Copper(II)-Catalyzed Synthesis of Pyrimidines from Propargylic Alcohols and Amidine: A Propargylation–Cyclization–Oxidation Tandem Reaction

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Abstract: A new approach to the tandem synthesis of 2,4-disubstituted or 2,4,6-trisubstituted pyrimidines from propargylic alcohols with amidine is described. This reaction is catalyzed by 20 mol% $Cu(OTf)_2$ to give pyrimidines in moderate to good yields via a propargylation–cyclization–oxidation tandem sequence.

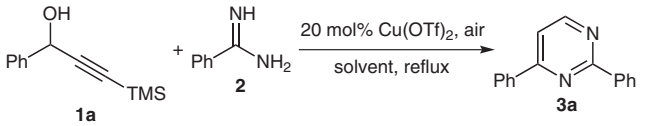
Key words: pyrimidine, propargylation, amidine, copper, annulation

Pyrimidine is a very important heterocyclic unit featuring prominently in pharmaceuticals, agrochemicals, biologically active molecules, and novel materials.[1] Accordingly, considerable attention has been paid to develop efficient methods for its synthesis.[2] Two general strategies are commonly used for the preparation of substituted pyrimidines: 1) functionalization of existing pyrimidine-containing precursors by introduction of new substituents, and 2) formation of a new pyrimidine ring through cyclization of acyclic substrates.[3] Among cyclization approaches, the classical condensation of N–C–N fragments, most often amidines or guanidines, with 1,3-dicarbonyl derivatives or their equivalents still remains the most powerful synthetic tool.[4] More recently, the application of alkynones and propargylic compounds in the assembly of pyrimidines has been attracting substantial attention from both academia and industry.[5] Müller and co-workers demonstrated a one-pot preparation of 2,4-disubtituted pyrimidines from TMS-ynones and amidinium salt.[5h,i] Bagley also described a microwave-assisted oxidation–heteroannulation sequence for the construction of 2,4-disubstituted pyrimidines from propargylic alcohols and amidines.[5j] In the latter case, however, only two synthetic examples were reported, and an excessive oxidant (MnO_2, 10 equiv) was required to convert the propargylic alcohols completely into the alkynones. Thus, development of more general, efficient as well as economic methodologies for the synthesis of pyrimidines is in high demand.

As the results of development on the transition-metal-catalyzed propargylic substitution reactions in our group,[6] herein we wish to report a highly efficient propargylation–cyclization–oxidation tandem reaction for the synthesis of substituted pyrimidines directly from propargylic alcohols with amidine using copper(II) triflate as the catalyst.

Not only can the reaction be carried out under mild conditions, giving water as the only byproduct and oxidized by atmospheric air, but also all of the propargylic alcohols used are readily available.

Table 1 Optimization of Reaction Conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	–	PhCl	24	40
2	$BiCl_3$	PhCl	24	25
3	$InCl_3$	PhCl	24	53
4	$FeCl_3$	PhCl	3.5	52
5	$Cu(OTf)_2$	PhCl	1.5	87
6	$Bi(OTf)_3$	PhCl	24	21
7	$Zn(OTf)_2$	PhCl	24	41
8	AgOTf	PhCl	24	45
9	PTSA	PhCl	0.2	0
10	CF_3COOH	PhCl	24	0
11	$Cu(OTf)_2$	PhCl	8	78[c]
12	$Cu(OTf)_2$	CH_3CN	24	57
13	$Cu(OTf)_2$	DCE	24	71
14	$Cu(OTf)_2$	CH_3NO_2	18	55
15	$Cu(OTf)_2$	DCM	24	0
16	$Cu(OTf)_2$	PhMe	8	78

[a] Reaction conditions: catalyst (20 mol%), **1a** (0.5 mmol, 1.0 equiv), and **2** (1 mmol, 2 equiv) in a solvent (2 mL) at refluxing temperature.
[b] Isolated yields.
[c] 10 mol% $Cu(OTf)_2$.

In the initial study, we chose the propargylic alcohol **1a** and benzamidine **2** as the substrates. The reaction was run in the absence of any catalyst, using chlorobenzene as the solvent. A low yield of pyrimidine **3a** was obtained after

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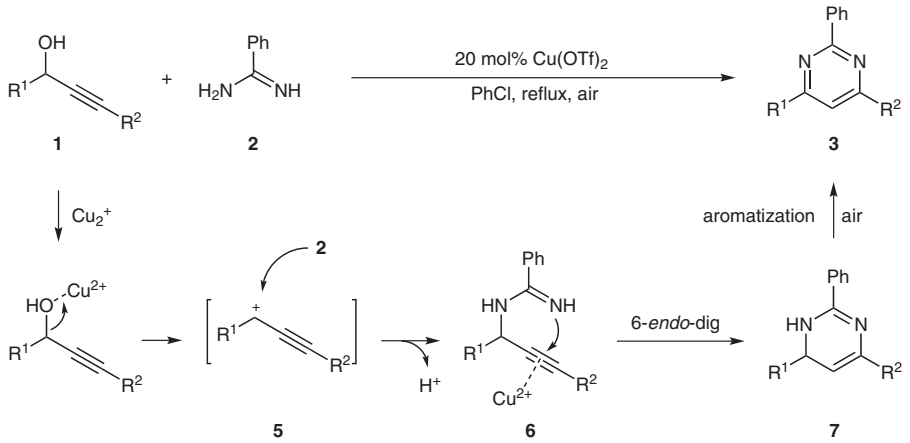
24 hours (Table 1, entry 1). The reaction was further tested in the presence of various Lewis acids such as $BiCl_3$, $InCl_3$, $FeCl_3$, $Cu(OTf)_2$, $Bi(OTf)_3$, $Zn(OTf)_2$, and AgOTf.

We found that 20 mol% copper(II) triflate could efficiently promote the tandem reaction at reflux for 1.5 hours, and the desired product **3a** was isolated in 87% yield (Table 1, entry 5). With other Lewis acids, the tandem reaction proceeded slowly to afford pyrimidines **3a** in low yields (Table 1, entries 2–4 and 6–8). It is worth noting that Bi(III) catalysts had a negative effect on this reaction (Table 1, entries 1, 2, and 6). A slower reaction rate and lower yield was observed when the catalytic amount of $Cu(OTf)_2$ was decreased to 10 mol% (Table 1, entry 11). Brønsted acids, such as PTSA and TFA, failed to catalyze the tandem reaction (Table 1, entries 9 and 10). In addition, it was found that the solvent played a crucial role in this tandem reaction (Table 1, entries 5 and 12–16). Acetonitrile, 1,2-dichloroethane, nitromethane, and toluene as solvents were also able to facilitate the reaction. However, the use of chlorobenzene obviously reduced the reaction time and improved the yield (Table 1, entries 12–14 and 16). Dichloromethane failed to promote this reaction (Table 1, entry 15). The results of solvents screening showed that the reaction rate was influenced by various factors such as boiling point and polarity. Among these factors, the boiling point of solvents might be a main factor. However, the detailed mechanism was still not clear.

With the optimal conditions, the substrate scope of this tandem reaction was examined. As depicted in Table 2, a variety of propargylic alcohols underwent this tandem reaction to give the corresponding substituted pyrimidines in moderate to good yields. Various secondary phenyl-substituted propargylic alcohols **1a–c** were examined. The propargylic alcohol **1a** (R^2 = TMS) gave the most desirable result, providing the substituted primidines in good yield (Table 2, entry 1). Propargylic alcohol **1h** possessing an electron-donating group at the aryl ring (R^1 = 4-$MeOC_6H_4$) reacted smoothly with amidine affording the pyrimidine **3h** in 91% yield (Table 2, entry 8). However, the substrate **1g** (R^1 = 4-BrC_6H_4) containing a weakly electron-deficient aryl ring was also successfully employed in the tandem reaction to give the pyrimidine **3g** in 74% yield (Table 2, entry 7). Obviously, electron-rich propargylic alcohols provided the desired products in higher yields than electron-poor propargylic alcohols. Internal propargylic alcohols **1c** and **1d** (R^2 = Ph, *n*-Bu) were also subjected to the reaction conditions, and the desired pyrimidines were obtained in moderate yields (Table 2, entries 3 and 4). The reaction of terminal propargylic alcohol **1b** (R^2 = H) with **2** afforded **3a** in moderate yield after a somewhat longer reaction time (Table 2, entry 2). Additionally, propargylic alcohols **1e**, **1f**,and **1i** (R^1 = 1-naphthyl and 2-thienyl) readily underwent this tandem reaction to afford the substituted pyrimidines **3e** and **3i** in moderate to good yields (Table 2, entries 5, 6, and 9). Similarly, propargylic alcohol **1j** also afforded moderate yield of pyrimidine **3j** (Table 2, entry 10). However, the results suggested that the aliphatic propargylic alcohols, such as substrate **1k** (R^1 = CH_3, R^2 = Ph), failed to afford the substituted pyrimidine.

Instability of the propargylic cation intermediate probably made the tandem reaction less favorable. For the aromatic propargylic alcohols, the reaction was completed under mild conditions. No added oxidant was needed, and oxygen in the air was sufficient to ensure formation of pyrimidines. A wide range of secondary propargylic alcohols bearing not only terminal alkyne groups but also internal alkyne groups could effectively be employed, and a number of functional groups, such as bromo, methoxy, and cyclohexenyl, were tolerated under the reaction conditions.

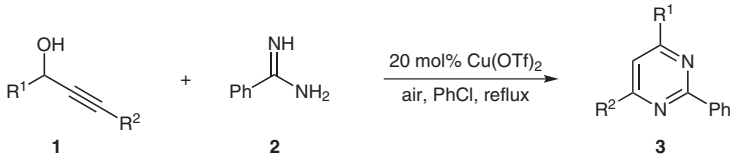
We next examined the reaction of propargylic alcohol **1a** under the optimized conditions in the absence of amidine. No oxidation of alcohol was observed. Thus, we speculated that this reaction underwent a new procedure other than 'oxidation–heteroannulation' mechanism.[5j–l] On the other hand, we have demonstrated a propargylation–cycloisomerization tandem reaction of propargylic alcohols and amides to provide oxazoles.[6c] We therefore hypothesized that the reaction of propargylic alcohols and benzamidine would undergo a similar process. As a working hypothesis, we propose the following mechanism for the pyrimidine ring formation (Scheme 1). First, $Cu(OTf)_2$-induced S_N1 substitution of propargyl alcohol **1** leads to **6**, which upon intramolecular nucleophilic attack of amidine



Scheme 1 Mechanistic rationale for Cu(II)-catalyzed tandem synthesis of pyrimidines

nitrogen at the Cu-activated triple bond of alkyne produces cyclic dihydropyrimidine intermediate **7** (6-*endo*-dig). Then, the dihydropyrimidine **7** can aromatize to the pyrimidine ring via oxidation by air. It was noteworthy that the $Cu(OTf)_2$ acted as a bifunctional catalyst, not only did it assist in the leaving of the hydroxyl group from the propargylic alcohol, furnishing the propargylic cation **5**, but also activated the triple bond rendering the cyclization process more facile.

Table 2 Synthesis of Substituted Pyrimidines **3**[7] from Propargylic Alcohols **1** and Amidine **2**[a]



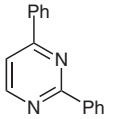
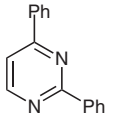
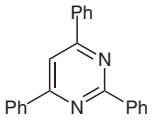
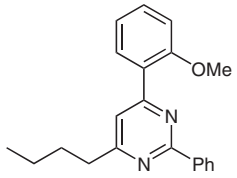
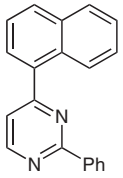
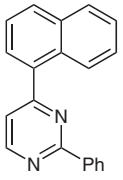
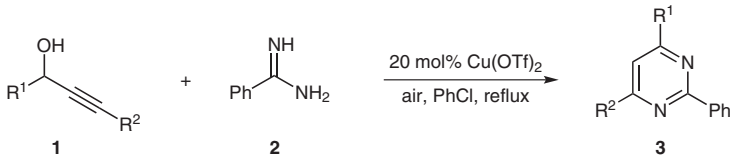
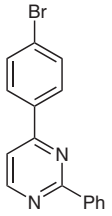
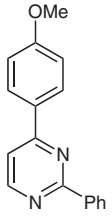
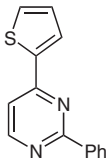
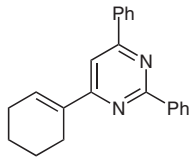
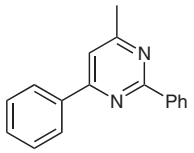
Entry	Propargylic alcohol	Product	Time (h)	Yield (%)[b]
1	**1a** R^1 = Ph, R^2 = TMS	 **3a**	1.5	87
2	**1b** R^1 = Ph, R^2 = H	 **3a**	6	68
3	**1c** R^1 = Ph, R^2 = Ph	 **3c**	3	79
4	**1d** R^1 = 2-$MeOC_6H_4$, R^2 = *n*-Bu	 **3d**	24	75
5	**1e** R^1 = 1-naphthyl, R^2 = TMS	 **3e**	1.5	89
6	**1f** R^1 = 1-naphthyl, R^2 = H	 **3e**	6	69

Table 2 Synthesis of Substituted Pyrimidines **3**[7] from Propargylic Alcohols **1** and Amidine **2**[a] (continued)



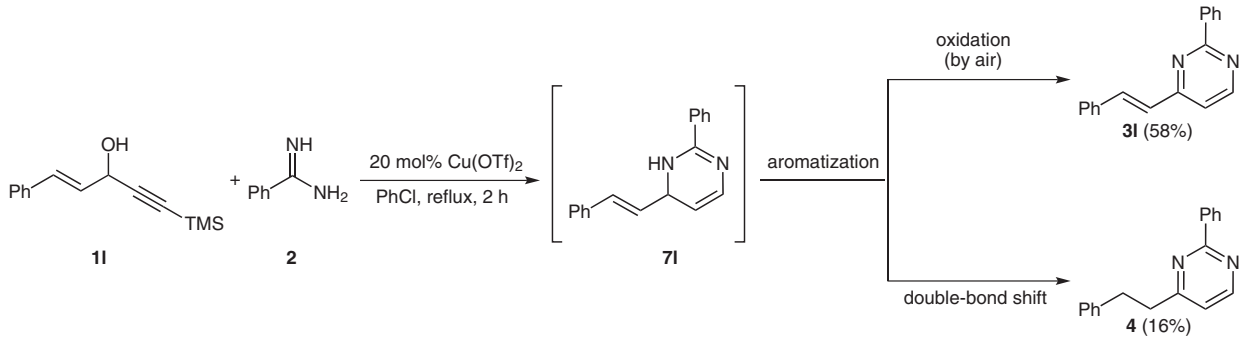
Entry	Propargylic alcohol	Product	Time (h)	Yield (%)[b]
7	**1g** R^1 = 4-BrC_6H_4, R^2 = TMS	 **3g**	3	74
8	**1h** R^1 = 4-$MeOC_6H_4$, R^2 = TMS	 **3h**	1.5	91
9	**1i** R^1 = 2-thienyl, R^2 = TMS	 **3i**	2	85
10	**1j** R^1 = Ph, R^2 = 1-cyclohexenyl	 **3j**	4.5	73
11	**1k** R^1 = Me, R^2 = Ph	 **3k**	24	0

[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), and $Cu(OTf)_2$ (0.1 mmol) in chlorobenzene (2 mL) at reflux.
[b] Isolated yields.

We also sought to extend the substrate to alkenyl-substituted propargyl alcohol **1l** (Scheme 2). Interestingly, it was found that the expected product **3l** was obtained along with a double-bond-hydrogenated product **4**. We speculated that the dihydropyrimidine intermediate **7l** was first formed via substitution–cyclization sequence as described above (Scheme 1).

Then, this dihydropyrimidine could aromatize to the corresponding pyrimidine ring **3l** or **4** through two competitive aromatization processes: 1) oxidation by the air, and 2) migration of the exocyclic double bond. Thus, with the dominant (more rapid) oxidation process, **3l** was furnished as the main product. Such a result provided an additional support for the propargylation–cyclization–oxidation mechanism.

In summary, we have developed a $Cu(OTf)_2$-catalyzed tandem reaction of propargylic alcohols with amidine, providing a general and facile approach to 2,4-disubstituted or 2,4,6-trisubstituted pyrimidines. The copper salt as catalyst, broad substrates scope, operational simplicity, mild reaction conditions, no added oxidant, and minimal



Scheme 2 Cu(II)-catalyzed formation of pyrimidines from alkenyl propargyl alcohol **1l** and amidine **2**

waste generation of this process would be beneficial for its large-scale use.

Acknowledgment

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(7) **General Procedure for the Synthesis of Substituted Pyrimidines**
To a solution of propargylic alcohol **1** (0.5 mmol) and amidine **2** (1 mmol) in PhCl (2 mL), $Cu(OTf)_2$ (0.1 mmol) was added, and it was stirred at reflux. When the reaction was completed (monitored by TLC), the solvent was removed under vacuum, and then the residue was further purified by silica gel column chromatography (PE and EtOAc) to afford pyrimidine.