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Task-specific acidic ionic liquid-catalyzed efficient synthesis of β-enaminolactones from alkynoates and β-amino alcohols†

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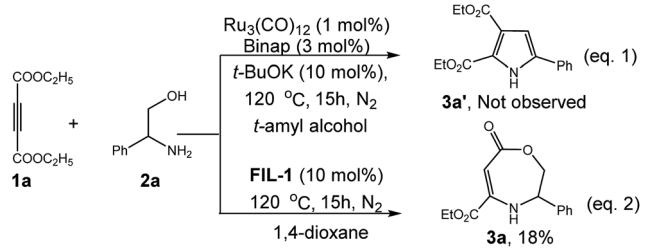
By employing task-specific acidic ionic liquid as an efficient catalyst, a new method for the straightforward synthesis of β-enaminolactones has been demonstrated. A series of alkynoates in combination with various β-amino alcohols was efficiently converted into the desired products in good to excellent yields upon isolation. The skeleton of the seven-membered ring is generated *via* tandem intermolecular hydroamination and intramolecular transesterification processes. The developed synthetic protocol furnishes the desired products in a step- and atom-economic fashion with the advantages of high yields, broad substrate scope, good functional tolerance, and operational simplicity, offering an important basis for the construction of β-enaminolactones.

β-Amino acids constitute a highly significant branch in organic chemicals, which have been found to possess diverse bioactivities and are employed as useful building blockings for the preparation of β-lactam antibiotics and heterocycles. In addition, β-amino acid derivatives frequently occur in numerous biologically active natural products.[1] Among various compounds investigated to date, β-enaminolactone derivatives, the precursors of enantiopure β-amino acids, are the main structural components of many bioactive natural products that have attracted significant attention.[2]

Owing to the abovementioned interesting functions of β-enaminolactone, several synthetic protocols have been nicely demonstrated during the past few decades to access these compounds.[3–8] For instance, Abarbri and coworkers[3] first reported the reaction of ethyl perfluorobut-2-ynoate with amino alcohols to generate 5-(perfluoroalkyl)-3,4-dihydro-2*H*-[1,4] oxazepin-7-ones *via* the intermolecular Michael addition and lactone formation. In 2005, Dechoux's group reported an efficient method for the synthesis of β-enaminolactones[4] *via* the condensation of acetonedicarboxylate with β-amino alcohols followed by an intramolecular cyclization step. However, during this synthesis, the reaction intermediates needed to be isolated and it required excess NaH to achieve the cyclization; moreover, an additional neutralization manipulation by adding NH_4Cl/H_2O was essential to obtain the desired products after the completion of the reaction. From the viewpoint of green chemistry, the development of efficient shortcuts for accessing β-enaminolactones from easily available feedstocks would be of high significance.

As a part of our program aimed at developing new synthetic methodologies for the construction of heterocycles,[17] we initially had the idea to develop a ruthenium-catalyzed synthesis of ester-substituted pyrrole **3a′** from alkynoate **1a** and β-amino alcohol **2a** *via* dehydrogenative cyclization (Scheme 1, eqn (1)). However, we failed to obtain even traces of the anticipated product, and a small portion of β-enaminolactone **3a** was obtained. Further investigations showed that the ruthenium catalyst was not essential for the product formation (**3a**), whereas the presence of 10 mol% of $AlCl_3$ was able to improve the yield of **3a** to 18% (eqn (2)). Upon a thorough investigation of this new observation, a straightforward method for the efficient synthesis of β-enaminolactones from alkynoates and β-amino alcohols using a task-specific sulfonic ionic liquid as the catalyst was realized and has been reported herein.

Our initial investigation was to develop a more efficient reaction system by choosing the synthesis of β-enaminolactone **3a** from diethyl but-2-ynedioate **1a** and 2-amino-2-phenylethanol **2a** as a model reaction. First, the reaction in



Scheme 1 The new observation leading to β-enaminolactone.

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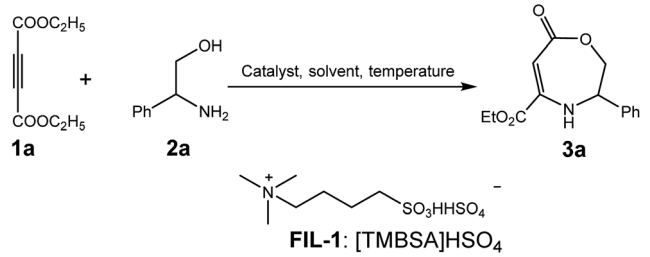
t-amyl alcohol was performed at 120 °C for 12 h, and several conventional Lewis acid catalysts were tested (Table 1, entries 1–7); it was found that $Cu(OTf)_2$ or $Zn(OTf)_2$ shows good performance in affording the desired product **3a**. However, in the absence of an acid catalyst, the desired product was not obtained (Table 1, entry 8), indicating that the acidic catalyst played a crucial role in the reaction. Moreover, attracted by the significant advantages, such as the designability, easy recovery, and reusability,[9–15] of task-specific acidic ionic liquids, we evaluated the utility of a sulfonic-functionalized ionic liquid[16] (TSFIL-1: $[TMBSA]HSO_4$) as a catalyst. Gratifyingly, this catalyst exhibited an excellent activity in the production of product **3a** (entries 9–11), and 10 mol% catalyst loading was essential to afford a satisfactory yield (entry 9). Further, changes in the reaction temperatures led to diminished product yields (Table 1, entries 12 and 13), implying that a lower temperature significantly decreased the reaction rate, whereas increasing this parameter would lower the product stability. However, use of toluene, DMF, DMAc, DMSO, and 1,4-dioxane as the solvents proved to be totally ineffective or less effective for the formation of products when compared with *t*-amyl alcohol (Table 1, entries 14–18). Finally, $[TMBSA]HSO_4$ was used as both the solvent and the catalyst and it only gave a 77% yield, which could be rationalized since a viscous ionic liquid was not beneficial for the interaction of substrates. Based on these results, the optimal reaction conditions were obtained and are indicated in entry 9 of Table 1.

Table 1 Screening of the reaction conditions[a]



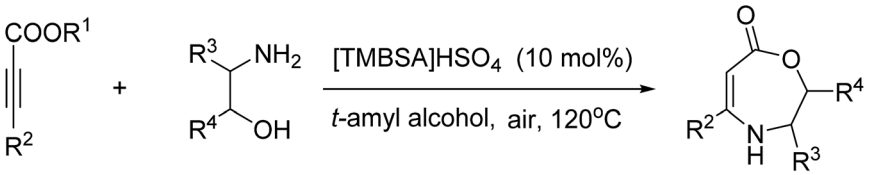
Entry	Catalyst (mol%)	Temp. (°C)	Solvent (2.0 mL)	Yield[b] (%)
1[c]	$AlCl_3$ (10)	120	*t*-Amyl alcohol	18
2	$ZnCl_2$ (10)	120	*t*-Amyl alcohol	35
3	$FeCl_3$ (10)	120	*t*-Amyl alcohol	40
4	$Yb(OTf)_3$ (10)	120	*t*-Amyl alcohol	40
5	$Cu(OTf)_2$ (10)	120	*t*-Amyl alcohol	78
6	$Al(OTf)_3$ (10)	120	*t*-Amyl alcohol	80
7	$Zn(OTf)_2$ (10)	120	*t*-Amyl alcohol	84
8	None	120	*t*-Amyl alcohol	—[d]
9	TSILs (10)	120	*t*-Amyl alcohol	94
10	TSILs (5)	120	*t*-Amyl alcohol	92
11	TSILs (15)	120	*t*-Amyl alcohol	90
12[c]	TSILs (10)	100	*t*-Amyl alcohol	36
13	TSILs (10)	140	*t*-Amyl alcohol	87
14	TSILs (10)	120	Toluene	—[d]
15	TSILs (10)	120	DMF	—[d]
16	TSILs (10)	120	DMAc	22
17	TSILs (10)	120	DMSO	56
18	TSILs (10)	120	1,4-Dioxane	14
19	TSILs (1 mL)	120	None	77

[a] Reaction conditions: unless otherwise stated, the reaction mixture of dimethyl acetylenedicarboxylate (**1**) (0.5 mmol), 2-amino-2-phenylethanol (**2**) (0.6 mmol), catalyst loaded in different solvents (2.0 mL) was stirred at 120 °C for 12 h under atmospheric condition. [b] GC yield using *n*-hexadecane as an internal standard. [c] Under a N_2 atmosphere. [d] No product detectives.

With the availability of the optimized reaction conditions, we subsequently examined the generality of the synthetic protocol. A variety of alkynoates (**1**) in combination with β-amino alcohols (**2**) were tested. As shown in Table 2, all the reactions smoothly proceeded and furnished the desired products in good to excellent isolated yields. Diethyl but-2-ynedioate **1a** reacted with 2-amino-2-phenylethanol **2a** and 2-amino-3-phenylpropan-1-ol **2c** to provide the products **3a** and **3c** in 86% and 94% yields, respectively (Table 2, entries 1 and 3). Moreover, even a steric-hindered substrate, such as 2-amino-1,2-diphenylethanol **2b**, also underwent smooth transformation with 2-amino-2-phenylethanol **2a**, affording the desired product in 78% yield (Table 2, entry 2). Similarly, the reactions of **1a** with amino alcohols **2d** and **2e** produced the corresponding products **3d** and **3e** in excellent yields (Table 2, entries 4 and 5), respectively. Interestingly, the less reactive ethyl 3-phenylpropiolate **1c** could also generate the desired coupling products in moderate to good yields, demonstrating that the developed chemistry was applicable for a broad substrate scope (Table 2, entries 6–10). Note that amino alcohols (**2a** and **2c**) with a phenyl group or a benzyl substituent could afford higher yields (Table 2, entries 6 and 9) than those with an alkyl group (Table 2, entries 1 and 3–5). Moreover, amino alcohols with an isopropyl group gave a relatively lower yield (Table 2, entry 8), presumably because of the influence of its strong electron-donating effect, thus deactivating the ester group. On the other hand, the secondary alcohols such as 1-aminopropan-2-ol **2f** reacted with alkynoate **1c** to give the corresponding product **3j** in 74% yield (Table 2, entry 10). Note that various functional groups such as 4-Cl, 4-Br, 4-F, and 4-CH_3CO on the phenyl ring of alkynoates (**1d–1g**) were well tolerated, affording the corresponding products in good to excellent yields (Table 2, entries 12–14, 19 and 20). Similarly, electron-donating groups on the aryl ring of the substrates **2** were also compatible with the transformation (Table 2, entries 15–17). The retention of these functional groups would offer the potential for further molecular complexity *via* chemical transformation.

To gain insight into the reaction information, we performed the control experiments. It was found that hydroamination between alkynoate **1a** and amino alcohol **2a** completed in 5 minutes without any catalyst or additive. Then, the resulting enamine intermediate (**3a–l**) under standard conditions furnished the cyclization product **3a** in an almost quantitative yield (Scheme 2). This result, in combination with the fact that in the absence of a catalyst, product **3a** cannot be formed (Table 1, entry 8), indicates that the acidic catalyst plays a crucial role in the activation of the ester group. These findings suggest that the product formation is initiated by fast intermolecular hydroamination followed by $[TMBSA]HSO_4$-catalyzed intramolecular transesterification.

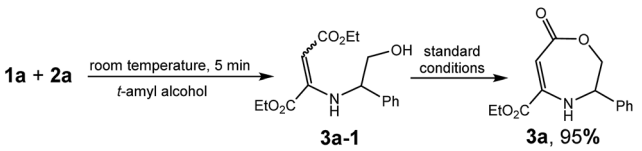
Table 2 Efficient synthesis of 3,4-dihydro-1,4-oxazepin-7(2*H*)-one derivatives[a]



1 2 3

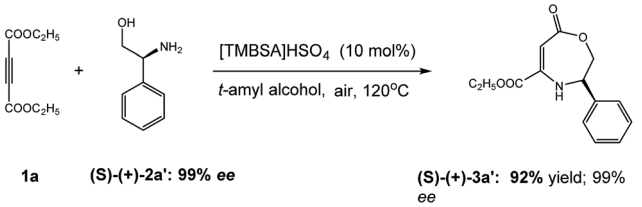
Entry	1	2	3, yield (%)
1	**1a**: R^1 = Et, R^2 = CO_2Et	**2a**: R^3 = Ph, R^4 = H	**3a**, 86
2	**1a**: R^1 = Et, R^2 = CO_2Et	**2b**: R^3 = Ph, R^4 = Ph	**3b**, 78
3	**1a**: R^1 = Et, R^2 = CO_2Et	**2c**: R^3 = $PhCH_2$, R^4 = H	**3c**, 94
4	**1b**: R^1 = CH_3, R^2 = CO_2CH_3	**2a**: R^3 = Ph, R^4 = H	**3d**, 80
5	**1b**: R^1 = CH_3, R^2 = CO_2CH_3	**2c**: R^3 = $PhCH_2$, R^4 = H	**3e**, 90
6	**1c**: R^1 = Et, R^2 = Ph	**2a**: R^3 = Ph, R^4 = H	**3f**, 68
7	**1c**: R^1 = Et, R^2 = Ph	**2d**: R^3 = CH_3, R^4 = H	**3g**, 78
8	**1c**: R^1 = Et, R^2 = Ph	**2e**: R^3 = $(CH_3)_2CH$, R^4 = H	**3h**, 58
9	**1c**: R^1 = Et, R^2 = Ph	**2c**: R^3 = $PhCH_2$, R^4 = H	**3i**, 68
10	**1c**: R^1 = Et, R^2 = Ph	**2f**: R^3 = H, R^4 = CH_3	**3j**, 74
11	**1d**: R^1 = Et, R^2 = 4-ClPh	**2d**: R^3 = CH_3, R^4 = H	**3k**, 84
12	**1e**: R^1 = Et, R^2 = 4-BrPh	**2d**: R^3 = CH_3, R^4 = H	**3l**, 89
13	**1d**: R^1 = Et, R^2 = 4-ClPh	**2e**: R^3 = $(CH_3)_2CH$, R^4 = H	**3m**, 60
14	**1e**: R^1 = Et, R^2 = 4-BrPh	**2e**: R^3 = $(CH_3)_2CH$, R^4 = H	**3n**, 62
15	**1h**: R^1 = Et, R^2 = 4-CH_3Ph	**2d**: R^3 = CH_3, R^4 = H	**3o**, 72
16	**1i**: R^1 = Et, R^2 = 4-CH_3OPh	**2d**: R^3 = CH_3, R^4 = H	**3p**, 70
17	**1h**: R^1 = Et, R^2 = 4-CH_3Ph	**2e**: R^3 = $(CH_3)_2CH$, R^4 = H	**3q**, 56
18	**1i**: R^1 = Et, R^2 = 4-CH_3OPh	**2e**: R^3 = $(CH_3)_2CH$, R^4 = H	**3r**, 50
19	**1f**: R^1 = Et, R^2 = 4-FPh	**2d**: R^3 = CH_3, R^4 = H	**3s**, 70
20	**1g**: R^1 = Et, R^2 = 4-CH_3COPh	**2d**: R^3 = CH_3, R^4 = H	**3t**, 75

[a] Reaction conditions: unless otherwise stated, the reaction mixture of dimethyl acetylenedicarboxylate (**1**) (0.5 mmol), 2-amino-2-phenylethanol (**2**) (0.6 mmol), and [TMBSA]HSO_4 (10 mol%) in *t*-amyl alcohol (2.0 mL) was stirred at 120 °C for 12 h under atmospheric condition.



Scheme 2 Control experiments.

Finally, we demonstrated the utility of the developed new method. The reaction of the diethyl but-2-ynedioate **1a** with enantiopure amino alcohol (*S*)-(+)-**2a**′ produced the enantiopure enaminolactone (*S*)-(+)-**3a**′ in an excellent yield with retention of the chiral configuration (Scheme 3). This result shows that the task-specific acidic ionic liquid-catalyzed protocol is also applicable for the preparation of chiral β-enaminolactones from chiral amino alcohols.



Scheme 3 Synthesis of chiral β-enaminolactone.

In summary, by employing a task-specific sulfonic ionic liquid as the catalyst, we demonstrated an environmentally friendly and straightforward approach for the versatile synthesis of β-enaminolactones from readily available amino alcohols and alkynoates for the first time. The synthetic protocol proceeds *via* tandem intermolecular hydroamination and intramolecular transesterification processes; moreover, it furnished the desired products in a step- and atom-economic fashion with the advantages of high isolated yields, broad substrate scope, good functional tolerance, and operational simplicity, which offers an important basis for the construction of β-enaminolactones.

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