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An Unprecedented Approach to 4,5-Disubstituted Pyrimidine Derivatives by a $ZnCl_2$-Catalyzed Three-Component Coupling Reaction

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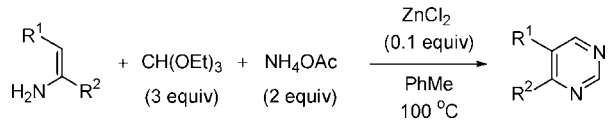
ABSTRACT



We have developed a $ZnCl_2$-catalyzed three-component coupling reaction involving a variety of functionalized enamines, triethyl orthoformate, and ammonium acetate, which leads to the production of 4,5-disubstituted pyrimidine derivatives in a single step. The procedure can be successfully applied to the efficient synthesis of mono- and disubstituted pyrimidine derivatives, using methyl ketone derivatives instead of enamines.

The 4,5-disubstituted pyrimidine nucleus is commonly found in biologically active and naturally occurring compounds[1] such as voriconazole[2] and avitriptan[3] and has been utilized as a central and precious intermediate for clinical drug discovery.[4] Although a number of approaches to the preparation of the pyrimidine framework have been developed by a number of organic/pharmaceutical chemists,[5,6] a general and highly selective preparation for the 4,5-disubstituted pyrimidine skeleton has rarely been studied. The Bredereck-type synthesis,[7]which is well-known as a conventional preparation of pyrimidine derivatives, is one notable exception. This procedure generally requires a reaction temperature of more than 160 °C, which results in a decrease in the product yield. Alternatively, other reported methodologies

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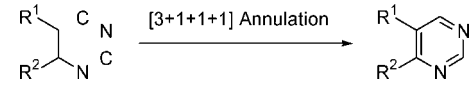
include a Pinner-type synthesis[8] and a skeletal or functional group transformation from nitrogen-containing heterocycles such as polysubstituted pyrimidines and *s*-triazine.[9,10] These procedures have disadvantages inasmuch as they involve stoichiometric additives, such as strong bases and acids, relatively inaccessible reagents, multiple-step syntheses, and harsh reaction conditions. Thus, the need remains for a novel synthetic process for the highly efficient preparation of 4,5-disubstituted pyrimidines via a single-step procedure.

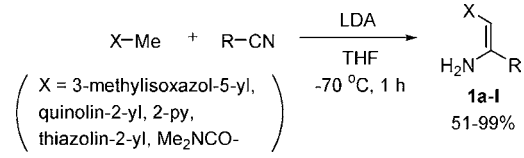
We previously found that intermolecular annulation and intramolecular cyclization with an *N*-silyl-1-azaallylic anion[11] and its synthetic equivalent, an *N*-silylenamine, can efficiently produce a variety of nitrogen-containing heterocycles.[12] During our ongoing studies of Lewis acid mediated synthesis of nitrogen-containing heterocycles with functionalized enamines,[13] we found that zinc chloride ($ZnCl_2$) effectively catalyzes the three-component coupling reaction of an enamine, triethyl orthoformate, and ammonium acetate to produce a 4,5-disubstituted pyrimidine derivative in a single step. To the best of our knowledge, this type of [3 + 1 + 1 + 1] annulation process, shown in Scheme 1, has not previously been reported. In this communication, we report the preliminary results of this unprecedented approach to the preparation of heterocycles. We also disclose the use of methyl ketone derivatives, instead of enamines, for the production of monosubstituted pyrimidine derivatives in good yield.

Scheme 1. New Approach to 4,5-Disubstituted Pyrimidines



Initially, we prepared commercially unavailable functionalized enamines **1a**−**l** (Scheme 2).[12a] For example, when the reaction of 3,5-dimethylisoxazole with benzonitrile, in the presence of LDA, was carried out in THF at −70 °C for 1 h, quenching with H_2O led to the corresponding enamine **1a** in 90% yield.

Scheme 2. Synthesis of Enamines **1a**−**l**



On the basis of our previous studies, the three-component coupling reaction of enamine **1a**, orthoester **2**, and ammonium acetate (NH_4OAc) was then examined, and the results are summarized in Table 1. First, when the reaction of enamine **1a** with 3 equiv of orthoester **2** and 2 equiv of NH_4OAc (**3**) was conducted in toluene at 100 °C for 20 h, the desired disubstituted pyrimidine **4a** was obtained in a 61% yield (run 1). The structure of pyrimidine **4a** was unambiguously confirmed by spectral data, elemental analysis, and X-ray crystallographic analysis.

Addition of a typical Lewis acid, such as $InCl_3$, $Cu(OTf)_2$, or $Yb(OTf)_3$, was ineffective for improvement of the product yield (runs 2−4). Interestingly, the use of a zinc catalyst, such as $ZnCl_2$, $ZnBr_2$, or $Zn(OTf)_2$, remarkably enhanced the yield of product **4a** (runs 5−7). In addition, employment of acetonitrile or 1,2-dichloroethane as a solvent and ammonium chloride (NH_4Cl) instead of NH_4OAc as the nitrogen source resulted in decreased yields (runs 8−10). Thus, we found that heating in PhMe at 100 °C in the presence of 0.1 equiv of $ZnCl_2$ were the best conditions for a coupling reaction.

To extend the generality of this coupling process, annulation using various multifunctionalized enamines was examined under our optimized conditions. The results are summarized in Table 2.

Enamines **1b**−**d** with an electron-donating group and an electron-withdrawing group on the benzene ring produced the

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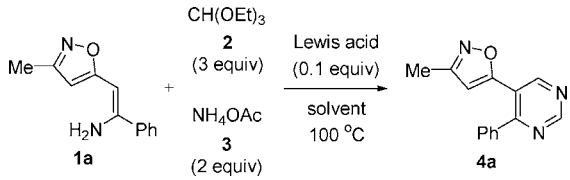
Table 1. Examination of the One-Pot Three-Component Coupling Reaction



run	Lewis acid	solvent	time (h)	yield (%)[a]
1	non	PhMe	20	61
2	$InCl_3$	PhMe	24	71
3	$Cu(OTf)_2$	PhMe	24	65
4	$Yb(OTf)_3$	PhMe	24	78
5	$ZnCl_2$	PhMe	20	(99)
6	$ZnBr_2$	PhMe	20	99
7	$Zn(OTf)_2$	PhMe	24	90
8[b]	$ZnCl_2$	MeCN	20	77
9[b]	$ZnCl_2$	DCE	20	84
10[c]	$ZnCl_2$	PhMe	24	39

[a] NMR yield (isolated yield). [b] The reaction was carried out at 80 °C. [c] NH_4Cl was employed instead of NH_4OAc.

desired pyrimidine derivatives **4b**−**d** in good to excellent yield (runs 2−4). Surprisingly, the reaction with enamine **1e**, having a MOM group, was complete within 3 h and gave the corresponding product **4e** in 82% yield (run 5). Similarly, quinolin-2-yl-substituted enamines **1f**−**i** also afforded good to excellent yields of pyrimidines **4f**−**i** (runs 6−9). In contrast, when the coupling reaction with enamine **1j**, containing a pyridin-2-yl group, was performed under these conditions, formation of the unexpected trisubstituted pyrimidine derivative **5** was observed with formation of the desired disubstituted pyrimidine **4j** (run 10). The structure of pyrimidine **5** was confirmed using spectral data, elemental analysis, and an X-ray crystallographic analysis, but we have not been able to explain a reasonable route for the formation of the pyrimidine. When enamines **1k** and **1l**, possessing a thiazolin-2-yl group and an amide group, were used, the corresponding pyrimidines **4k** and **4l** were produced in moderate yield alongside the undesired products **6** and **7** (runs 11 and 12). However, enamine **1m**, possessing an ester group, gave a 71% yield of the expected product **4m** with a 21% yield of the unexpected product **7** (run 13). Interestingly, enamines **1n** and **1o**, with a methyl group instead of a phenyl group, afforded the corresponding disubstituted pyrimidine derivatives **4n** and **4o** as sole products in good yield (runs 14 and 15).

Finally, to further illustrate the utility of our reaction procedure, we applied the $ZnCl_2$-catalyzed multicomponent coupling reaction for the synthesis of a simple and less-substituted pyrimidine derivative using ketone **8** instead of enamine **1** (Table 3). Although all reactions required 72 h to complete the intermolecular coupling and subsequent intramolecular cyclization, most reactions proceeded cleanly to produce the corresponding mono- and disubstituted pyrimidine derivatives **9a**−**e** in moderate to good yields (runs 1−7). Use of cyclic

Table 2. Single-Step Synthesis of Disubstituted Pyrimidines **4**[a]

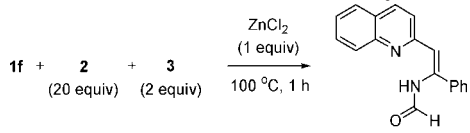
run	enamine **1**	time (h)	product(s)
1	R = Ph **1a**	20	**4a**: 99%
2	R = 4-MeO-C_6H_4- **1b**	24	**4b**:80%
3	R = 4-Me-C_6H_4- **1c**	14	**4c**: 97%
4	R = 4-Cl-C_6H_4- **1d**	20	**4d**: 80%
5	R = $MeOCH_2$- **1e**	3	**4e**: 82%
6	R = Ph **1f**	24	**4f**: 91%
7	R = 4-MeO-C_6H_4- **1g**	20	**4g**: 90%
8	R = 4-Me-C_6H_4- **1h**	20	**4h**: 94%
9	R = 4-Cl-C_6H_4- **1i**	48	**4i**: 77%
10	**1j**	20	**4j**: 46%; **5**: 48%
11	**1k**	48	**4k**: 24%; **6**: 48%
12	**1l**	48	**4l**: 26%; **7**: 66%
13	**1m**	48	**4m**: 71%; **7**: 21%
14	R = CN **1n**	15	**4n**: 65%
15	R = COOEt **1o**	5	**4o**: 77%

[a] Isolated yield.

(14) When the reaction of enamine **1a** with acetal **2** was carried out in PhMe at 100 °C for 16 h, 2-azadiene **10a** was obtained in a 34% NMR yield and the starting material **1a** was recovered in a 50% NMR yield.

10a: 34%

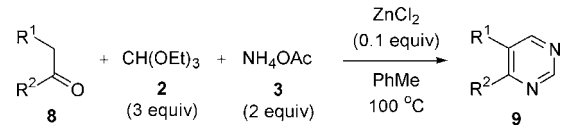
(15) When the coupling reaction of enamine **1f**, 20 equiv of acetal **2**, and 2 equiv of NH_4OAc in the presence of 1 equiv of $ZnCl_2$ was run at 100 °C for 1 h, compound **13a** that was produced by hydrolysis of intermediates **10** or **11** was obtained in a 33% NMR yield.

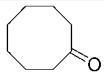
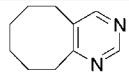
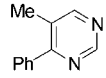
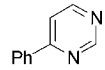
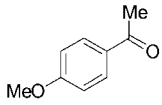
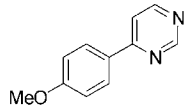
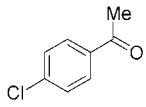
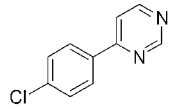


13a: 33%

Additionally, pyrimidines **6** and **7** generated from intramolecular cyclization of intermediates **11** were obtained (runs 11−13 in Table 2).

Table 3. One-Pot Synthesis of Substituted Pyrimidines **9**

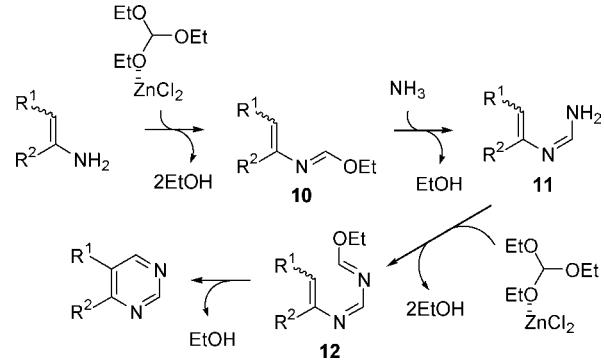


run	ketone **8**		pyrimidine **9**		yield[a] (%)
1		**8a**		**9a**	86
2		**8b**		**9b**	70
3		**8c**		**9c**	70
4		**8d**		**9d**	54
5		**8e**		**9e**	61

[a] Isolated yield.

ketone derivative **8a** effectively gave bicyclic pyrimidine derivative **9a** in good yield (run 1). When acetophenone (**8c**) was utilized as the reaction substrate, monosubstituted 6-phenylpyrimidine (**9c**) was obtained in 70% yield (run 3). This method successfully accommodated other acetophenone derivatives with an electron-donating group and an electron-withdrawing group (runs 4 and 5). A plausible mechanism for the coupling reaction is shown in Scheme 3. First, $ZnCl_2$ coordination with the orthoester is followed by a reaction of the activated acetal with the starting enamine (or the enamine intermediate generated from an α-acidic ketone and NH_4OAc), which leads to the formation of intermediate **10** with liberation of ethanol.[14] Intermediate **10** then reacts with the ammonia liberated from NH_4OAc to produce the isolable vinylamidine intermediate **11**.[15] Finally, the reaction of vinylamidine **11** with another

Scheme 3. A Plausible Mechanism



acetal, which is activated by $ZnCl_2$, leads to formation of the corresponding pyrimidine derivative through intramolecular cyclization of the intermediate **12**.

Thus far, we have demonstrated a simple and efficient synthesis of 4,5-disubstituted pyrimidine derivatives via a $ZnCl_2$-catalyzed three-component coupling reaction of a functionalized enamine, or an α-acidic ketone, with an orthoester and ammonium acetate. This has proven to be a facile and practical method for the preparation of a pyrimidine skeleton.

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Supporting Information Available: Detailed experimental procedures and characterization data for novel compounds, ORTEP diagram of **4a**, **5**, and **13a**, X-ray data for **4a**, **5**, and **13a** in CIF format, and copies of ^1H and ^{13}C NMR spectra of novel products. This material is available free of charge via the Internet at http://pubs.acs.org.

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