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Regioselective TfOH-mediated hydroamidation of ynamides with nitriles

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ABSTRACT

A new TfOH-mediated reaction of ynamides with nitriles as nucleophiles has been developed. The reaction works efficiently under mild reaction conditions to afford a new class of α-acylaminoenamides readily via the intermediacy of keteniminium ion. The reaction displays generality and a broad substrates scope. Additionally, the α-acylaminoenamides could be transformed to highly substituted pyridine, 4-aminopyrimidine or isoquinoline cores.

1. Introduction

N-vinyl amide derivatives, a fundamental sort of compounds, have been proved to be the elemental, significant, and versatile building blocks in organic synthesis, as well as a skeletal part of the massive and diverse natural products.[1] For example, *N*-vinyl amides have been widely used to construct nitrogen heterocyclic frameworks, such as pyridines, pyrimidines, and isoquinolines.[2] To the best of our current knowledge, the conventional preparative methods mainly depend on direct addition of amides to alkynes,[3] the coupling reaction of amides with olefin,[4] and acylation of imines.[5] However, these protocols suffered from either low yields or lack of regiocontrol on the double bond geometry. Thus, the development of novel approaches, especially as part of functionalized scaffolds with high efficiency, flexibility, and good regioselectivity, remains an urgent and challenging synthetic goal.

Ynamides which constitute an important subgroup of alkynes, represent one of the most significant and versatile *N*-containing building blocks in organic synthesis.[6] Cyclization reactions using ynamides generally lead to heterocyclic compounds with very high regio- and stereoselectivity.[7] Recently, Zhao reported ynamides could be used as coupling reagents to construct amide and peptide bonds through the hydroacyloxylation of ynamides and the subsequent aminolysis of α-acyloxyenamide.[8] Keteniminium ion, a reactive cationic intermediate conveniently prepared from ynamide, has proven to be an especially useful subclass.[9] A brønsted acid introduced formal [2+2+2] cycloadditions of ynamides with nitriles for de novo synthesis of highly substituted pyridine cores were developed.[10] Lately, our group developed the TfOH-mediated [2+2+2] cycloadditions of ynamides with nitriles, which afforded 4-aminopyrimidine derivatives efficiently (Scheme 1).[11] In this paper, we describe such a TfOH-mediated amidation, allowing the facile and efficient synthesis of various α-acylaminoenamides. And the α-acylaminoenamide reacted with nitriles or alkynes to further generate highly substituted pyridine, 4-aminopyrimidine or isoquinoline cores.

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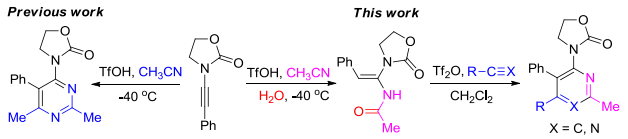


Scheme 1. TfOH-mediated Intermolecular Reaction of Ynamides with Nitriles.

2. Results and discussion

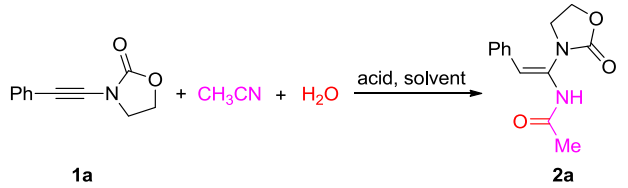
In our previous work, *N*-vinyl amides could be isolated when the ynamides reacted with acetonitrile in the presence of H_2O. Based on this result, we began our studies by utilizing **1a** as model material to optimize the reaction conditions. At the onset, the desired product **2a** was obtained in 86% yield when treated with 1.0 equivalent of TfOH in acetonitrile (Table 1, entry 1). Among the TfOH evaluated, different intensity of acids were also tested, but the latter were not superior in terms of yield and *E*/*Z* selectivity (entries 2–7). We also screened some other solvents, the reaction only proceeded in dichloromethane, and we separated the target product in 69% yield (entry 8). Attempts to change the amount of the acid or temperature, resulted in the decrease of the yields (entries 12–16).

Having the optimized reaction conditions in hand, we then explored the substrates scope and limitations of the reaction (Table 2). We initially focused on the reactivity of ynamides **1a**–**n** bearing oxazolidinone as an electron withdrawing group. Besides ynamide **1a**, compounds **1b**–**e** with a phenyl group bearing *para*-substituents (electron donating groups or electron withdrawing, such as methyl, methoxyl and trifluoromethyl) at the R^1 position were well tolerated, which afforded the desired products **2b**–**e** in 66–92% yields. Notably, when ynamide **1e** was employed, the reaction delivered the desired product as a *Z*/*E* isomer mixture with a ratio of 1:2.6. The reaction still performed nicely when the ynamides **1f**–**h** containing fluoro, chloro and bromo groups to provide the products in yields of 61–87%. Gratifyingly, the ynamides containing *ortho* or *meta*-substituents (**1i** and **1j**) of the phenyl group were well tolerated, which converted to the corresponding target products in fair to good yields. The ynamides **1k**–**m** (with different substituents of the oxazolidinone groups) fruitfully delivered the corresponding target products **2k**–**m** in good yields. We also investigated the reactivity of ynamide substituted by alkyl chain at the R^1 position. In this case **2n** was isolated in 71% yield and as *Z*/*E* isomers with a ratio of 1:1. Among the oxazolidinone groups evaluated, the reactions were also found to be compatible with tosyl (**2o**–**q**) or mesyl (**2r**) as electron withdrawing group, and the latter being inferior in terms of yields. Table 2 indicated that oxazolidinone groups remain as the preferred protecting groups over tosyl or mesyl because of the satisfactory yields. This phenomenon could be attributed to a portion of the keteniminium ions protected by tosyl or mesyl underwent hydrolysis to deliver the byproducts.

In addition, to further test the efficiency of the TfOH-mediated reaction and push it to its limits, we next investigated the possibility of ynamide **1a** reacted with other nitriles in dichloromethane (Scheme 2). In consideration of the decrease of concentration of nitriles, we decided to raise the amount of TfOH to 2.0 equivalents to perform the reaction. Firstly, we focused our attention on alkyl nitriles. Not surprisingly, the valeronitrile and 2-(4-methoxyphenyl) acetonitrile performed excellently to afford the desired products **3a** and **3b** in 91% and 83% yields, respectively. Interestingly, when benzonitrile, 4-chlorobenzonitrile or cinnamonitrile were employed, phenylacetylamides **4a**–**c** were isolated in the yields of 28%–47%.

Further chemical transformation of the as synthesized *N*- vinyl amides **2a** or **2h** were also explored, as depicted in Scheme 3. For example, the reaction of amides with acetonitrile or valeronitrile in dichloromethane could furnish the corresponding pyrimidine derivative products in moderate yields. Phenylacetylene was also tested in the same conditions, afforded the pyridine derivatives **6a** in 33% yield or **6b** in 35% yield.[12] And when dichloroethane was used as solvent, the amides could generate the isoquinoline derivatives **7a** in 30% yield or **7b** in 31% yield at 80 °C.

Table 1
Optimization Studies.[a]



entry	acid	solvent	T (°C)	yield[b] (%)
1	TfOH	CH_3CN	−40	86
2	Tf_2NH	CH_3CN	−40	80[c]
3	HPF_6[d]	CH_3CN	−40	85[e]
4	TsOH	CH_3CN	−40	0
5	CSA	CH_3CN	−40	0
6	HCl	CH_3CN	−40	0
7	$BF_3{\cdot}Et_2O$	CH_3CN	−40	31
8[f]	TfOH	CH_2Cl_2	−40	69
9[f]	TfOH	THF	−40	0
10[f]	TfOH	toluene	−40	0
11[f]	TfOH	dioxane	15	0
12	TfOH	CH_3CN	−20	75
13	TfOH	CH_3CN	0	46
14	TfOH	CH_3CN	20	21
15[g]	TfOH	CH_3CN	−40	25
16[h]	TfOH	CH_3CN	−40	81

[a] Unless noted otherwise, all reactions were conducted using 0.15 mmol of ynamide **1a** in the presence of acid (1.0 equiv) and H_2O (2.0 equiv) under N_2 atmosphere for 0.5 h at −40 °C.
[b] Isolated yields.
[c] *Z*:*E* = 3:1.
[d] HPF_6 (wt% 60–65% solution in water).
[e] *Z*:*E* = 3:1.
[f] CH_3CN (1.2 equiv) was added.
[g] TfOH (0.2 equiv).
[h] TfOH (2.0 equiv).

2.1. Proposed mechanism

We also proposed a plausible mechanism for the formation of **2** (**3**) and **4**. As depicted in Scheme 4, ynamide **1a** was activated by H^+ in the presence of TfOH to produce keteniminium ion **I**.[13] Nitriles attacked keteniminium ion **I** to form intermediate **II**. Then intermediate **II** was attacked by H_2O to produce intermediate **III**. **2(3)** were subsequently obtained through tautomerization. With arylnitriles (R_3 = Aryl) as the reactants, intermediate **III** was more stable due to the conjugated structure and afforded the imine **IV** in the presence of TfOH. Then H_2O attacked the imine **IV**, forming the hydroxyl-substituted amides **V**. Finally, the departure of 2-oxazolidone of **V** gave the products **4**.

3. Conclusion

In summary, we had demonstrated an efficient, facile, and flexible strategy for the preparation of synthetically useful α-acylaminoenamides through TfOH-mediated amidation of ynamides with nitriles. This reactivity could be exploited for other notable features, providing a straightforward, modular access to desired

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