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Cyclization of Ketones with Nitriles under Base: A General and Economical Synthesis of Pyrimidines

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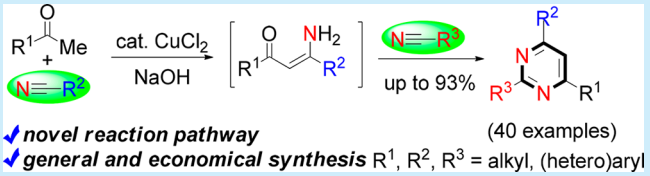
Supporting Information

ABSTRACT: A facile, general, and economical synthesis of diversely functionalized pyrimidines has been realized under basic conditions via the copper-catalyzed cyclization of ketones with nitriles. The reaction proceeds via a novel pathway involving the nitriles acting as electrophiles and consecutive C−C bond and two C−N bond formations and shows broad substrate scope and good tolerance of many important functional groups. This strategy represents a new platform for constructing pyrimidine structures.



Pyrimidines are fundamental structural motifs found in many kinds of functional compounds, such as natural products, drugs, bioactive molecules, supramolecules, and biogenetic and photophysical materials (Figure 1).[1,2] Numerous pyrimidine-containing functional compounds have been synthesized by using simple pyrimidines as basic chemical raw materials. Therefore, pyrimidines are consumed in large quantities in the biological, medical, and chemical industries, and their facile, general, and economical synthesis holds extreme significance.

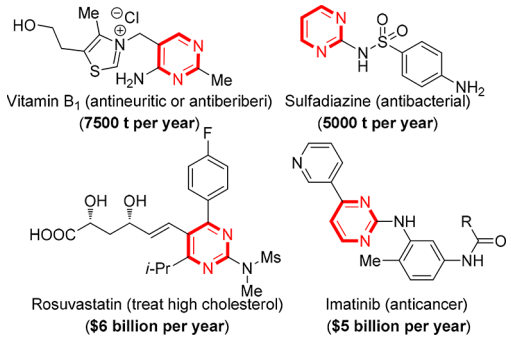
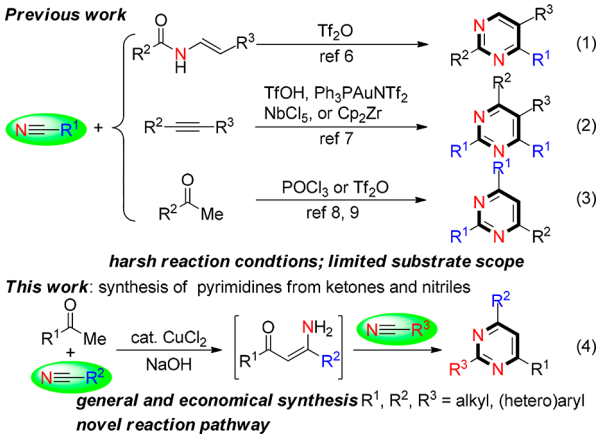


Figure 1. Representative pyrimidine compounds.

Traditionally, pyrimidine structures are constructed by the condensation of amidines with 1,3-dicarbonyl compounds or surrogates.[3] In recent years, numerous attempts have been made toward the synthesis of pyrimidines in the pursuit of less expensive and more readily available nitrogen sources, more convenient 1,3-dicarbonyl equivalents, milder reaction conditions, and more facile operational procedures, as well as improving access to more structurally diverse pyrimidines.[3−5] In these regards, readily available nitriles have been employed as nitrogen sources, instead of amidines. Notable advances are achieved by the reactions of nitriles with *N*-vinylamides and alkynes (Scheme 1, eqs 1 and 2).[6,7]

Scheme 1. Synthesis of Substituted Pyrimidines from Nitriles



Ketones are abundant, structurally diverse, and inexpensive chemicals, and the reaction of ketones with nitriles would be an ideal strategy for the synthesis of pyrimidines. In 1985, Zielinski[8] first reported the treatment of two nitriles with one ketone for the synthesis of pyrimidines in the presence of phosphoryl chloride. In later years, many improvements to the reaction have been made by the use of Tf_2O (Scheme 1, eq 3).[9] However, serious shortcomings remain. Anhydrous conditions are required, and a stoichiometric amount of Tf_2O is rather expensive. Furthermore, because of the release of a strong organic acid, TfOH, functional groups containing lone pairs of electrons, such as NH_2, OH,

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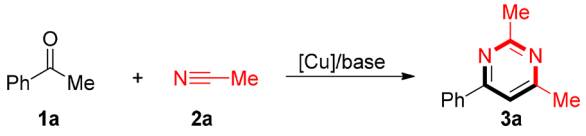
thiophene, and pyridine, are not tolerated. These drawbacks restrict the application of these methods.

To achieve a facile, general, and economical synthesis of pyrimidines, we developed a novel approach for accessing pyrimidines from ketones and nitriles via copper catalysis. (Scheme 1, eq 4). The reaction proceeds under basic conditions by using nitriles as electrophiles, which is quite different from the known methods that nitriles are used as nucleophiles.[6−9] A variety of 2,4,6-trisubstituted pyrimidines are efficiently constructed with good tolerance for many functional groups, especially thiophene, pyridine, OBn, SMe, NH_2, and OH.

As shown in Table 1, a 62% yield of 2,4-dimethyl-6-phenylpyrimidine **3a** was produced by the treatment of

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

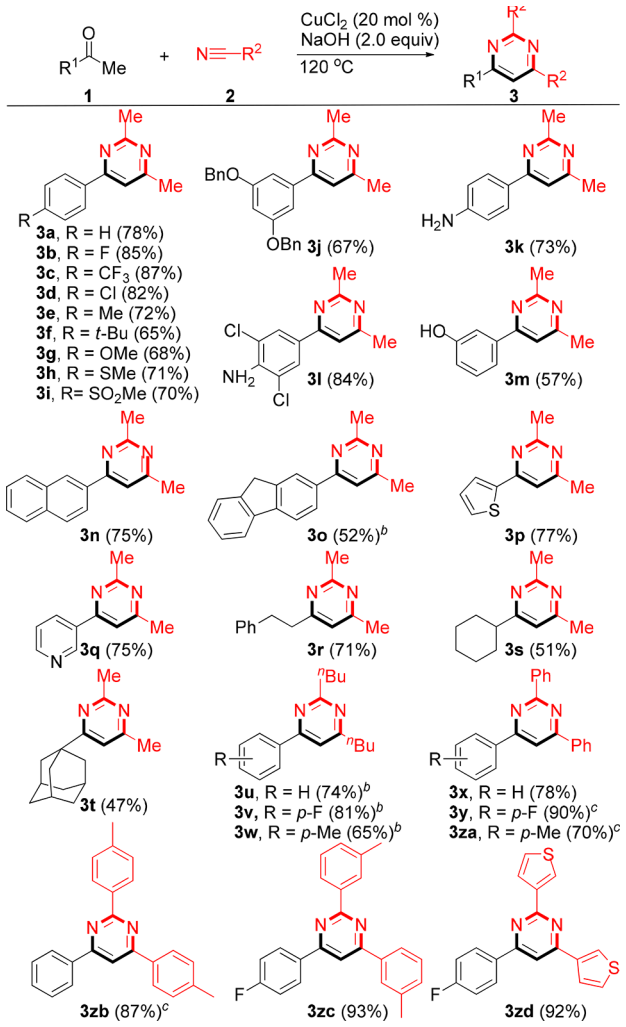
entry	cat.	base	temp (°C)	conv[b] (%)	yield[c] (%)
1	CuI	NaOH	120	90	62
2	CuCl	NaOH	120	86	53
3	CuBr	NaOH	120	78	39
4	$CuCl_2$	NaOH	120	97	82
5	$CuBr_2$	NaOH	120	88	68
6	$Cu(OAc)_2$	NaOH	120	90	45
7	$Cu(OH)_2$	NaOH	120	85	21
8	CuO	NaOH	120	89	16
9	$ZnCl_2$	NaOH	120	82	nd
10	AgOTf	NaOH	120	35	nd
11	$FeCl_3$	NaOH	120	100	nd
12	$CoBr_2$	NaOH	120	100	nd
13	$CuCl_2$	*t*-BuONa	120	90	38
14	$CuCl_2$	*t*-BuOK	120	93	11
15	$CuCl_2$	KOH	120	95	18
16	$CuCl_2$	Na_2Co_3	120	<5	nd
17	$CuCl_2$	Et_3N	120	0	nd
18	$CuCl_2$		120	0	nd
19	$CuCl_2$	NaOH	130	100	80
20	$CuCl_2$	NaOH	110	60	46

[a]Reaction conditions: **1a** (0.3 mmol), catalyst (0.06 mmol, 20 mol %), base (0.6 mmol, 2 equiv) in CH_3CN **2a** (0.6 mL) for 24 h under N_2. [b]Conversion of **2a**. [c]GC yields using *n*-tridecane as an internal standard.

acetophenone **1a** with acetonitrile **2a** at 120 °C in the presence of 20 mol % of CuI and 2.0 equiv of NaOH (Table 1, entry 1). In our investigation of the Cu salts (Table 1, entries 1−8), $CuCl_2$ gave the highest yield (82%). $Cu(OH)_2$ and CuO showed low catalytic efficiencies in this reaction (Table 1, entries 7 and 8), which could probably be attributed to their poor solubility. Other metal catalysts such as $ZnCl_2$, AgOTf, $FeCl_3$, and $CoBr_2$ were also tested; however, no desired product was obtained (Table 1, entries 9−12). The screening of the bases revealed that NaOH played a unique role in this transformation; both stronger bases and weaker bases gave very low yields of **3a** (Table 1, entries 13−17). In the absence of NaOH, the reaction did not take place (Table 1, entry 18). A comparable yield (80%) was observed at 130 °C. However, when the reaction temperature was lowered to 110 °C, only 46% yield of **3a** was obtained (Table 1, entries 19 and 20).

With the optimal conditions in hand, we next examined the scope of the substrates, and the results are summarized in Scheme 2. The reaction of acetonitrile **2a** with aromatic ketones

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.6 mL), $CuCl_2$ (20 mol %), NaOH (0.6 mmol), at 120 °C for 24 h under N_2. Isolated yield is given. [b]48 h. [c]30 h.

with electron-withdrawing substituents such as F (**3b**), CF_3 (**3c**), and Cl (**3d**) provided high isolated yields (82−87%) of the corresponding products. In comparison, slightly lower yields (65−72%) were observed when the aromatic ring had electron-donating substituents (**3e**−**h**). This electronic effect is attributed to the fact that the electron-withdrawing (donating) groups facilitate (disfavor) the formation of enolic intermediate **I** (vide infra). Reactive functional groups, such as SO_2Me (**3i**), OBn (**3j**), and NH_2 (**3k**,**l**), were also well-tolerated in this reaction, and the desired products were produced in 67−84% yields. Notably, phenolic OH group, which is sensitive to base, was also compatible; although, **3m** was isolated in only 57% yield. Sterically hindered polycyclic aromatic ketones also reacted efficiently with **2a** and produced the corresponding pyrimidines in good yields (**3n** and **3o**). Heteroaromatic ketones that contain thiophene and pyridine were also good substrates and afforded desired products **3p** and **3q** in 77% and 75% yields, respectively. Functional groups such as NH_2, OH, and pyridine are very

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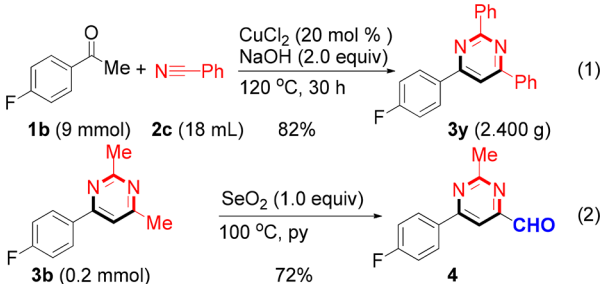
important and are frequently found in functional pyrimidine derivatives.[1a−d] The known methodologies that require Tf_2O or Lewis acids are not compatible with these functional groups.[6−9]

The developed reaction was also successfully applied to aliphatic ketones. For example, the treatment of 4-phenylbutan-2-one with **2a** afforded the corresponding product **3r** in 71% yield. When the sterically hindered ketones adamantanone and 1-cyclohexylethanone were subjected to the reaction system, the desired products were furnished in moderate yields (**3s**, 51%; **3t**, 47%). Beside acetonitrile, other aromatic and aliphatic nitriles, such as benzonitrile, 4-methylbenzonitrile, 3-methylbenzonitrile, and pentanenitrile were good substrates for this transformation, giving the desired products in good to excellent yields (**3u−zc**, 65−93%). Heteroaryl nitrile 3-thiophenecarbonitrile also reacted smoothly with 1-(4-fluorophenyl)ethanone, and **3zd** was produced in 92% yield.

Considering the synthetic usefulness of this reaction, we further illustrated its scalability. When the reaction was scaled up to 9 mmol (gram scale), the desired product **3y** was isolated in 82% yield (Scheme 3, eq 1). Because methyl heteroarenes are

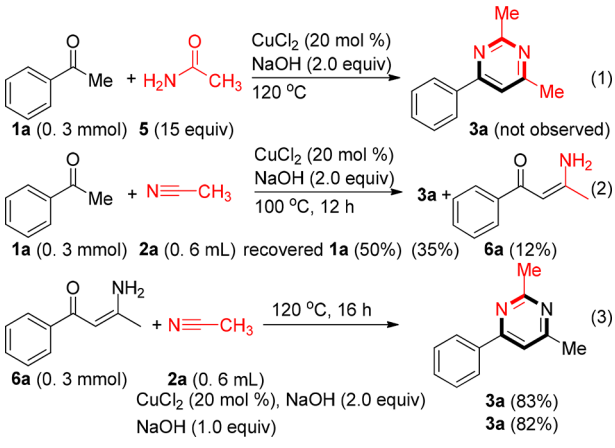
Scheme 3. Synthetic Utility



good substrates for C(sp^3)−H activation,[10] the direct oxidation of 4-(4-fluorophenyl)-2,6-dimethylpyrimidine **3b** was investigated, and the selective methyl oxidation product, aldehyde **4**, was obtained in 72% yield (Scheme 3, eq 2).[11]

Several control experiments were performed to elucidate the mechanism of this reaction. The reaction of **1a** with ethanamide **5** did not give the desired product, suggesting that the cycloaddition of **1a** with a primary amide via hydroxylation of a nitrile is not involved (Scheme 4, eq 1). The reaction of acetophenone **1a** with acetonitrile at 100 °C for 12 h resulted in a 12% GC yield of (*Z*)-3-amino-1-phenylbut-2-en-1-one **6a**

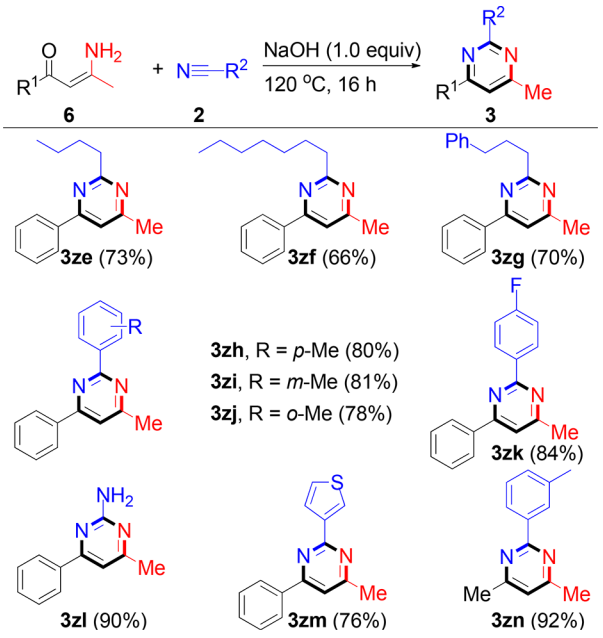
Scheme 4. Control Experiments



(Scheme 4, eq 2). Indeed, **6a** could be smoothly converted into the target product **3a** under the optimal conditions (83% yield) and even under copper-free conditions (82% yield, Scheme 4, eq 3). These results illustrate that enaminone **6a** probably served as the reaction intermediate in this annulation reaction, and a copper catalyst was essential for converting the ketones to enaminones.[12a] This finding also indicates that structurally diverse 2,4,6-trisubstituted pyrimidines could be constructed by employing nitriles and enaminones as starting materials under copper-free conditions.

As shown in Scheme 5, a variety of nitriles worked well with enaminones, producing the corresponding pyrimidines in good

Scheme 5. Synthesis of Highly Substituted Pyrimidines[a]



[a]Reaction conditions: **6** (0.3 mmol), **2** (0.6 mL), and NaOH (0.3 mmol), at 120 °C for 16 h under N_2. Isolated yield is given.

to excellent yields. Aromatic nitriles (**3zh−zk**) (78−84%) are more reactive than alkyl nitriles (**3ze−zg**) (66−73%), which is probably due to the stronger electrophilicity of the C−N triple bonds of aromatic nitriles (vide infra). Cyanamide underwent the annulation reaction with **6a** to provide 2-amino-substituted pyrimidine **3zl** in 90% yield. A heteroaryl nitrile, exemplified by 3-thiophenecarbonitrile, also reacted efficiently with **6a**, giving the desired product **3zm** in 76% yield. In addition, aliphatic enaminone (*Z*)-4-aminopent-3-en-2-one reacted effectively with 3-methylbenzonitrile to afford the desired pyrimidine **3zn** in 92% yield. Thus, a concise approach for accessing highly substituted pyrimidines from two different nitriles with a ketone via enaminone has been developed, and these products cannot be accessed by the known reaction systems.[8,9]

On the basis of the results of the above studies and the literature reports,[5,12] a plausible reaction pathway was proposed as shown in Scheme 6. First, enolic intermediate **I** is formed via the dehydration of ketone **1** with NaOH, which nucleophilically attacks the carbon atom of nitrile **2** that has been activated by $CuCl_2$ to produce imine intermediate **II** via C−C bond formation. The isomerization of **II** gives enaminone **III**.[5b,c] Dehydrogenation of **III** results in negative enaminone ion **IV**, which then nucleophilically attacks another equivalent of nitrile

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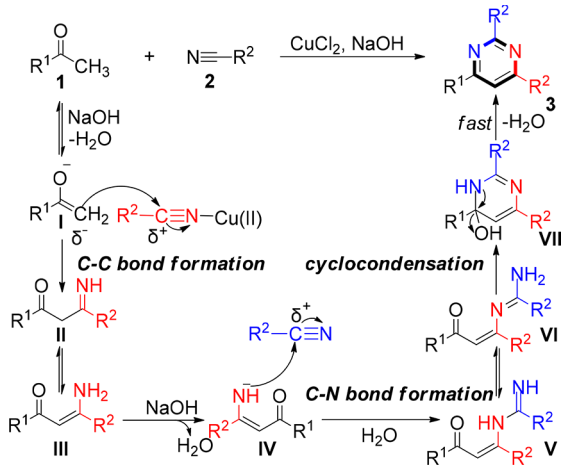
Scheme 6. Possible Reaction Mechanism



to form intermediate **V** via C−N bond formation, and its isomer **VI** is formed. Finally, the corresponding product **3** is produced via the cyclocondensation and subsequent dehydration of **VI**.[5c]

In conclusion, we have developed a facile, general, and efficient synthesis of diversely functionalized pyrimidines from inexpensive and readily available materials, namely, ketones, nitriles, NaOH, and $CuCl_2$. This new procedure is applicable to a wide range of substrates, including aromatic, heteroaromatic, and aliphatic ketones and nitriles, and is tolerant of many important functional groups, especially thiophene, pyridine, OBn, SMe, NH_2, and OH. The reaction proceeds via a novel pathway, in which the nitriles act as electrophiles, and consecutive C−C bond and two C−N bond formations are involved. This simple and economical protocol represents a new platform for the construction of pyrimidine structures, and it will be extensively applied in chemical research and in the chemical industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01324.

Experimental procedures, full spectroscopic data, and ^1H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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