure, analytic data and NMR spectrums]. See DOI: 10.1039/x0xx00000x

12	KO^{t}Bu (2)	120	73

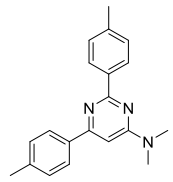
a: reaction condition: benzonitrle (3 equiv.), base, DMAc (2 mL), 16 h. b: GC yield, hexadecane as the internal standard. c: isolated yield.

Initially, various inorganic bases were examined in 2 mL of DMAc with benzonitrile at 100 ℃ (Table 1, entries 1-7). To our delight, 68 % of the target product was produced with the KO^{t}Bu as the base (Table 1, entry 1). The other tested bases included NaO^{t}Bu, K_2CO_3, KOAc, K_3PO_4 and KOH were ineffective here. No improvement on yield could be obtained when neither lowering nor increasing the amounts of KO^{t}Bu (Table 1, entries 8 and 9). Delightly, 84% of the desire product can be isolated when the reaction was conducted at 110℃ (Table 1, entry 11).

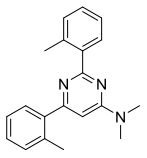
Table 2. Synthesis of pyrimidines from benzonitriles and DMAc.[a]



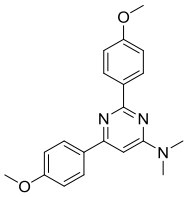
1 2a 3



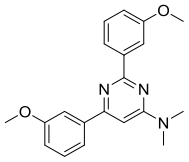
3ba 71%



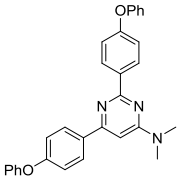
3ca 10%



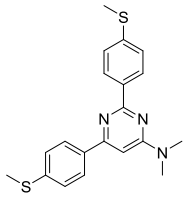
3da 45%



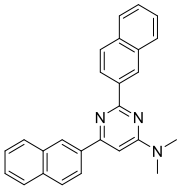
3ea 78%



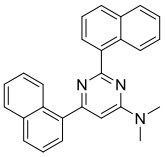
3fa 81%



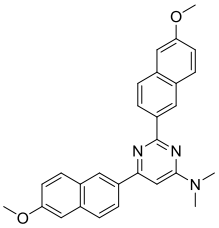
3ga 75%



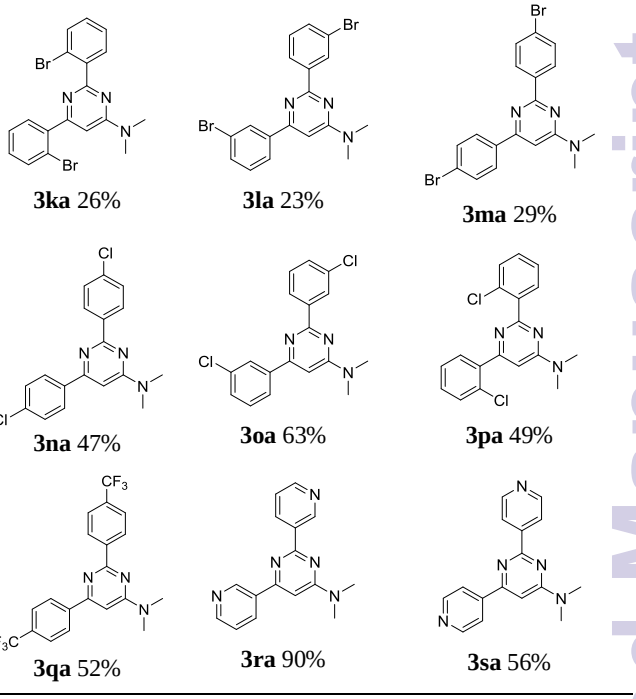
3ha 87%



3ia 51%



3ja 51%



3ka 26% **3la** 23% **3ma** 29%

3na 47% **3oa** 63% **3pa** 49%

3qa 52% **3ra** 90% **3sa** 56%

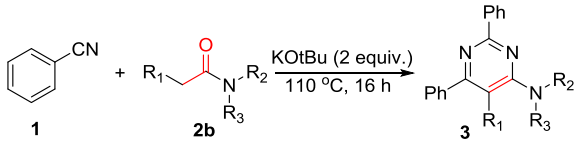
a: reaction condition: **1** (3 equiv.), K^{t}OBu (2 equiv.), DMAc (2 mL), 110 ℃, 16 h, isolated yield.

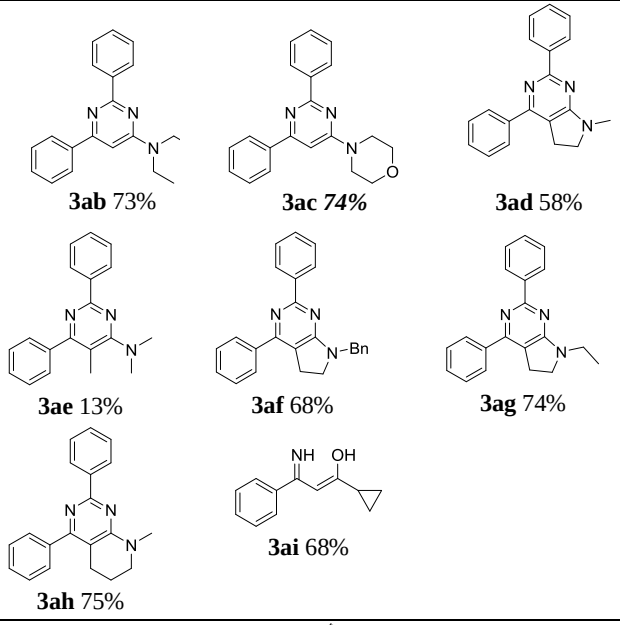
With the best reaction condition in hand (Table 1, entry 11), we investigated the generality of this reaction. As shown in Table 2, electron-donating and electron-withdrawing substituents and even heterocyclic aromatic nitriles can be applied as the substrates in this new procedure. 71% of the desired pyrimidine (**3ba**) was produced from 4-methylbenzonitrile and DMAc. However, the yield decreased to 10 % when the methyl group substituted at *ortho* position, which can be explained by steric hindrance. Ether and thioether group can well tolerated and gave the corresponding pyrimidines in good to excellent yields **3da-3ga**. Naphthonitriles were also tested under our conditions and gave the desired products in good yields **3ha-3ja**. In the cases of halogen substituted benzonitriles, the yields of the targets pyrimidines decreased. This phenomena can be explained by the nucleophilic substitution between the halogen groups and DMAc decomposed *N*,*N*-dimethyl amine to give the corresponding *N*,*N*-dimethyl aniline derivatives. To our delight, 90% of *N*,*N*-dimethyl-2,6-di(pyridin-3-yl)pyrimidin-4-amine **3ra** can be isolated when nicotinonitrile was applied the starting material. However, aliphatic nitriles were failed here and no desired products could be obtained.

Subsequently, various DMAc derivatives were examined with benzonitrile. As illustrated in Table 3, moderate to good yields can be achieved in all the cases. As a limitation of this procedure, no primary and secondary amides can be applied

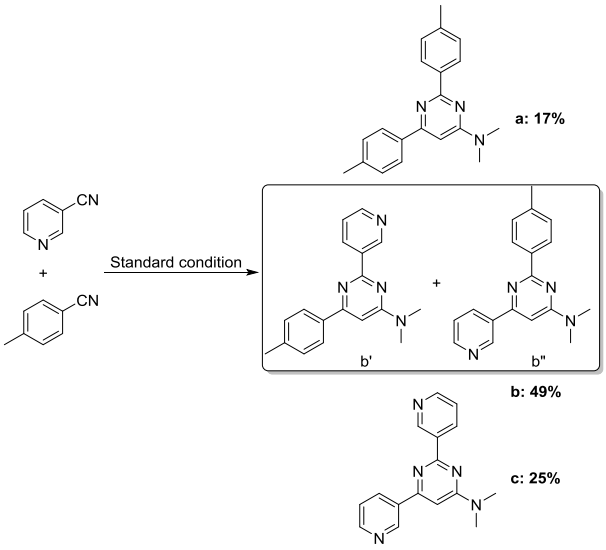
Additionally, besides amides, acetone, acetophenone, 2-phenyl acetophenone, 1-cyclopropylethan-1-one, DMSO and etc. were tested as well. Rather than the desired pyrimidines, enaminones were obtained as the main products **3ai**. From synthetic point of view, it's interesting to prepare cross-cyclized pyrimidines. Hence, we applied 3-cynaopyridine (1.5 equiv.) and *p*-methylbenzonitrile (1.5 equiv.) as two different starting materials in DMAc under our best reaction conditions (Scheme 2). From the obtained results, we see no selectivity could be achieved here.

Table 3. Synthesis of pyrimidines from DMAc derivatives.[a]



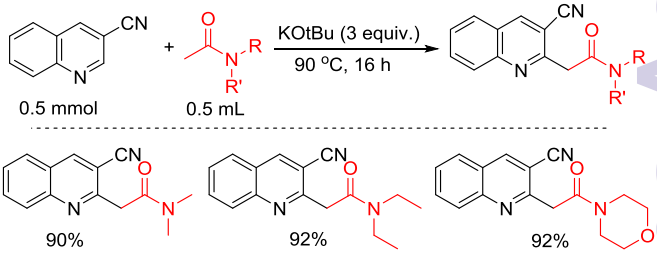


a: reaction condition: **1** (3 equiv.), K^{t}OBu (2 equiv.), **2** (2 mL), 110 ℃, 16 h, isolated yield.



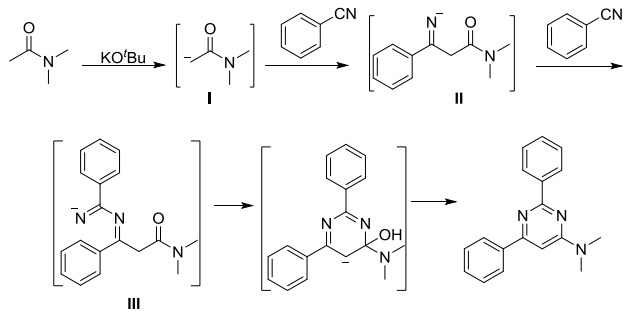
Scheme 2. Synthesis of different 2, 6-substituted pyrimidine.

Interestingly, when quinoline-3-carbonitrile was tested as substrate under our conditions, only 2-(3-cyanoquinolin-2-yl)-*N*,*N*-dimethylacetamide was formed and isolated. After further optimizations, the yield can be improved to 90% with 3 equiv. of KOtBu. Instead of DMAc, *N*,*N*-diethylacetamide and 1-morpholinoethan-1-one are suitable solvent and substrates as well (Scheme 3).



Scheme 3. Direct functionalization of quinoline-3-carbonitrile.

Based on the obtained results, a possible reaction pathway is been proposed (Scheme 4). In the presence of KO^{t}Bu, the activated α-H of DMAc could be trapped and transformed into a carbon anion **I**. Then nucleophilic addition of the in situ formed carbon anion to nitrile group took and afforded the intermediate enaminone **II**. The amidine intermediate **III** could be formed after enaminone **II** reacted with another molecular of nitrile. Then the nitrogen anion in amidine intermediate **III** go through intramolecular nucleophilic addition to the carbonyl group to give the target molecular through nucleophilic addition to the enol form of **III**.



Scheme 4. Proposed reaction mechanism.

Conclusions

In conclusion, we have presented a new pathway for the synthesis of pyrimidine derivatives. This procedure has advantages included highly economic efficient and convenient. All the reactions were conducts in one-pot one-step manner and without the additions of transition metal catalysts. Moderate to excellent of the desired multi-substituted 4-aminopyrimidines were isolated in moderate to excellent yields from commercially available benzonitriles and aliphatic amides with KO^{t}Bu as the only promoter.

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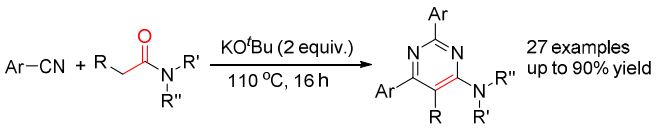

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