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Strategy for the Synthesis of Pyrimidine Derivatives: $NbCl_5$-Mediated Cycloaddition of Alkynes and Nitriles

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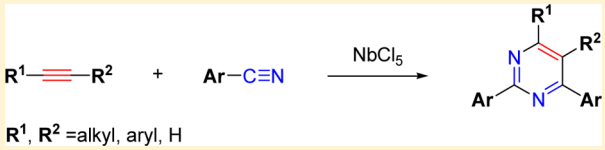
Supporting Information

ABSTRACT: Intermolecular cycloadditions of alkynes (terminal alkynes and internal alkynes) with aryl nitriles were successfully achieved, using an $NbCl_5$ complex, to give substituted pyrimidine derivatives in high yields with excellent chemo- and regioselectivity.



Pyrimidine derivatives are an important class of aza-heterocyclic compounds.[1] Pyrimidine derivatives are key structures in many natural products and biologically active substances, including minoxidil, thiamine, meridianin D, and pyrimethamine (Figure 1).[1] In addition, some pyrimidines are

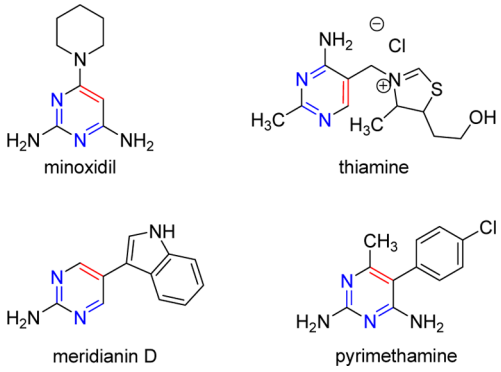


Figure 1. Biologically active compounds.

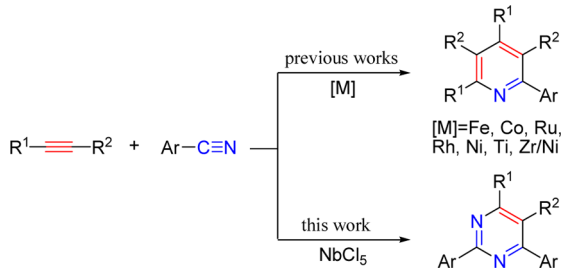
used in polymer and supramolecular chemistry.[2,3] These compounds have therefore attracted much attention from synthetic chemists for use in efficient syntheses.[4,5]

Since Brugnatelli synthesized pyrimidines,[4a] many synthetic organic chemists have studied preparations of pyrimidine derivatives. Many of the reported reactions are synthetic methods that do not use transition metals, such as condensations of N—C—N fragments and ketones, condensations of formamidine acetate with ketones,[4b] and reactions of *N*-vinylamides with nitriles.[4c] Various other synthetic methods for the synthesis of pyrimidine derivatives have been reported, such as transition-metal-mediated or -catalyzed condensation reactions of amidines with propargylic alcohols[5a] and three-component coupling reactions of functionalized enamines, triethyl orthoformate, and potassium aryltrifluoroborates with pyrimidine chlorides.[5d]

Intermolecular cycloaddition of one alkyne molecule and two nitrile molecules is one of the simplest and atom-economical methods for preparing pyrimidine derivatives. Previously, Martinez, Hanack, and co-workers reported the reaction of alkynes and nitriles to afford trisubstituted pyrimidine derivatives by using a strong acid such as CF_3SO_3H.[4h]

Alternatively, transition-metal-mediated/-catalyzed [2 + 2 + 2] intermolecular cycloaddition of alkynes and nitiriles is one of the most efficient, simple, and atom-economical methods for preparing pyrimidine derivatives. However, such a cycloaddition reaction exclusively afforded pyridines, not pyrimidines (Scheme 1, previous work).[6]

Scheme 1. Transition-Metal-Catalyzed or -Mediated Reactions of Alkynes and Nitriles



Recently, we reported that low-valent Nb catalysts ($NbCl_3(DME)$[7] and $NbCl_5$/hydrosilane system[8d]) are useful for cycloaddition reactions of terminal alkynes, internal alkynes, and alkenes to give 1,3-cyclohexadienes.[8]

In this paper, we report a simple strategy for the $NbCl_5$-mediated synthesis of tri- and tetrasubstituted pyrimidine derivatives using excellently chemoselective and highly regioselective intermolecular cycloaddition reactions of one alkyne molecule and two nitrile molecules (Scheme 1, this work).

Initially we chose 4-octyne (**1a**) and benzonitrile (**2a**) as model substrates and performed intermolecular cycloaddition

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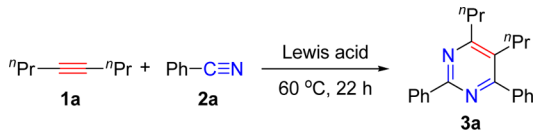
reactions using various transition-metal catalysts (Table 1). For instance, **1a** (1 mmol) was reacted with **2a** (2 mmol) in the

Table 1. Optimization of the Model Reaction[a]



entry	Lewis acid (amt (equiv))	yield of **3a** (%)[b]
1[c]	$NbCl_5$ (0.2)	10
2	$NbCl_5$ (0.2)	21
3	NbF_5 (0.2)	12
4	$TaCl_5$ (0.2)	9
5	$ZrCl_4$ (0.2)	trace
6	$AlCl_3$ (0.2)	12
7	$FeCl_3$ (0.2)	trace
8	$CeCl_3$ (0.2)	n.d.[d]
9	$NbCl_5$ (1.2)	50
10[e]	$NbCl_5$ (1.2)	86 (79)

[a]Reaction conditions: **1a** (1 mmol), **2a** (2 mL) and Lewis acid (amount based on **1a**) at 60 °C for 22 h under Ar (entries 2−8). [b]GC yields except for the value in the parentheses. [c]Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), and $NbCl_5$ (0.2 mmol) in 1,2-dichloroethane (1 mL) at 60 °C for 22 h under Ar. [d]Not detected by GC. [e]The reaction was performed by adding $NbCl_5$ (0.2 mmol) in six portions every 2 h over 22 h ($(0.2\ mmol/2\ h)_6$).

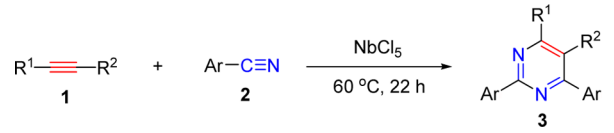
presence of $NbCl_5$ (0.2 mmol) in 1,2-dichloroethane (1 mL) at 60 °C for 22 h. 2,4-Diphenyl-5,6-*n*-dipropylpyrimidine (**3a**) was obtained in 10% yield with excellent chemoselectivity (Table 1, entry 1). When 2 mL of **2a** was used instead of 1,2-dichloroethane, **3a** was obtained in 21% yield (entry 2).

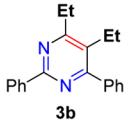
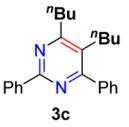
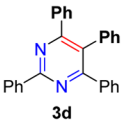
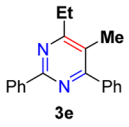
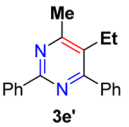
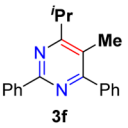
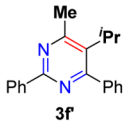
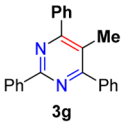
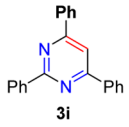
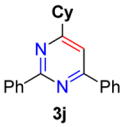
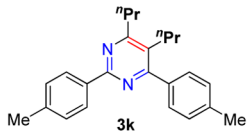
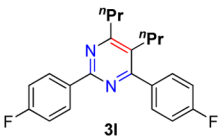
To optimize the reaction, we compared $NbCl_5$ with different metal salts (NbF_5, $TaCl_5$, $ZrCl_4$, $AlCl_3$, $FeCl_3$, and $CeCl_3$) (entries 3−8). The catalyst precursor significantly influenced the reaction activity. The best results for the model cycloaddition reaction were observed in the presence of an $NbCl_5$ catalyst. We tried to increase the yield of **3a**. In one of many attempts, we tried a stoichiometric reaction; this gave **3a** in 50% yield (entry 9). We succeeded in obtaining **3a** in 86% yield by adding $NbCl_5$ (0.2 mmol) to the reaction mixture six times every 2 h (entry 10). Surprisingly, 1,2,3,4,5,6-hexapropylbenzene from cyclotrimerization of 4-octyne was not formed in the present reaction.[9] Here, low-valent Nb compounds such as $NbCl_3(DME)$[7,8]did not afford **3a** at all under these conditions.

Under the optimized reaction conditions, i.e., Table 1, entry 10, we investigated the scope of the reaction using various alkynes (Table 2). For instance, the internal alkynes 4-octyne (**1a**), 3-hexyne (**1b**), and 5-decyne (**1c**) participated in the reaction and the corresponding pyrimidine derivatives (**3a−c**) were obtained in 72−82% isolated yields with excellent chemo- and regioselectivities (entries 1−3).

However, the reaction with diphenylacetylene (**1d**) did not give any of the corresponding pyrimidine (**3d**; entry 4). The regioselectivities of the desired products from the reactions of unsymmetrical alkynes (**1e−g**) and **2a** were influenced by electronic effects on the unsymmetrical internal alkynes (entries 5−7). For instance, 2-pentyne (**1e**) and 4-methyl-2-pentyne (**1f**) gave the corresponding products in good yields as a mixture of regioisomers (**3e,f** and **3e′,f′**); these were characterized by ^1H and ^{13}C NMR spectroscopy, and the resonances were assigned using 2D-HMQC and HMBC.

Table 2. Scope of Reaction of Alkynes 1 with Aryl Nitrile 2[a]



Entry	products (**3**) yield(%)[b]		
1	 **3a**	2  **3b**	3  **3c**
	79	72	82
4	 **3d**	5  **3e**	 **3e'**
	n.d.[c]	75(**3e**:**3e'**=61:39)	
6	 **3f**	 **3f'**	7  **3g**
	75 (**3f**:**3f'**=61:39)		76
8	 **3h**	9  **3i**	10  **3j**
	74(>95)[d]	50	57
11	 **3k**	12  **3l**	
	57	39	

[a]Reaction conditions: see optimized conditions (Table1, entry 10). [b]Isolated yields. [c]Not detected by GC. [d]The values in parentheses show the selectivity (%) of 2,4,6-substituted adducts.

However, when 1-phenyl-1-propyne (**1g**) was used, **3g** was obtained in 76% yield with >99% regioselectivity. The reactions of trimethylsilylacetylene and ethyl propiolate did not afford the products **3**.

We next investigated the scope of the reaction with terminal alkynes. The reaction was successful using terminal alkynes with *n*-octyl, phenyl, and cyclohexyl groups. The terminal alkynes 1-decyne (**1h**), phenylacetylene (**1i**), and cyclohexylacetylene (**1j**) gave the corresponding desired products (**3h−j**) in 50−74% yields with >95% regioselectivity and excellent chemoselectivity (entries 8−10). In addition, 4-methylbenzonitrile (**2b**) and 4-fluorobenzonitrile (**2c**) were also employed in the reaction, affording the corresponding products (entries 11 and 12). The reaction of an aliphatic nitrile such as octanonitrile or trimethylsilyl cyanide proved to be sluggish under these conditions.

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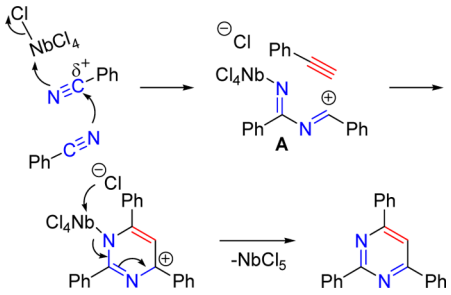
On the basis of these experiments, we propose the reaction mechanism shown in Scheme 2. The reaction initiates $NbCl_5$-assisted reaction of nitrile to form *N*-benzylidenebenzamidine (**A**). Subsequent cycloaddition of **A** with phenylacetylene (**1i**) on the benzylidene carbon results in the formation of 2,4,6-triphenylpyrimidine (**3i**).

Scheme 2. Plausible Mechanism for the Reaction of Phenylacetylene (1i) and Benzonitrile (2a)



The results in Table 1 show that $NbCl_5$ gives the best yields of **3a**. This is a result of differences in affinity toward the nitriles. Acetonitrile has been used as a probe molecule to observe Lewis acidities in various IL (ionic liquids)−metal chloride pairs via FTIR analysis.[10] We attempted to observe differences in Lewis acidities using ^{13}C NMR spectroscopy (Figure S1 in the Supporting Information). The difference between the Lewis acidity of $NbCl_5$ and that of $AlCl_3$ was confirmed experimentally by adding $NbCl_5$ (0.7 mmol) to benzonitrile (1 mL). The reaction mixture was stirred at 60 °C for 10 h. In the $^{13}C\{^1H\}$ NMR spectrum of the $NbCl_5$−CN reaction mixture after the addition of benzene-d_6 at 20 °C, nitrile carbon peaks appeared at 174.7 and 178.1 ppm. However, when $AlCl_3$ was used as the Lewis acid instead of $NbCl_5$, similar peaks were not observed. Therefore, $NbCl_5$ has effectual affinity[11] toward nitriles.

In summary, we have proposed a practical, general, and efficient method for the preparation of polysubstituted pyrimidine derivatives. These synthetic methods are the first examples of transition-metal-mediated cycloaddition reactions of one alkyne molecule and two nitrile molecules to give pyrimidines with excellent chemoselectivities and high regioselectivities.

Further investigations with regard to the detailed reaction mechanism, scope, and applications of this reaction are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, and tables giving experimental and characterization data and original ^1H, ^{13}C, HMQC, and HMBC NMR spectra for products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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