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Synthesis of Highly Substituted 4*H*-Pyrido[1,2-*a*]pyrimidines via a One-Pot Three-Component Condensation Reaction

Kai Yang, Jinbao Xiang, Guochen Bao, Qun Dang*, and Xu Bai*

The Center for Combinatorial Chemistry and Drug Discovery, The School of Pharmaceutical Sciences and The College of Chemistry, Jilin University, 1266 Fujin Road, Changchun, Jilin 130021, P. R. China

KEYWORDS: MCRs, multicomponent reactions, three-component reaction, 2-aminopyridine, 4*H*-pyrido[1,2-*a*]pyrimidine

ABSTRACT: A one-pot three-component reaction, involving condensation of 2-aminopyridines, aldehydes and ketones/aldehydes under trifluoromethanesulfonic acid catalysis, provides rapid access to highly substituted novel 4*H*-pyrido[1,2-*a*]pyrimidines.

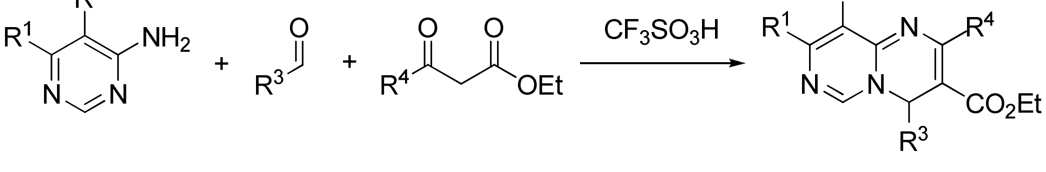
INTRODUCTION

Pyridopyrimidines are an important class of nitrogen-containing heterocycles since many of them exhibit a plethora of interesting biological activities.[1–10] For example, pyrido[1,2-*a*]pyrimidine constitutes the core structure of some marketed drugs, including the antiasthmatic agent pemirolast,[11] the tranquilizer pirenperone,[12] and the antiallergic agent barmastine.[13] Other pyrido[1,2-*a*]pyrimidine derivatives are known for their antidepressant,[14] gastrointestinal protective,[15] neurotropic and stress-protecting,[16] and anticancer properties.[17]

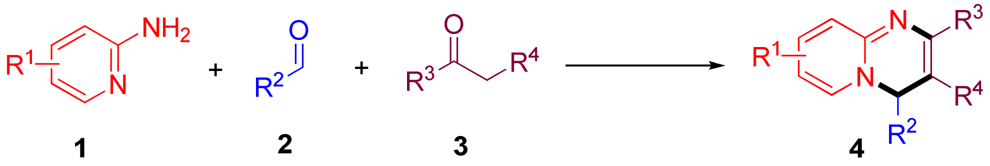
Over the past decades, a number of approaches to the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidines have been described, and these methodologies focused on the traditional two-component condensation of 2-aminopyridines with a variety of bifunctional electrophiles.[10,18–26] Multicomponent reactions (MCRs) have emerged as powerful methods for creating molecular complexity and diversity, and are recognized as important tools for a successful drug discovery program to access drug-like molecules in a rapid and efficient manner.[27–31] However, multicomponent reactions for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidines are scarce in general.[32,33] To the best of our knowledge, there is no report on the synthesis of 4-alkyl/aryl substituted 4*H*-pyrido[1,2-*a*]pyrimidines via MCRs.

The Biginelli reaction is a commonly used three-component reaction involving one-pot condensations of urea, aldehydes, and β-ketoesters.[34] Recently, we reported a versatile three-component reaction of 4-aminopyrimidines, aldehydes and β-ketoesters leading to 4*H*-pyrimido[1,6-*a*]pyrimidines (Scheme 1).[35] As part of our ongoing efforts to develop methodologies to prepare libraries of novel heterocycles,[36–41] we set out to discover and develop novel reactions to extend the scope of the well-known Biginelli reaction through the use of readily available ketones/aldehydes in place of β-ketoesters (active methylene compound) in 2-aminopyridine systems as shown in Scheme 2. Herein, the details of these studies are presented.

Scheme 1. Three-component reaction of 4-aminopyrimidines, aldehydes and β-ketoesters



Scheme 2. Three-component reaction of 2-aminopyridines **1**, aldehydes **2** and ketones/aldehydes **3**



RESULTS AND DISCUSSION

Initially, 2-aminopyridine **1**{*1*}, 4-chlorobenzaldehyde **2**{*1*}, and cyclohexanone **3**{*1*} were selected to investigate the reaction conditions suitable to generate product **4**{*1,1,1*} (Scheme 3). First, the previously reported conditions for the pyrimidine system was studied, only 41% yield of the desired product **4**{*1,1,1*} was obtained by heating 0.5 equiv CF_3SO_3H, 1.0 equiv **1**{*1*}, 3.0 equiv **2**{*1*} and 3.0 equiv **3**{*1*} for 46 hours at 110 ^{o}C; another product was also isolated and identified as compound **5**{*1,1,1*} (13%).[42] The above results prompted us to screen for an optimized condensation condition, and the results are summarized in Table 1. Treatment of compound **1**{*1*} (1.0 equiv) with compounds **2**{*1*} (1.1 equiv) and **3**{*1*} (1.1 equiv) in the presence of CF_3SO_3H (0.5 equiv) in refluxing acetonitrile for 130 hours gave the desired product **4**{*1,1,1*} in 45% yield and side product **5**{*1,1,1*} in 17% yield (entry 2, table 1). Variation of solvents (entries 3–5, table 1) did not lead to significant improvement in the yield of compound **4**{*1,1,1*}, but using toluene as the solvent did shorten the reaction time possibly due to the higher reaction temperature (entry 5, table 1). Next, other acids, including pTsOH, TFA, AcOH, and PPA, were screened but neither did produce higher yield of compound **4**{*1,1,1*} nor reduce the amount of side product **5**{*1,1,1*} (entries 6–9, table 1). Reaction concentration was also investigated: conducting the reaction at a dilute concentration of compound **1**{*1*} (0.5 M, entry 10, table 1) or under a solvent-free condition (entry 11, table 1) did not increase the yield of compound **4**{*1,1,1*}. Formation of the side product **5**{*1,1,1*} indicates that two molecules of aldehyde **2**{*1*} participated in the reaction, therefore optimization of the stoichiometry of reactants could minimize the formation of compound **5**{*1,1,1*} leading to the higher yield of product **4**{*1,1,1*}. As expected, increasing ketone **3**{*1*} produced more desired product **4**{*1,1,1*} and less side product **5**{*1,1,1*} (entries 13–15, table 1), while reducing the amount of ketone **3**{*1*} led to even more side product **5**{*1,1,1*} (entry 12, table 1). An acceptable condition was discovered as heating a mixture of 0.5 equiv CF_3SO_3H, 1.0 equiv **1**{*1*}, 1.1 equiv **2**{*1*}, and 3.0 equiv **3**{*1*} in toluene for 21 hours at reflux (entry 14, table 1), which gave product **4**{*1,1,1*} in 69% yield and only 8% of side product **5**{*1,1,1*}. Therefore the reaction condition of entry 14 was applied to further studies.

Scheme 3. Three-component reaction of 2-aminopyridine **1**{*1*}, 4-chlorobenzaldehyde **2**{*1*} and cyclohexanone **3**{*1*}

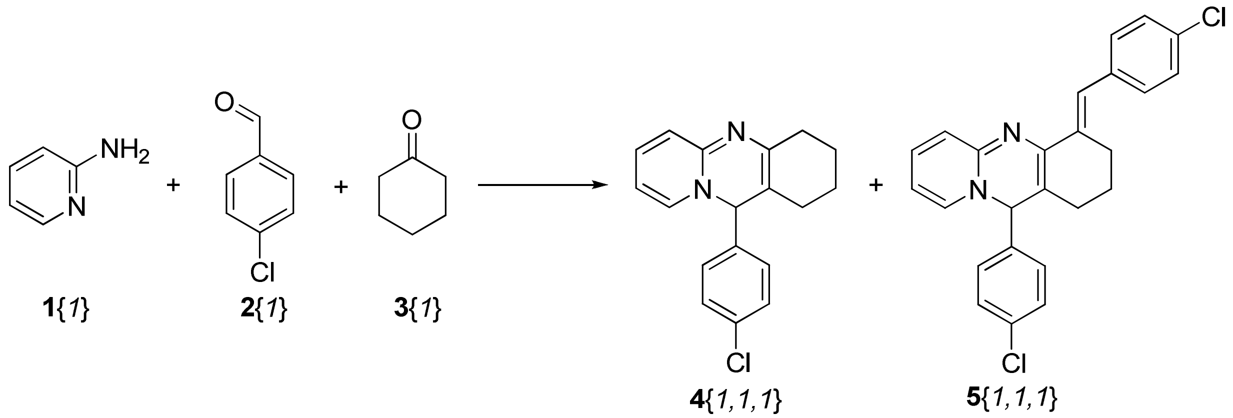


Table 1. Optimization of the three-component reaction[a]

entry	**2**{*1*} (eq)	**3**{*1*} (eq)	acid (0.5 eq)	solvent	temp. (°C)	[**1**{*1*}] (M)	time (h)	**4**{*1,1,1*}/**5**{*1,1,1*} (yield, %)[b]

1	3.0	3.0	CF_3SO_3H	none	110	--	46	41/13
2	1.1	1.1	CF_3SO_3H	CH_3CN	reflux	2.0	130	45/17
3	1.1	1.1	CF_3SO_3H	EtOH	reflux	2.0	120	39/16
4	1.1	1.1	CF_3SO_3H	DMF	110	2.0	20	50/15
5	1.1	1.1	CF_3SO_3H	toluene	reflux	2.0	18	51/19
6	1.1	1.1	pTsOH	toluene	reflux	2.0	19	30/25
7	1.1	1.1	TFA	toluene	reflux	2.0	22	49/19
8	1.1	1.1	AcOH	toluene	reflux	2.0	48	23/14
9	1.1	1.1	PPA	toluene	reflux	2.0	32	27/20
10	1.1	1.1	CF_3SO_3H	toluene	reflux	0.5	35	42/25
11	1.1	1.1	CF_3SO_3H	none	110	--	12	43/12
12	1.1	0.5	CF_3SO_3H	toluene	reflux	2.0	48	10/50[c]
13	1.1	2.0	CF_3SO_3H	toluene	reflux	2.0	18	56/14
14	***1.1***	***3.0***	***CF_3SO_3H***	***toluene***	***reflux***	***2.0***	***18***	***69/8***
15	1.1	5.0	CF_3SO_3H	toluene	reflux	2.0	18	58/6

[a] All reactions were conducted with 1.0 mmol of **1**{*1*}. [b] Isolated yield. [c] Yield based on cyclohexanone **3**{*1*}.

To explore the scope of this one-pot three-component reaction, various 2-aminopyridines **1**{*1−4*}, aldehydes **2**{*1−15*} and ketones/aldehydes **3**{*1−9*} were employed under the above optimized reaction conditions (Scheme 2, Figure 1). The results are summarized in Table 2 and Table 3.

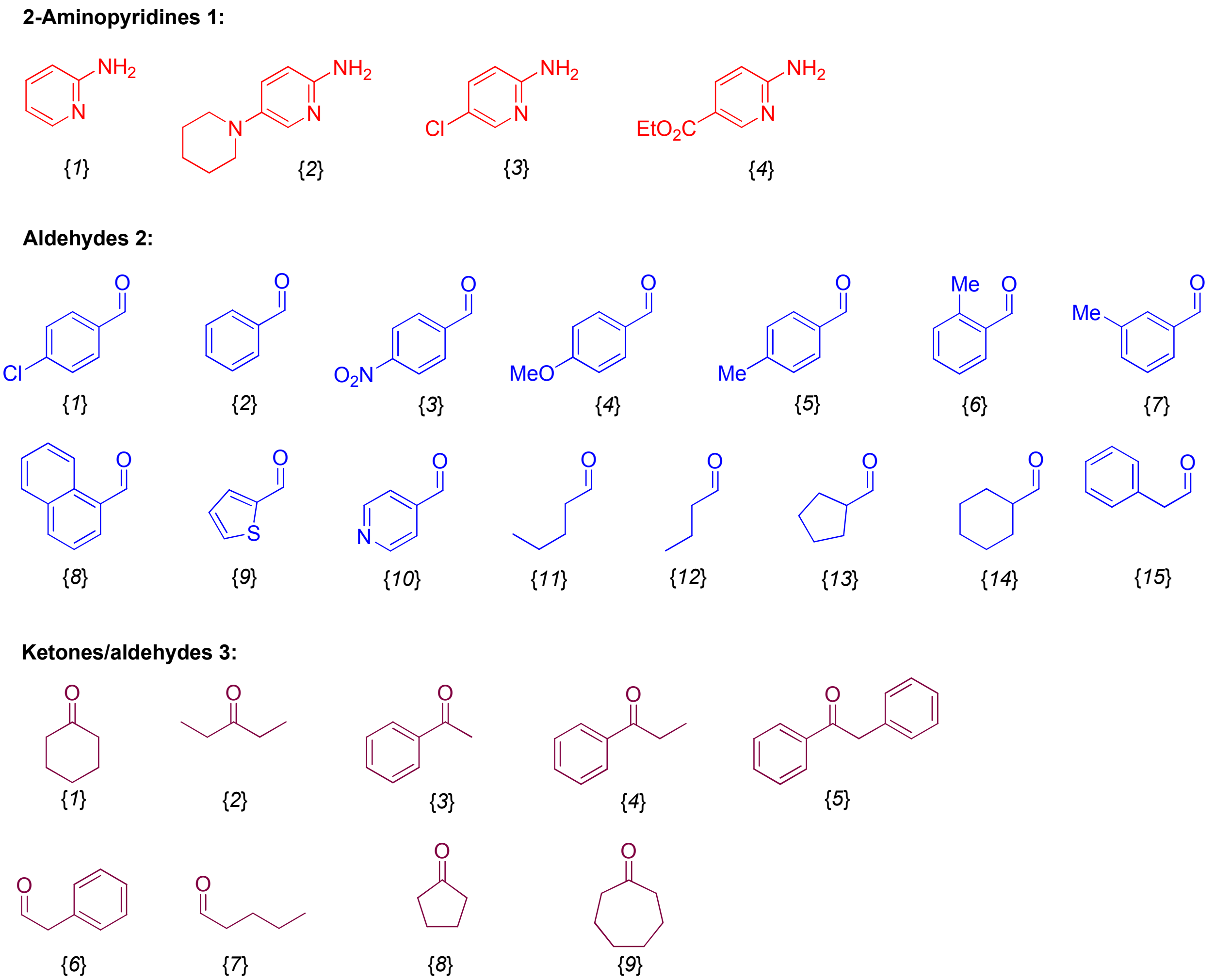
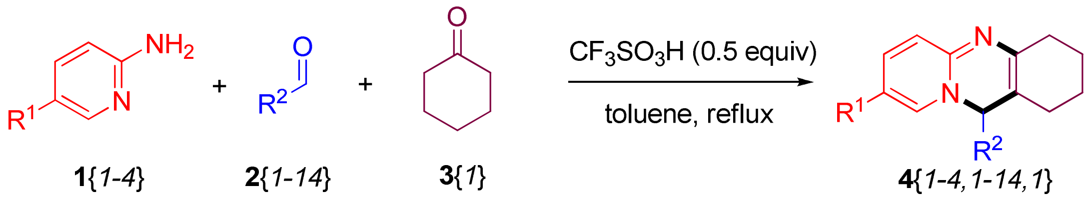


Figure 1. Diversity elements employed during library synthesis. 2-Aminopyridines **1**{*1−4*}, aldehydes **2**{*1−15*}, and ketones/aldehydes **3**{*1−9*}

Table 2. Three-component reaction of 2-aminopyridines **1**{*1−4*}, aldehydes **2**{*1−14*} and cyclohexanone **3**{*1*}[a]



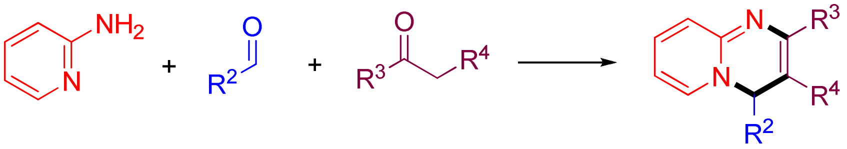
entry	**1**{*1−4*}	**2**{*1−14*}	time (h)	product	yield (%)[b]

1	{*1*}	{*2*}	17	**4**{*1,2,1*}	67
2	{*1*}	{*1*}	18	**4**{*1,1,1*}	69
3	{*1*}	{*3*}	48	**4**{*1,3,1*}	53
4	{*1*}	{*4*}	14	**4**{*1,4,1*}	75
5	{*1*}	{*5*}	16	**4**{*1,5,1*}	65
6	{*1*}	{*6*}	28	**4**{*1,6,1*}	55
7	{*1*}	{*7*}	18	**4**{*1,7,1*}	68
8	{*1*}	{*8*}	36	**4**{*1,8,1*}	53
9	{*1*}	{*9*}	17	**4**{*1,9,1*}	38
10	{*1*}	{*10*}	40	**4**{*1,10,1*}	50
11	{*1*}	{*11*}	16	**4**{*1,11,1*}	48
12	{*1*}	{*12*}	18	**4**{*1,12,1*}	46
13	{*1*}	{*13*}	24	**4**{*1,13,1*}	85
14	{*1*}	{*14*}	24	**4**{*1,14,1*}	87
15	{*2*}	{*1*}	14	**4**{*2,1,1*}	62
16	{*3*}	{*1*}	20	**4**{*3,1,1*}	68
17	{*4*}	{*1*}	32	**4**{*4,1,1*}	65

[a] Reagents and conditions: CF_3SO_3H (0.5 equiv), **1**{*1−4*} (1.0 equiv), **2**{*1−14*} (1.1 equiv), and **3**{*1*} (3.0 equiv) in toluene, reflux. [b] Isolated yield.

The scope of aldehydes (R^2CHO) was investigated using cyclohexanone and results are disclosed in Table 2. Various benzaldehydes are suitable substrates leading to the desired products in good to high yields (entries 1–7, Table 2). Both electron-withdrawing and electron-donating groups are tolerated although 2-methylbenzaldehyde (entry 6, Table 2) gave slightly lower yield compared to benzaldehyde (entry 1, Table 2), indicating possible steric hindrance effects. Other aryl and heteroaryl aldehydes (entries 8–10, Table 2) are also tolerated but gave the desired products in lower yields compared to benzaldehyde (entry 1, Table 2). Aliphatic aldehydes were also studied and the desired products were obtained in good to high yields. It is interesting to note that simple straight chain aliphatic aldehydes gave moderate yields (entries 11 and 12, Table 2), while cyclic aliphatic aldehydes produced excellent yields (entries 13 and 14, Table 2). To test the electronic effects for the substituents of the 2-aminopyridines, both electron-donating and electron-withdrawing groups were tested (entries 15–17, Table 2). Tuning the electron density of the 2-amino group had little effect on product yields, but it appears that the reaction proceeded faster when there is an electron-donating group on 2-aminopyridines (entry 15 vs. entries 16 and 17, Table 2). Having completed the investigation of the scope of aldehydes **2**{*1−14*}, various carbonyl compounds **3**{*2−9*} were studied and results are summarized in Table 3.

Table 3. Scope of the three-component reaction of 2-aminopyridine **1**{*1*}, aldehydes **2**{*1*} or **2**{*14−15*} and ketones/aldehydes **3**{*2−9*}[a]



1{*1*} **2**{*1*}, **2**{*14-15*} **3**{*2-9*} **4**{*1,1,2-9*}, **4**{*1,14-15,6*}

entry	**2**{*1*}/**2**{*14−15*}	**3**{*2−9*}	time (h)	product	yield (%)[b]
1	{*1*}	{*2*}	24	**4**{*1,1,2*}	47
2	{*1*}	{*3*}	24	**4**{*1,1,3*}	0
3	{*1*}	{*4*}	84	**4**{*1,1,4*}	41
4	{*1*}	{*5*}	168	**4**{*1,1,5*}	26
5	{*1*}	{*6*}	24	**4**{*1,1,6*}	62[c]
6	{*1*}	{*7*}	24	**4**{*1,1,7*}	43[c]

7	{*14*}	{*6*}	24	**4**{*1,14,6*}	65[c]
8	{*15*}	{*6*}	16	**4**{*1,15,6*}	62[d]
9	{*1*}	{*8*}	24	**4**{*1,1,8*}	0
10	{*1*}	{*9*}	24	**4**{*1,1,9*}	73

[a] Reagents and conditions (except designated): CF$_3$SO$_3$H (0.5 equiv), **1**{*1*} (1.0 equiv), **2**{*1*} (1.1 equiv), and **3**{*2−5*} or **3**{*8−9*} (3.0 equiv) in toluene, reflux. [b] Isolated yield. [c] CF$_3$SO$_3$H (0.5 equiv), **1**{*1*} (1.0 equiv), **2**{*1*} or **2**{*14*} (2.0 equiv), and **3**{*6−7*} (1.1 equiv) in toluene, reflux. [d] CF$_3$SO$_3$H (0.5 equiv), **1a** (1.0 equiv), and phenylacetaldehyde (4.1 equiv) in toluene, reflux.

As evident from Table 3, acyclic ketones (R^{3}COCH$_2$R^4) are also compatible for the current reactions to yield the expected products (entries 1, 3 and 4, Table 3) with the exception of acetophenone. The reaction of acetophenone led to complex reaction mixtures which might be due to the instability of product **4**{*1,1,3*} under the current reaction conditions. It is noteworthy that the reaction also can be extended to aliphatic aldehydes, although moderate yields were obtained for reactions involving phenylacetaldehyde and pentanal (entries 5–7, Table 3).[43] The self-condensation reactions of phenylacetaldehyde on treatment with 2-aminopyridine **1**{*1*} was also investigated, which produced the desired product **4**{*1,15,6*} in 62% yield (entry 8, Table 3). The case of cyclopentanone was surprising and failed to give the desired product **4**{*1,1,8*} (entry 9, Table 3). On the other hand, the reaction of cycloheptanone proceeded smoothly to form the desired product **4**{*1,1,9*} in good yield (entry 10, Table 3). To unambiguously identify the structures of compound **4**, compound **4**{*1,1,6*} X-ray crystallographic analysis was performed (Figure 2).[44]

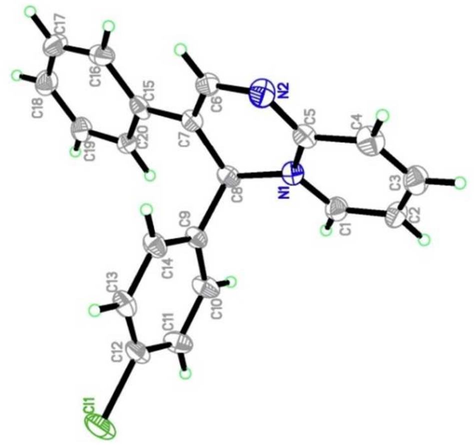
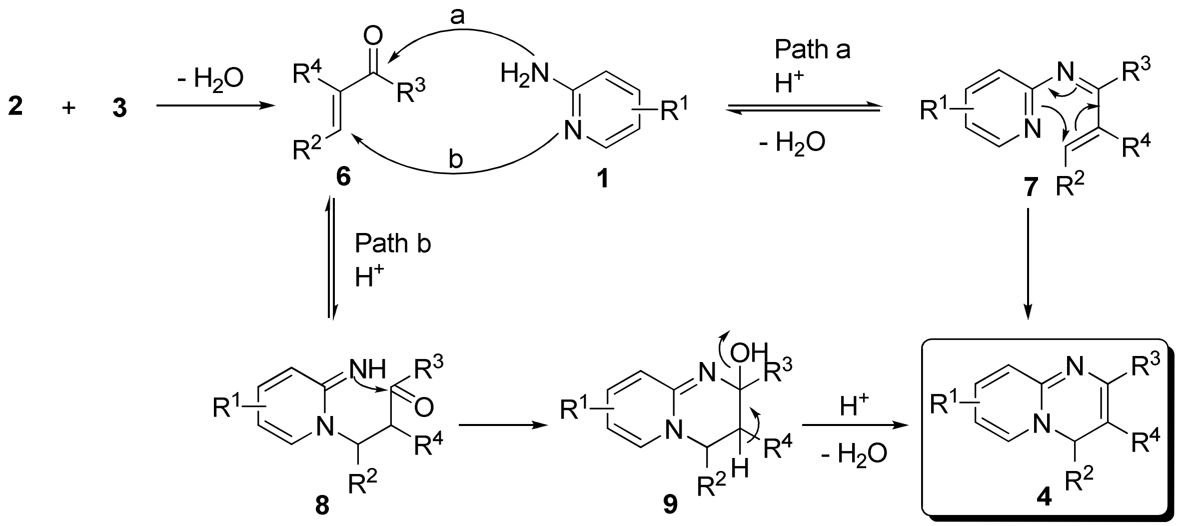


Figure 2. ORTEP diagram of compound **4**{*1,1,6*}

Mechanistically, several reaction pathways could be envisioned to generate products **4** in the current MCR. After carefully examination of our experimental results and considering existing literature reports,[21,24,43,45–47] we propose two potential mechanistic pathways as shown in Scheme 4 to account for the current multicomponent reactions. The first step of the current MCR is the formation of intermediate **6** through CF_3SO_3H promoted Knoevenagel condensation of aldehyde **2** and ketone/aldehyde **3**. Intermediate **6** was indeed detected and identified in the reaction mixture by mass spectroscopy and TLC analysis during the reaction. Subsequently, 2-aminopyridine **1** can react with intermediate **6** via two reaction pathways. For pathway **a**, condensation of 2-aminopyridine **1** with intermediate **6** under acid-catalyzed conditions to give imine **7**,[21,24] and then imine **7** underwent an intramolecular cyclization reaction to generate product **4**. On the other hand, it is plausible that the current MCR could follow reaction pathway **b**: Michael addition by the nucleophilic pyridine ring N atom of intermediate **6** to afford ketone intermediate **8**,[45] then an intramolecular cyclization of the imine group of intermediate **8** onto the keto moiety to give **9**, and finally an acid-catalyzed elimination of water to afford product **4**.

Scheme 4. Proposed reaction mechanism



CONCLUSIONS

In summary, we have demonstrated that 2-aminopyridines, aldehydes and ketones/aldehydes undergo a productive three-component reaction to provide 4*H*-pyrido[1,2-*a*]pyrimidines in moderate to high yields. This new MCR proved to have a broad scope since many aliphatic aldehydes, aromatic aldehydes, heterocyclic aldehydes, cyclic ketones and acyclic ketones are suitable substrates for the current MCR. Moreover, the current MCR is operationally simple therefore this new methodology should allow the rapid assembly of heterocyclic scaffolds with highly substituted 4*H*-pyrido[1,2-*a*]pyrimidines. This synthetic methodology complements the well-known Biginelli reaction and existing pyridine chemistry by allowing access to libraries of the pyridine-fused heterocycles.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, full characterization data, copies of LC-MS-ELSD and NMR spectra for all products, and crystallographic data of **4**{*1,1,6*} (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Tel: +86-431-85188955; Fax: +86-431-85188900; E-mail: jbxiang@jlu.edu.cn, qdang@jlu.edu.cn

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Notes

The authors declare no competing financial interest.

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