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Synthesis of Substituted Pyridines from Cascade [1 + 5] Cycloaddition of Isonitriles to *N*-Formylmethyl-Substituted Enamides, Aerobic Oxidative Aromatization, and Acyl Transfer Reaction

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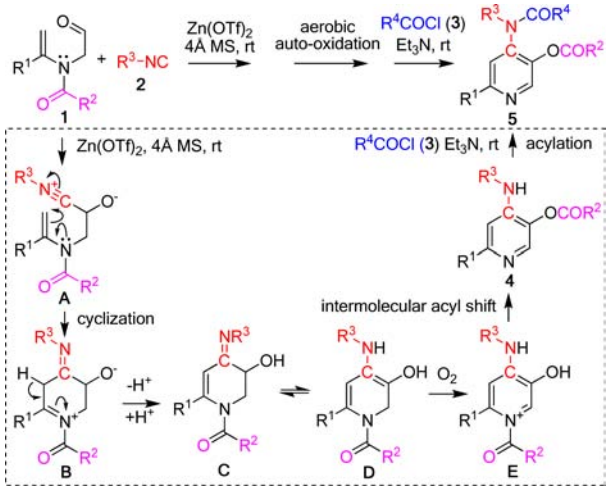
Supporting Information

ABSTRACT: A novel strategy for de novo synthesis of pyridines featuring an unprecedented α-addition of aldehyde and enamide to isonitrile as a key step is described. Under mild conditions, a cascade reaction involving $Zn(OTf)_2$-promoted [1 + 5] cycloaddition of isonitrile with *N*-formylmethyl-substituted enamide, facile aerobic oxidative aromatization and intermolecular acyl transfer from the pyridinium nitrogen to the 5-hydroxy oxygen, and finally acylation of the 4-amino group by an external acyl chloride efficiently afforded 2-substituted 4-acylamino-5-acyloxypyridines in good to excellent yields.

Substituted pyridines occur widely as natural products, pharmaceuticals, agrochemicals, and functional materials and are also useful intermediates in organic synthesis.[1,2] As a consequence, a wealth of synthetic methods has been developed.[1−3] Among them, [5 + 1] cyclocondensation reactions using ammonia as the nitrogen source,[3] [3 + 3] cyclocondensation reactions using enamines as three-atom components,[4] and metal-catalyzed or -mediated [4 + 2][5] and [2 + 2 + 2][6] cycloaddition reactions and cycloisomerizations[7] are notable examples. However, efficient synthesis with high chemo- and regioselectivity, which would enable access to tailor-made functionalized pyridines, still remains challenging.[8,9]

We have recently demonstrated that tertiary enamides, which are known to be stable and chemically inert because of the electron-withdrawing acyl group, are unique nucleophiles.[10−14] In the presence of a Lewis or Brønsted acid, "stable" tertiary enamides can undergo intramolecular nucleophilic addition to a range of electrophiles, including epoxides,[10] aldehydes,[11] imines,[12] and activated ketones,[13] yielding diverse heterocyclic compounds with excellent selectivity. As a continuation of this research program, we designed an unprecedented [1 + 5] strategy for the construction of a six-membered nitrogen heterocyclic framework. The key step involves an α-addition of a tertiary enamide and an aldehyde to an isocyanide carbon,[15] which was envisioned to act as a one-carbon component. We were pleased to discover that cascade reactions involving a [1 + 5] cycloaddition between isonitriles and *N*-formylmethyl-substituted tertiary enamides followed by oxidative aromatization and intermolecular acyl transfer indeed provide an efficient approach to substituted pyridines (Scheme 1).

Scheme 1. De Novo Synthesis of Substituted Pyridines



We initiated our study by examining the reaction between *N*-formylmethyl-substituted tertiary enamide **1a** and 4-methoxyphenyl isonitrile (**2a**) (Table 1). In acetonitrile at ambient temperature, Lewis acids such as $FeCl_3$, $Co(OAc)_2$, $NiCl_2$, $CuBr_2$, $Cu(OAc)_2$, $[Cu(CH_3CN)_4]PF_6$, and $InCl_3$ catalyzed either no reaction or the oligomerization of isonitrile (Table 1, entries 1−9). While virtually no reaction took place when 20 mol % $Sc(OTf)_3$, $Sm(OTf)_3$, or $SnCl_2$ was used (entries 10−12), a stoichiometric amount of $SnCl_2$ was found to be effective in promoting the reaction of **1a** with **2a** (entry 13). $Zn(OTf)_2$ was also able to drive the reaction to completion, albeit with a

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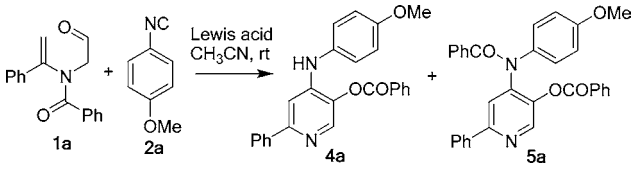
Table 1. Lewis Acid-Effected Reactions of 1a with 2a[a]



entry	Lewis acid (mol %)	time	product (% yield[b])
1	$FeCl_3$ (20)	7 days	–[c]
2	$FeCl_3$ (100)	15 min	oligomers[d]
3	$FeCl_3 \cdot 6H_2O$ (100)	1 day	oligomers[d]
4	$Co(OAc)_2$ (20)	1 day	–[c]
5	$NiCl_2$ (20)	3 days	–[c]
6	$CuBr_2$ (20)	1 day	oligomers[d]
7	$Cu(OAc)_2$ (20)	2 days	oligomers[d]
8	$[Cu(CH_3CN)_4]PF_6$ (20)	2 days	–[c]
9	$InCl_3$ (20)	2 days	–[c]
10	$Sc(OTf)_3$ (20)	6 days	**4a** (trace)
11	$Sm(OTf)_3$ (20)	3 days	**4a** (trace)
12	$SnCl_2$ (20)	9 days	**4a** (trace)
13	$SnCl_2$ (100)	2.5 h	**4a** (45) + **5a** (19)
14	$Zn(OTf)_2$ (100)	1 day	**4a** (45) + **5a** (16)
15[e]	$SnCl_2$ (100)	2.5 h	**4a** (59) + **5a** (17)
16[e]	$Zn(OTf)_2$ (100)	1 day	**4a** (63) + **5a** (18)

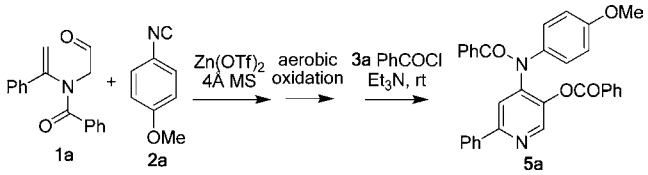
[a]The **1a**/**2a** ratio was 1:1.2, and the concentration of **1a** in acetonitrile was 20 mM. [b]Isolated yields. [c]No reaction. [d]Oligomers of isonitrile of **2a**. [e]4Å MS was added.

longer reaction time (entry 14). The addition of 4 Å molecular sieves (4Å MS) was beneficial to the reaction, leading to the formation of 5-benzoyloxy-4-(4-methoxyphenyl)amino-2-phenylpyridine (**4a**) and 4-[*N*-benzoyl-*N*-(4-methoxyphenyl)-amino]-5-benzoyloxy-2-phenylpyridine (**5a**) in yields of 63 and 18%, respectively, after workup (entry 16).

While other reactions such as direct intramolecular attack by the enamide at the tethered aldehyde, leading to dihydropyrrole,[13] and the Passerini reaction[16] could have taken place, insertion of isonitrile **2a** into enamide **1a** prevailed over these competitive pathways under the above-described conditions. In addition, the formation of pyridines **4a** and **5a** implied that oxidative aromatization and benzoyl transfer occurred. On the basis of this mechansitic hypothesis and also to facilitate isolation of the product, we slightly modified the workup procedure to include leaving the crude organic extracts exposed to air at room temperature overnight followed by addition of an excess amount of benzoyl chloride (**3a**). To our delight, the reaction produced **5a** exclusively in 91% yield (Table 2, entry 1). Solvent screening indicated that dichloromethane, tetrahydrofuran (THF), and toluene were less effective reaction media, leading to decreased yields and long reaction times (entries 2–4). Although heating accelerated the reaction, the yield deteriorated (entries 5 and 6). Performing the reaction in the presence of 0.5 equiv of $Zn(OTf)_2$ still produced **5a** in a good yield (entry 7). However, further reducing the $Zn(OTf)_2$ loading lowered the reaction efficiency significantly (entries 8 and 9). Increasing the concentration from 20 to 100 mM led to faster conversion of reactants at the expense of a reduced yield of **5a**, as the Passerini reaction involving water to give the corresponding α-hydroxyacetamide[16] became competitive (entry 10 vs entry 1).

Under the optimized conditions, the reaction scope was investigated (Table 3). All of the tested aryl-substituted tertiary

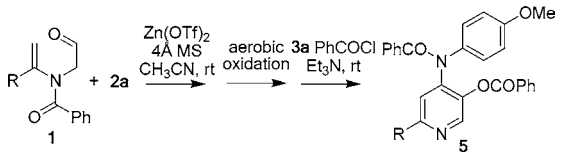
Table 2. $Zn(OTf)_2$-Mediated Reaction of 1a with 2a[a]



entry	$Zn(OTf)_2$ (mol %)	solvent	temp	time	yield (%)[b]
1	100	CH_3CN	rt	10 h	91
2	100	CH_2Cl_2	rt	3 h	75
3	100	THF	rt	3 days	19
4	100	toluene	rt	4 days	23
5	100	CH_3CN	40 °C	7 h	89
6	100	CH_3CN	reflux	1.5 h	61
7	50	CH_3CN	rt	2 days	86
8	20	CH_3CN	rt	2 days	trace
9	10	CH_3CN	reflux	2 days	trace
10[c]	100	CH_3CN	rt	6 h	77

[a]The **1a**/**2a** ratio was 1:1.2, and the concentration of **1a** in acetonitrile was 20 mM. [b]Isolated yields. [c]The concentration of **1a** was 100 mM.

Table 3. Synthesis of Substituted Pyridines 5[a]



entry	**1**	R	time (h)	**5**	yield (%)[b]
1	**1a**	Ph	10	**5a**	91
2	**1b**	4-FC_6H_4	7	**5b**	85
3	**1c**	4-ClC_6H_4	8	**5c**	75
4	**1d**	3-ClC_6H_4	7	**5d**	90
5	**1e**	2-ClC_6H_4	7	**5e**	82
6	**1f**	4-BrC_6H_4	8	**5f**	91
7	**1g**	2,4-$Cl_2C_6H_3$	10	**5g**	87
8	**1h**	4-$NO_2C_6H_4$	16	**5h**	64
9	**1i**	4-PhC_6H_4	8	**5i**	82
10	**1j**	4-MeC_6H_4	5	**5j**	84
11	**1k**	4-$MeOC_6H_4$	5	**5k**	77

[a]The **1a**/**2a** ratio was 1:1.2, and the concentration of **1** in acetonitrile was 20 mM. [b]Isolated yields.

enamides acted as excellent substrates to react with isonitrile **2a**, producing corresponding products **5a–k** in good to excellent yields. However, the reaction rate was influenced by the nature of the substituent on the enamide benzene ring. For example, halogen- (**1b–g**) and phenyl-substituted (**1i**) enamides completed the reaction with **2a** within 10 h (entries 1–7 and 9), while 4-nitrophenyl-substituted reactant **1h** took a longer reaction time (16 h) to form **5h** in 64% yield (entry 8). The presence of an electron-donating group on the phenyl moiety significantly accelerated the rate of reaction, as the reactions of **1j** and **1k** with **2a** reached completion in 5 h, forming **5j** and **5k** in good yields (entries 9–11). Since the nucleophilic addition of isonitrile **2a** to the aldehyde of **1** to afford a nitrilium intermediate was the common initiating step for all of the enamides, we assumed that the overall reaction rate was mainly determined by the reactivity of the tertiary enamide moiety. Tertiary enamides containing an electron-richer aromatic substituent clearly showed higher enaminic reactivity.

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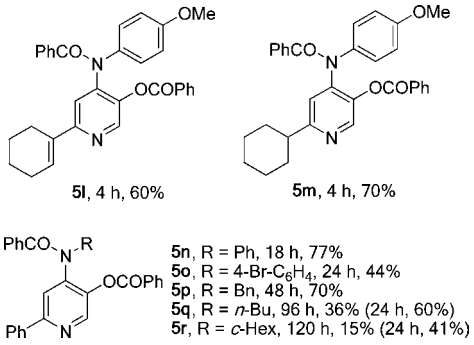
In addition to aryl-substituted enamides **1a**–**k**, enamides bearing an alkenyl or alkyl substitutent participated in the reaction equally well. Under identical conditions, 2-cyclohexenyl- and 2-cyclohexyl-substituted pyridine derivative **5l** and **5m** were synthesized in yields of 60 and 70%, respectively (Chart 1).

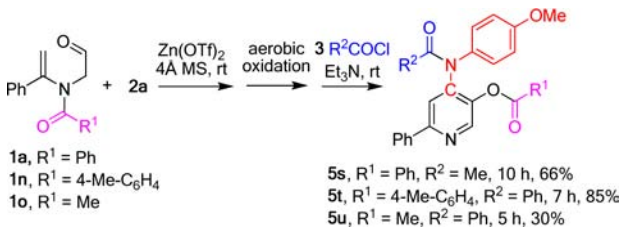
Chart 1. Synthesized Pyridine Derivatives 5l–r



The reaction was readily expanded to other isonitriles, including aliphatic ones. The reaction of phenyl isonitrile (**2b**) with **1a**, for instance, furnished product **5n** in 77% yield. 4-Bromophenyl isonitrile (**2c**), a less nucleophilic isonitrile, underwent a similar reaction to afford product **5o**, albeit with a decreased reaction velocity and a diminished yield. When aliphatic isonitriles were employed under identical conditions, unexpected and markedly varied results were obtained. For example, benzyl isonitrile (**2d**) needed 48 h to complete its reaction with enamide **1a** to afford **5p** in 70% yield. The reactions of *n*-butyl isonitrile (**2e**) and cyclohexyl isonitrile (**2f**) were extremely slow, affording products **5q** and **5r** in yields of 36 and 15% after 4 and 5 days, respectively (Chart 1). As revealed by ^{1}H NMR spectroscopy [see the Supporting Information (SI)], the strikingly abnormal reactivity of **2e** and **2f** was due to their strong association with zinc ion. To circumvent this problem, excess amounts of these aliphatic isonitriles were used. In the presence of 4 equiv of **2e** or **2f**, the reaction proceeded much more efficiently to give an improved yield of 60% for **5q** or 41% for **5r**, respectively, after an identical consecutive reaction sequence (Chart 1).

To understand the effect of the *N*-acyl group on the reactivity of the enamide and the regioselectivity of the acyl transfer process, three-component reactions were conducted using different enamides and acyl chlorides. The tandem reaction between **1a** and **2a** followed by oxidative aromatization and subsequent acylation with acetyl chloride (**3b**) yielded product **5s** in 66% yield (Scheme 2). A similar reaction of 4-methylbenzoylated enamide **1n** with **2a** and **3a** produced **5t** in 85% yield. It is noteworthy that the *N*-acyl group of enamide **1** is transferred chemoselectively to the 5-hydroxy oxygen atom while the externally added acyl chloride **3** acylates only the 4-amino group. No scrambling products were observed. Noticeably, the reaction of acetyl-substituted enamide **1o** with **2a** and **3a** furnished the desired product **5u** in only 30% yield along with the α-hydroxyacetamide byproduct derived from the Passerini reaction (21%).[16] This indicates the lower nucleophilic reactivity of acetyl-substituted enamide **1o** compared with aroyl-substituted enamides **1a** and **1n**, allowing the addition of a water molecule to the nitrilium intermediate. It is important to point out that in contrast to their secondary enamide analogues, which are aza–ene components in nucleophilic reactions,[17] the nucleophilicity of tertiary enamides **1** is correlated with the electron density of the enaminic carbon, which is mainly dictated by delocalization of nitrogen lone-pair electrons into carbon–carbon double bond. In comparison with acetyl-substituted enamide **1o**, the higher nucleophilicity of aroyl-substituted enamides is most likely due to the cross-conjugation effect between the aryl and carbonyl moieties, which concomitantly alleviates the delocalization of the nitrogen lone-pair electrons into the carbonyl group. The cross-conjugation effect has been substantiated by the observation of a lower energy barrier for $C_{C=O}$–N bond rotation in benzamide relative to acetamide.[18]

Scheme 2. Sequential Three-Component Reactions



To shed light on the mechanistic pathway for the N-to-O acyl transfer process, a crossover experiment was conducted. Treatment of equimolar amounts of enamides **1f** and **1n** with isonitrile **2a** followed by auto-oxidation and reaction with benzoyl chloride **3a** under our standard conditions led to the formation of a mixture of four pyridine products. As evidenced by HPLC-MS analysis, they are two pairs of constitutional isomers, with one isomer containing an *O*-benzoyl substituent and the other an *O*-4-methylbenzoyl substituent. These results indicate that the acyl group is transferred in an intermolecular fashion. This point was further validated by adding external 3-hydroxypyridine into the reaction mixture, which led to the observation of 3-benzoyloxypyridine (see the SI).

On the basis of the aforementioned experimental results, the plausible reaction mechanism shown in Scheme 1 is proposed. $Zn(OTf)_2$-promoted nucleophilic addition of isonitrile **2** to the aldehyde of enamide **1** affords nitrilium intermediate **A**, which is trapped by the enamide to provide *N*-acyliminium ion **B**. Tautomerization then gives a mixture of heterocyclic intermediates **C** and **D**. Oxidative aromatization of **D** proceeds under aerobic conditions to afford *N*-acylpyridinium ion **E**, which is an excellent acylating agent by analogy to the *N*-acyl-4-dimethylaminopyridine adduct. Intermolecular transfer of the *N*-acyl group to the 5-hydroxy group yields trisubstituted pyridine **4**. Acylation of the 4-amino group by external acyl chloride **3** then furnishes the final product **5**. While trapping of reactive nitrilium intermediates by heteroatom nucleophiles is well-known,[15] carbon nucleophiles have been rarely used for this purpose.[19] To the best of our knowledge, the work reported here represents the first example wherein enamides serve as nucleophiles to intercept nitrilium intermediates.

In summary, we have established an unprecedented method for the construction of pyridine rings through a cascade reaction of tertiary enamides with isonitriles. The sequence leading to the pyridine comprises an initial [1 + 5] cycloaddition of an isonitrile with an *N*-formylmethyl-substituted enamide, a facile aerobic oxidative aromatization, intermolecular acyl transfer from the pyridinium nitrogen to the oxygen of the 5-hydroxy group, and finally acylation of the 4-

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amino group by an external acylating agent. The high reaction efficiency and wide reaction scope make this method a fast and straightforward route to diversely substituted pyridines that are analogues of acetylcholinesterase (AChE) inhibitors.[20] The finding that the enamide is an effective C-nucleophilic partner in the α-addition of the isonitrile should open new avenues for further exploration of the synthetic potential of isonitriles.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, characterization and spectroscopic data, X-ray structures (CIF). 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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