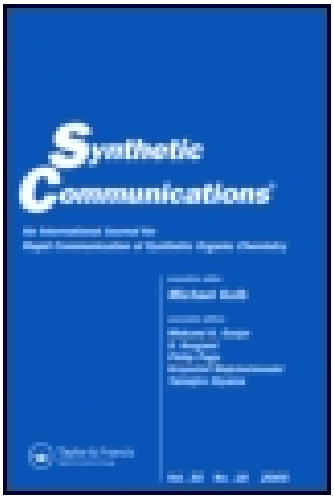

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Ytterbium(III) Triflate-Catalyzed Stereoselective Synthesis of β-Lactams via [2+2] Cyclocondensation in Ionic Liquid

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Ytterbium(III) Triflate–Catalyzed Stereoselective Synthesis of β-Lactams via [2 + 2] Cyclocondensation in Ionic Liquid

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Abstract: Catalyzed by ytterbium(III) triflate [$Yb(OTf)_3$], β-lactams were stereoselectively synthesized from imines and acetyl chlorides in ionic liquid under mild conditions. The ionic liquid and catalyst could be recycled and reused as opposed to traditional solvent–catalyst systems.

Keywords: [2 + 2] Cyclocondensation, ionic liquid, β-lactams, ytterbium triflate

INTRODUCTION

β-Lactams, as the key components of many biologically active compounds such as penicillin and cephalosporin antibiotics, have already been intensively studied.[1–3] There are many of methods for the construction of the azetidinone ring,[1] such as rhodium-catalyzed carbonylation of an aziridine,[4] rhodium-catalyzed intramolecular insertion of an α-diazo amide into a C-H bond,[5] copper-catalyzed coupling of an alkyne with nitrone,[6,7] amino-ether-catalyzed reaction of ester enolates with imines,[8] ketene–imine cycloaddition,[9–15] and so on.[16] Among them, the annelation of acetylchlorides with imines has proven to be a versatile and convenient procedure. However, the reaction requires more than a stoichiometric amount of

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triethylamine (about 3 equiv.), which cannot be recovered and reused after the usual aqueous workup. Particularly, this reaction also needs a large amount of organic solvents, which generate large amounts of waste in industrial processes. Considering the ecological problems, an environmentally acceptable process will be of high interest.

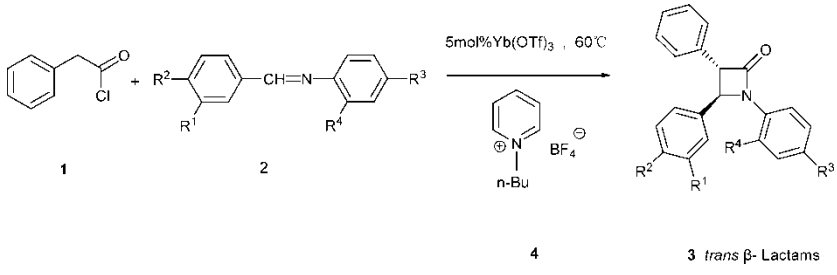
In recent years, ionic liquids (ILs) have emerged, which are organic salts whose ions do not pack well and remain liquid at room temperature.[17,18] They have unique properties such as a wide liquid range, good solvency, tunable polarity, high thermal stability, negligible vapor pressure, and ease of recyclability. In addition, ytterbium(III) triflate is a novel, recyclable catalyst that has been applied in many organic reactions.[19–22] In this article, we report that ytterbium(III) triflate catalyzed the synthesis of β-lactams in ionic liquid [Nbupy][BF_4] (**4**) (Scheme 1).

RESULTS AND DISCUSSION

The preparation of β-lactams involves two steps: (a) generation of ketenes in situ by dehydrohalogenation of acetylchlorides in the presence of ILs and $Yb(OTf)_3$, and (b) [2 + 2] cyclocondensation of imines with ketenes.

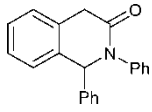
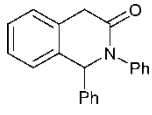
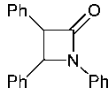
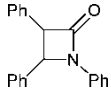
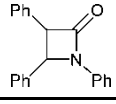
Initially, we want to synthesize N-substituted 1-aryl-3-oxo-1,2,3,4-tetrahydroisoquinolines, which, according to the work of Venkov and Mollov,[23] were synthesized from arylacetyl chlorides and Schiff bases in the presence of aluminum chloride as catalyst. However, when the reaction was catalyzed by $Yb(OTf)_3$ in [Nbupy][BF_4], we gained not isoquinolines but β-lactams. Furthermore, the result of the use of ILs and $Yb(OTf)_3$ was similar to that of only ILs, but the yield of the former was higher than that of the latter. We assumed that one side of pyridinium-based IL was alkaline, and ketene was generated in it; the other side of the carbonyl of ketenes was activated by $Yb(OTf)_3$ and the electronegativity of α-carbon was increased to accelerate the reaction. The result is shown in Table 1.

The yield of β-lactams in the presence of IL and $Yb(OTf)_3$ was more than that of Et_3N. Hence the $Yb(OTf)_3$/IL system was selected. The results are summarized in Table 2.



Scheme 1.

Table 1. Comparison of the reaction condition

Entry	Catalyst	Solvent	Product	Yield (%)
1	$AlCl_3$	$ClCH_2CH_2Cl$		40[23]
2	$Yb(OTf)_3$	$ClCH_2CH_2Cl$		12
3	None	[Nbupy][BF_4]		34
4	$Yb(OTf)_3$	[Nbupy][BF_4]		62
5	Et_3N	CH_2Cl_2/ benzene		30[13]

The reactions were stereoselective. When the reaction (Table 2, Entry 1) was operated at room temperature (20°C) for 24 h, the yield of β-lactams was low. From the ^{1}H NMR spectra of two hydrogens on the azetidinonic ring of the azetidinone **3a**, two diastereoisomers were formed: *cis* isomer (10%) (5.01, 1H, d, $J = 6.0$ Hz; 5.46, 1H, d, $J = 6.0$ Hz), *trans* isomer (90%) (4.28, 1H, d, $J = 2.4$ Hz; 4.96, 1H, d, $J = 2.4$ Hz). The coupling constant of *cis* azetidinone was higher than that of the *trans* isomer.[15] Fortunately when the temperature rose to 60°C, we got better results with only the *trans*-configuration. All products were determined as *trans*-configuration, as shown in Table 2. We conjectured that the products were governed by steric effects at 60°C.[15]

As shown in Table 2, only when R^1 were electron-withdrawing groups and R^3, R^4 were electron-donor groups were the reactions achieved easily. In other cases, only trace products could be obtained, and acylamides were the main products. We assumed that the zwitterionic intermediate (**6**) was more stable in IL when R^1 was an electron-withdrawing group and R^3, R^4 were electron-donor groups (Scheme 2).

In addition, the reactions were slow with some aliphatic imines such as N-benzylidene (phenyl) methanamine and N-benzylidene (4-methoxyphenyl) methanamine. It was assumed that those zwitterionic intermediates were unstable in ionic liquid.

Table 2. Synthesis of β-lactams in the presence of [Nbupy][BF_4] and Yb($OTf)_3$

Entry	R^1	R^2	R^3	R^4	Product[a,b]	Yield (%)[c]
1	H	H	H	H	**3a**	62
2	H	H	CH_3	H	**3b**	73
3	NO_2	H	H	H	**3c**	75
4	NO_2	H	CH_3	H	**3d**	72
5	H	CH_3O	H	H	**3e**	Trace
6	H	CH_3O	CH_3	H	**3f**	Trace
7	H	CH_3O	NO_2	H	**3g**	Trace
8	H	H	H	Cl	**3h**	65
9	H	H	H	C_2H_5	**3i**	76
10	H	H	H	CH_3	**3j**	62

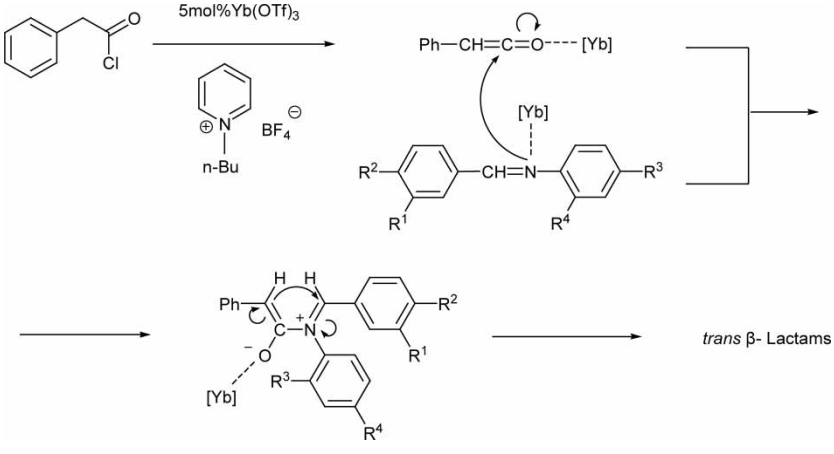
[a]The C_3–C_4 relative configuration was determined by ^{1}H NMR spectroscopy; all products have *trans*-stereochemistry and are racemic mixtures.

[b]All compounds were identified by their physical properties and analytical data.

[c]Report yields after crystallization from EtOAc–cyclohexane. Purification of the products by column chromatography, silica gel 200–300 mesh, eluent, EtOAc/cyclohexane = 1:4.

The reactions were also affected by the steric factors. When ketimine was used, the reaction failed because of the steric constraints imposed by two substituted groups.

To evaluate the possibility of recycling the ILs and Yb($OTf)_3$ used for the reaction, the recovered ILs were concentrated in vacuo. Then the reaction was performed with recycled ILs and Yb($OTf)_3$, and the process was repeated four times. There is little decline in the rate or yield of the reaction during each cycle. For example, for the product **3a**, the yields were 62%, 60%, 59%, and 59%.



Scheme 2.

In conclusion, the present method provided an environmentally friendly, efficient, and convenient procedure to synthesize β-lactams in the presence of [Nbupy][BF_4] and Yb(OTf)$_3$. All products are *trans*-configuration. The [Nbupy][BF_4] and Yb(OTf)$_3$ can be recovered, avoiding the use of a large amount of organic liquids.

EXPERIMENTAL

All reagents are commercially available. Yb(OTf)$_3$ was prepared from ytterbium oxide with trifluoromethanesulfonic acid in water according to the literature;[24] [Nbupy][BF_4] was synthesized from pyridine, 1-bromobutane, and $NaBF_4$ by the literature procedure;[25] and imines and acetylchlorides were prepared by the usual method. All reactions were performed under an atmosphere of dry nitrogen. Melting points were taken on a digital melting-point apparatus WRS-1B and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400-MHz instrument using $CDCl_3$ as the solvent, and chemical shifts are expressed in parts per million (ppm) using TMS as an internal standard. IR measurements were carried out with Nicolet Aviatar 370 instrument. Mass spectra were measured with a Trace Finnigan DSQ. Optical rotation were measured with an Autopol IV polarimeter (A7040-12). Elemental analyses were recorded on a ThermoFinnigan Flash EA1112. All spectral data of the products were identical to authentic samples.

General Procedure for the Preparation of β-Lactams

The imine (4 mmol) was added to dry pyridinium-based ionic liquid (4 mL), and the mixture was stirred until the imine was dissolved in ionic liquid under N_2 protection at room temperature. Then the arylacetyl chloride (4 mmol) was injected. After 15 min, Yb(OTf)$_3$ (0.2 mmol) was added, and the temperature was raised to 60°C. The mixture was stirred for 2 h. When the reaction finished, the mixture was extracted with ether (6 × 10 mL). The organic extract was washed with 5% Na_2CO_3 (40 mL) and water (40 mL), dried with anhydrous magnesium sulfate, and evaporated in vacuo. The residual product was purified by recrystallization from AcOEt/cyclohexane or by column chromatography (silica gel, 200–300 mesh, eluent, cyclohexane/AcOEt = 4 : 1). Then the IL was concentrated in vacuo (10 Torr for 2 h at room temperature). The IL and Yb(OTf)$_3$ were recovered and could be used again.

Data

3a: White crystalline solid. Mp 130–131°C (lit.,[26] 129–130°C). IR (KBr) υ/cm^{-1}: 1753 (C═O), 1633, 1600, 1497, 753, 696. ^{1}H NMR: δ (ppm) 4.29

(d, 1H, $J = 2.4$ Hz), 4.96 (d, 1H, $J = 2.4$ Hz), 7.06–7.42 (m, 15H). ^{13}C NMR: δ (ppm) 63.7, 65.1, 117.2, 124.1, 125.9, 127.5, 127.9, 128.7, 129.0, 129.1, 129.3, 134.7, 137.4, 137.5, 165.6. M/Z (CI^+): 300 ($M + H^+$).

3b: White crystalline solid. Mp 178–180°C (lit.,[27] 176–177°C). IR (KBr) υ/cm^{-1}: 1743 (C═O), 1612, 1514, 1452, 817, 756, 698. ^{1}H NMR: δ (ppm) 2.27 (s, 3H), 4.26 (d, 1H, $J = 2.4$ Hz), 4.92 (d, 1H, $J = 2.4$ Hz), 7.06–7.08 (m, 2H), 7.24–7.40 (m, 12H). ^{13}C NMR: δ (ppm) 21.2, 63.9, 65.4, 117.5, 126.2, 128.2, 128.9, 129.1, 129.3, 129.6, 129.9, 134.0, 135.0, 135.2, 135.4, 137.9, 165.6. M/Z(CI^+): 314($M + H^+$).

3c: Yellowish crystalline solid. Mp 123–124°C. IR (KBr) υ/cm^{-1}: 1738 (C═O), 1601, 1532, 1497, 757, 743, 692. ^{1}H NMR: δ (ppm) 4.29 (d, 1H, $J = 2.4$ Hz), 5.06 (d, 1H, $J = 2.4$ Hz), 7.08–7.42 (m, 10H), 7.58–7.62 (m, 1H), 7.72–7.76 (m, 1H), 8.21–8.28 (m, 2H). ^{13}C NMR: δ (ppm) 62.9, 65.5, 117.3, 121.4, 124.0, 124.8, 127.9, 128.5, 129.5, 129.6, 130.9, 131.9, 134.1, 137.2, 140.2, 149.2, 165.1. M/Z (CI^+): 345 ($M + H^+$); anal. calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.27; H, 4.97; N, 7.76.

3d: Yellowish crystalline solid. Mp 126–127°C. IR (KBr) υ/cm^{-1}: 1752 (C═O), 1618, 1522, 1454, 817, 738, 695. ^{1}H NMR: δ (ppm) 2.29 (s, 3H), 4.27 (d, 1H, $J = 2.4$ Hz), 5.04 (d, 1H, $J = 2.4$ Hz), 7.08–7.42 (m, 9H), 7.58–7.62 (m, 1H), 7.72–7.74 (m, 1H), 8.22–8.26 (m, 2H). ^{13}C NMR: δ (ppm) 21.1, 62.8, 65.5, 117.3, 121.4, 123.9, 127.7, 128.5, 128.7, 129.4, 129.6, 129.7, 130.0, 130.8, 131.9, 134.2, 134.4, 134.7, 140.3, 149.1, 164.8. M/Z (CI^+): 359 ($M + H^+$); anal. calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.79; H, 5.28; N, 7.51.

3h: White crystalline solid. Mp 146–147°C (lit.,[28] 143°C). IR (KBr) υ/cm^{-1}: 1746 (C═O), 1596, 1492, 1455, 830, 753, 700. ^{1}H NMR: δ (ppm) 4.30 (d, 1H, $J = 2.4$ Hz), 4.94 (d, 1H, $J = 2.4$ Hz), 7.21–7.43 (m, 14H), ^{13}C NMR: δ (ppm) 63.7, 65.3, 118.3, 125.8, 127.3, 127.9, 128.8, 129.0, 129.1, 129.3, 134.37, 135.9, 137.0, 165.4; M/Z (CI^+): 334 ($M + H^+$).

3i: White crystalline solid. Mp 90–91°C; IR (KBr) υ/cm^{-1}: 1742 (C═O), 1602, 1493, 1455, 768, 700, 755; ^{1}H NMR: δ (ppm) 1.25–1.29 (t, 3H, $J = 6.3$ Hz), 2.77–2.88 (m, 2H, $J = 6.3$ Hz), 4.38 (d, 1H, $J = 2.4$ Hz), 5.11 (d, 1H, $J = 2.4$ Hz), 7.15–7.40 (m, 14H); ^{13}C NMR: δ (ppm) 14.3, 25.0, 64.1, 66.0, 123.7, 126.4, 126.5, 126.92, 127.5, 127.8, 128.6, 129.0, 129.4, 133.9, 135.0, 137.7, 138.2, 166.6; M/Z (CI^+): 328 ($M + H^+$); anal. calcd. for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.32; H, 6.23; N, 4.62.

3j: Yellowish crystalline solid. Mp 145–146°C (lit.,[29] 143–144°C); IR (KBr) υ/cm^{-1}: 1741 (C═O), 1602, 1496, 1456, 763, 756, 699; ^{1}H NMR: δ

(ppm) 2.47 (s, 3H), 4.35 (d, 1H, $J = 2.4$ Hz), 5.14 (d, 1H, $J = 2.4$ Hz), 7.09–7.39 (m, 14H); ^{13}C NMR: δ (ppm) 26.9, 64.1, 65.5, 122.8, 126.3, 126.4, 126.5, 127.5, 127.8, 128.6, 129.0, 129.1, 131.5, 132.2, 134.8, 134.9, 137.8, 166.1; M/Z (CI^+): 314 ($M + H^+$).

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