• ARTICLES • • SPECIAL ISSUE • Ionic Liquid and Green Chemistry

August 2012 Vol.55 No.8: 1627–1632 doi: 10.1007/s11426-012-4629-3

Development of sequential type iron salt-catalyzed Nazarov/Michael reaction in an ionic liquid solvent system

IBARA Chie, FUJIWARA Masamune, HAYASE Shuichi, KAWATSURA Motoi & ITOH Toshiyuki^{*}

Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan

Received January 26, 2012; accepted February 22, 2012; published online June 14, 2012

Sequential type one pot Nazarov/Michael reaction of pyrrole derivatives has been demonstrated using 5 mol% Fe(ClO₄)₃ · Al₂O as catalyst in an ionic liquid as solvent. We succeeded in obtaining 4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one derivative in good yield for five repetitions of the reactions without any addition of the catalyst using an ionic liquid, [bmim][NTf₂], as solvent system.

Nazarov cyclization, Michael reaction, green synthesis, iron catalyst, ionic liquids

1 Introduction

Iron is one of the most abundant and environmentally friendly metals on the earth and various types of iron metal-catalyzed organic transformations have been developed during the past decades [1]. We have also been investigating the possibility of iron-catalyzed reactions and have developed several of them, i.e., the intramolecular cyclization of cyclopropanedithioacetals [2], the [2+2]-cycloaddition of trans-anethol [3], the [2+3]-type cycloaddition of styrene derivatives with 1,4-benzoquinone [4], the 1,4-addition of β -ketoesters to vinyl ketones [5], the enantioselective Michael addition of thiols to α , β -unsaturated carbonyl compounds [6], Friedel-Crafts type alkylation of indoles [7] or pyrroles [8] with vinyl ketones, and the Nazarov type cyclization of several types of compounds [9–11].

Nazarov cyclization is one of the versatile methods for the synthesis of five-membered carbocycles, and it is known that several Lewis or Brønsted acids promote this reaction [12, 13]. However, Nazarov cyclization of pyrrole derivatives is not popular [12, 13], though the pyrrole moiety is very common in many biologically active or functional molecules. The reason that the reaction is not popular is assumed to be that pyrroles are easily polymerized in the presence of strong Lewis acid [13f].

We recently reported that the Nazarov cyclization of pyrrole derivatives 1 took place in the presence of 3-5 mol% of alumina-supported iron(III) perchlorate



Figure 1 Iron(III) salt-catalyzed sequential type Nazarov cyclization/ Michael reaction of pyrrole derivatives [10].

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^{*}Corresponding author (email: titoh@chem.tottori-u.ac.jp)

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 $(Fe(ClO_4)_3 \cdot Al_2O_3)$ to give the cyclized product 2, and the compound further reacted with vinyl ketone to afford the Michael product, 4,5-dihydrocyclopenta-[b]pyrrol-6(1*H*)- one derivative 3 with excellent stereoselectivity. A route to access 5,6-dihydrocyclopenta[b]pyrrol-4(1*H*)-one derivative 5 has also been accomplished through the same sequential reaction pathway from pyrrole derivative 4 (Figure 1) [10]. We succeeded in obtaining desired products 3 and 5 in excellent yield using dichloromethane (CH₂Cl₂) as solvent [10]. However, it has now been recognized that the use of halogenated alkanes as solvent should be avoided in organic synthesis. Therefore, development of a more environmentally benign reaction system using economical iron salt catalyst which is free of halogenated alkane solvent is required.

Ionic liquids (ILs) are well known to be suitable for use in organic reactions and to provide potential for improvement in control of product distribution, enhanced reactivity, ease of product recovery, catalyst immobilization, and recycling [14]. Therefore, we anticipated that recycled use of our iron catalyst might be possible using an ionic liquid as reaction medium. We now report that an efficient catalyst recycled use system of sequential type one pot Nazarov cyclization/Michael reaction of pyrrole derivative has been accomplished using an ionic liquid as solvent [15].

2 Results and discussion

Initially, we evaluated eight ILs, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF₆]), 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)amide ([bmim] [NTf₂]), 1-butyl-3-methylimidazolium tetrafluoroborate (pbmim)[BF₄]), 1-butyl-3-methylimidazolium trifluoromethylsulfonate ([bmim][OTf]), 1-butyl-3-methylimidazolium ethylsulfate ([bmim][EtSO₄]), tri(n-butyl)(2-methoxyethyl) phosphoniumbis(trifluoromethanesulfonyl)amide ([P_{444ME}] [NTf₂]) [16], *N*,*N*-diethyl-*N*-methyl, *N*-(2-methoxyethyl) ammonium bis(trifluoromethanesulfonyl)amide ([N_{221ME}] [NTf₂]), and *N*,*N*-diethyl-*N*-methyl, *N*-(2-metho-xyethyl) ammonium tetrafluoroborate ([N_{221ME}][BF₄]), for Nazarov cyclization of **1a** in the presence of 5 mol% Fe(ClO₄)₃· Al₂O₃ as catalyst.

The reaction proceeded smoothly in many ILs and corresponding cyclized product 2a was obtained with over 90% yield, while no reaction took place in [bmim][OTf] or [bmim][EtSO₄]. It was thus revealed that the reaction significantly depended on the counter anion part of ILs.

Although ILs which have PF_6 and BF_4 anion gave **2a** in excellent yield, neither salt are recommended as solvent because these anions are slightly sensitive to moisture and sometimes causes decomposition which produces hydrogen fluoride [17]. Therefore, we chose [bmim][NTf₂], [P_{444ME}] [NTf₂] and [N_{221ME}][NTf₂] as appropriate solvents for the present reaction and next attempted to demonstrate a catalyst recycled use system (Figure 2).



Figure 2 Catalyst recycled use system using anionic liquid solvent.

The reaction course was monitored by TLC analysis at one hour intervals, and the reaction was quenched by addition of a mixed solvent of hexane and ether (2:1) immediately after **1a** had been consumed.

As we had previously established that stereochemistry of the product **2a** did not depend on the E/Z ratio of the starting compound **1a** and the Nazarov cyclization product **2a** which had the *trans* relationship between the α -carbomethoxy group and the β -phenyl group was produced as a major isomer, while a trace amount of *cis* isomer was also produced in the CH₂Cl₂ solvent system [10]. To our delight, it was revealed that only the *trans* **2a** was obtained when the reaction was conducted in an ionic liquid solvent. It was also found that we needed no tedious argon atmospheric conditions for conducting the reaction; the reaction mixture was just stirred under air atmospheric conditions. Since iron catalyst remained in the ionic liquid layer, it was possible to use the catalyst repeatedly (Table 1).

The product **2a** was obtained in excellent yield in every run five consecutive times (Entries 2 and 3) and in acceptable yield nine times (Entry 4), while the reaction speed dropped with repetition of the reaction process. It took 25 h to complete the reaction after ten repetitions of the reactions when the reaction was carried out in $[N_{221ME}][NTf_2]$ (see the right column in Entry 5). A significant reduction of chemical yield of **2a** was also recorded in $[P_{444ME}][NTf_2]$ solvent

Table 1 Nazarov cyclization of 1a in ionic liquid solvent

	_		Solvent	
Entry	Run	$[P_{444ME}][NTf_2]$	[bmim][NTf ₂]	$[N_{221ME}][NTf_2]$
	_	yield of $2a^{a}$	yield of 2a ^{a)}	yield of 2a ^{a)}
1	1st	82% (3 h)	78% (3 h)	86% (4 h)
2	2nd	98% (5 h)	94% (5 h)	96% (5 h)
3	5th	98% (12 h)	94% (14 h)	93% (9 h)
4	9th	76% (24 h)	63% (24 h)	76% (24 h)
5	10th	35% (24 h)	62% (23 h)	78% (25 h)
6	$11 th^{b)}$	98% (3 h)	90% (3 h)	92% (3 h)

a) isolated yield; b) 5 mol% of Fe(ClO₄)₃ · Al₂O₃ was added.

(Entry 5, the left column). This drop in reaction rate was speculated to be from decomposition of iron catalyst that might occur due to moisture during the extraction process, because we carried out the process under ambient conditions. It was possible to recover both chemical yield and reaction rate by adding 5 mol% of the fresh catalyst as shown in Table 1 (Entry 6). We thus succeeded in demonstrating the recyclable use of iron(III)-salt catalyst in the ionic liquid solvent system.

We next attempted sequential type Nazarov/Michael reaction and found that the desired reaction proceeded smoothly in these ionic liquids. The most rapid reaction in the second step of Michael reaction was accomplished when the reaction was conducted in [bmim][NTf₂], while a poor reaction rate of the Michael reaction was observed in phosphonium IL ([P_{444ME}][NTf₂]) or ammonium IL ([N_{221ME}] [BF₄]), though the final products were obtained in acceptable yield in all ILs tested. Therefore, we decided to demonstrate one pot Nazarov cyclization and Michael reaction using [bmim][NTf₂] as solvent (Figure 3).

The desired reaction indeed took place, however, we encountered unexpected difficulty: isolation of the final product, 4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one derivative **3a** ($\mathbf{R} = \mathbf{Me}$), from the reaction mixture was unsuccessful because **3a** was very soluble in [bmim][NTf₂].

We anticipated that modification of the ester part of 1 to more hydrophobic one might solve this problem. Therefore, we prepared n-pentyl ester 1b and benzyl ester 1c and use them as substrates for the iron salt-catalyzed Nazarov/Michael reaction. To our delight, we succeeded in isolating the desired products, 3b and 3c, from the ionic liquid reaction mixture in acceptable yields: 78% for 3b and 70% for 3c, respectively (Figure 3). Stereochemistry of 3b was determined by X-ray crystallographic analysis as shown in



3b: R=n-Pent (78% isolated yield) **3c**: R= Bn (70% isolated yield)

Figure 3 Sequential type one pot Nazarov cyclization/Michael reaction of pyrrole derivatives 1 in $[\text{bmim}][\text{NTf}_2]$.

Figure 4 [18].

Better yield of the Nazarov/Michael reaction product was recorded when n-pentyl ester **1b** was subjected to the present iron salt-catalyzed reaction compared to when the reaction of benzyl ester **1c** was used as substrate, though it took longer reaction time to complete the Nazarov reaction process (step 1). We next demonstrated the catalyst recyclable use system employing n-pentyl ester **1b** in [bmim][NTf₂] as solvent.

Typically the reaction was carried out as illustrated in Figure 3. To a solution of **1b** (156 mg, 0.50 mmol) in [bmim][NTf₂] (1.0 mL) was added Fe(ClO₄)₃ · Al₂O₃ (60 mg, 10.7 wt% for Fe³⁺, 5 mol% vs. **1b**) in one portion, and the mixture was stirred at 80 °C. The reaction course was monitored by silica gel thin layer chromatography (TLC) analysis and 1-buten-2-one (70 mg, 1.0 mmol, 2.0 eq. vs. **1b**) was added after **1b** had been consumed.

The reaction mixture was stirred at 60 °C for 2 h until the spot of **2b** disappeared. After being cooled to room temperature (rt), addition of a mixed solvent (hexane and ether = 2:1) to the reaction mixture formed the biphasic layer and the product **3b** (278 mg, 0.73 mmol) was isolated from the ether layer in 78% yield as a sole stereo isomer. The same process was repeated, and the results are summarized in Table 2. We succeeded in obtaining **3b** in 78% yield after five repetitions of the reaction without any addition of the catalyst in [bmim][NTf₂] solvent system, while the reaction rate for the first step (Nazarov cyclization) had dropped significantly (Table 2, Entry 3).

3 Conclusions

We demonstrated the sequential type Nazarov cyclization/



Figure 4 ORTEP view of Nazarov cyclization/Michael reaction product 3b.

 Table 2
 Results of catalyst recycled use system of one-pot Nazarov cyclization/Michael reaction of 1b

Entry	Run	Yield of 3b
1	1st	78% (6 h ^{a)} and 2 h ^{b)})
2	3rd	73% (37 h^{a}) and 1 h^{b})
3	5th	78% (99 h^{a}) and 1 h^{b})

a) Reaction time for the first step; b) reaction time for the second step

Michael reaction of pyrrole derivatives using an economical $Fe(ClO_4)_3 \cdot Al_2O_3$ catalyst system with an ionic liquid as reaction medium. A catalyst recycled use system has been achieved: the product was obtained in good yields after five repetitions of the reaction without any addition of the catalyst. To the best of our knowledge, this is the first example of realization of recyclable catalyst in the sequential type one pot reaction in an ionic liquid solvent system. It should be emphasized that the reaction can be accomplished under very mild conditions and requires no tedious argon atmospheric conditions, although we should pay attention to moisture. Further investigation of the scope and limitations of this reaction will make it even more valuable.

4 Experimental

4.1 General procedures

Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Wako gel C-300 and Wako gel B5F were used for flash column chromatography and thin-layer chromatography (TLC), respectively. NMR spectra were recorded on JEOL MH-400 (¹H) or JEOL MH-500 (500 MHz for ¹H and 125 MHz for ¹³C) spectrometers, and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) in CDCl₃ as an internal reference. IR spectra were obtained on a SHIMADZU FTIR-8000 spectrometer. Ionic liquids were purchased from Kanto Reagents Co., Ltd. or Tokyo Chemical Industry Co., Ltd. were used for the reactions without any further purification.

4.2 Preparation of Fe(ClO₄)₃ · Al₂O₃[3]

Neutral alumina (714 mg, Aldrich) was added to a solution of $Fe(ClO_4)_3 \cdot nH_2O$ (286 mg) in freshly distilled CH₃CN (0.5 mL) and the solvent was removed at 60 °C under reduced pressure using a rotary evaporator. The mixture was dried under vacuum and the resulting uniformly orange powder was used for the reaction. The catalyst should be handled with care because it has been reported that iron(III) perchlorate salt explodes when subjected to mechanical or thermal shock. However, our catalyst is believed to be safe due to the support by neutral alumina. The content of Fe(III) ion was determined by iodometry titration in aqueous solution.

4.3 Methyl (*E*)-2-benzylidene-3-oxo-3-(1*H*-pyrrol-2-yl) propanoate (1a) [10]

KH (8.02 g, 60 mmol, 30% in mineral oil) and NaH (2.60 g, 65 mmol, 60% in mineral oil) were placed in a two necked flask under argon atmosphere and the mixture was diluted with THF (100 mL) at 0 °C. To this mixture were added a THF (50 mL) solution of 1-(1H-pyrrol-2-yl)ethanone (7) (5.46 g, 50 mmol) and dimethyl carbonate (15.76 g, 175 mmol) at 0 °C, then stirred at 40 °C for 3.5 h. After being cooled to room temperature (rt), the reaction was quenched by addition of water and the mixture was extracted with ethyl acetate. The combined organic layers were dried, evaporated and chromatographed on a silica gel flash column to give methyl 3-oxo-3-(1*H*-pyrrol-2-yl)propanoate (8) (7.51 g, 44.9 mmol) in 90% yield. Dried molecular sieves 4A (MS 4A) powder (10 g) was placed in a flask under argon and a CH₂Cl₂ (40 mL) solution of 8 (2.0 g, 12 mmol) was added. To this mixture were added piperidine (0.38 mL) and acetic acid (0.22 mL) at 0 °C and stirred at 0 °C for 5 min, then a CH₂Cl₂ (10 mL) solution of benzaldehyde (1.48 g, 14 mmol) was added and the resulting mixture was stirred at rt for 5 h. The reaction mixture was filtered through a glass sintered filter with a Celite pad and the filtrate was evaporated and chromatographed on a silica gel flash column to give 1a (3.06 g, 12 mmol) in quantitative yield. 1a: mp 95–97 °C (recrystallized from ethyl acetate); ¹H NMR (500 MHz, ppm, CDCl₃) δ 3.79 (3H, s), 6.16 (1H, m), 6.71 (1H, s), 7.08 (1H, m), 7.21-7.28 (3H, m), 7.40 (2H, d, J = 7.0 Hz), 7.94 (1H, s), 10.05-10.11 (1H, brs),N–H);¹³CNMR (125 MHz, ppm, CDCl₃) δ 52.59, 111.38, 119.71, 126.52, 128.66, 130.17, 130.24, 130.42, 131.70, 133.05, 142.88, 165.72, 183.67; IR (KBr) 3285, 1705(CO), 1624(CO), 1595, 1410, 1259, 1204, 1132, 752, 691 cm⁻¹; Anal. Calcd. for C₁₅H₁₃NO₃: C, 70.58; N, 5.49; H, 5.13 Found: C, 70.43; N, 5.47; H, 5.28.

4.4 n-Pentyl(*E*)-2-benzylidene-3-oxo-3-(1*H*-pyrrol-2-yl) propanoate (1b)

Methyl ester **1a** (1.73 g, 10.3 mmol) and molecular sieves 4A (5.0 g) were placed in a two necked flask under argon and the mixture was diluted with 25 mL of dry with toluene. To the mixture was added pentan-1-ol (1.2 mL, 11.6 mol) and stirred at 120 °C for 12 h. After being cooled at rt, to this mixture were added piperidine (0.20 mL, 2.1 mmol), acetic acid (0.1 mL, 2.1 mmol), and benzaldehyde (1.1 mL, 2.1 mmol) at 0 °C and the mixture was stirred for 5 min at the same temperature. The reaction mixture was allowed to warm to rt and stirred for 5 h at the same temperature; it was then diluted with ethyl acetate and filtered through a

glass sintered filter with a Celite pad to remove the piperidinium salt. The filtrate was evaporated and chromatographed on silica gel flash column (hexane:ethyl acetate = 1:1) to afford **1b** (2.95 g, 9.48 mol) in 92% overall yield.

1b: mp: 110–114 °C; R*f* = 0.52 (hexane/ethyl acetate = 2/1); ¹H NMR (500 MHz, CDCl₃): δ 0.83 (t, *J*=7.1 Hz, 3H), 1.17–1.62 (m, 4H), 1.60 (m, 2H), 4.20 (t, *J*=6.6 Hz, 2H), 6.17 (m, 1H), 6.71 (td, *J*=2.7 Hz, 1.7, 1H), 7.08 (td, *J*=2.7 Hz, 1.4, 1H), 7.21–7.28 (m, 3H), 7.41 (t, *J*=1.8 Hz, 1H) 7.42 (t, *J*=1.6 Hz, 1H), 7.89 (s,1H), 9.79 (s, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 13.8, 22.1, 27.8, 28.1, 65.5, 111.2, 119.3, 126.1, 128.11, 128.6, 129.0, 129.3, 130.1, 130.9, 131.8, 133.1, 142.4, 165.3, 183.7; IR (KBr) : 3275, 2935, 2860, 1701(CO), 1612(CO), 1546, 1406, 1255, 740 cm⁻¹; HRMS(ESI): *m/z*: calcd for [MH]⁺C₁₉H₂₂NO₃⁺: 312.15942, found: 312.15915

Using benzyl alcohol in the first step, benzyl etser **1c** was also prepared in 87% yield (two steps).

4.5 Benzyl (*E*)-2-benzylidene-3-oxo-3-(1*H*-pyrrol-2-yl) propanoate (1c)

mp: 99–104 °C; ¹H NMR (400 MHz, CDCl₃): δ 4.70 (s, 1H), 5.25 (s, 2H), 6.15–6.18 (brs, 1H), 6.65–6.70 (brs, 1H), 7.00–7.05 (brs, 1H), 7.20–7.30 (brs, 1H), 7.20–7.03 (m, 6H), 7.30–7.45 (m, 4H), 7.90–7.95 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 66.89, 111.3, 127.6, 128.0, 128.4, 128.6, 130.2, 130.3, 130.5, 131.8, 133.0, 135.7, 143.0, 165.1, 190.2; IR (KBr): 3269, 1718(CO), 1612(CO), 1545, 1496, 1406, 1251, 1190, 1122, 771 cm⁻¹; HRMS(ESI): *m/z*: calcd for [M+H]⁺ C₂₁H₁₈NO₃⁺: 332.12874, found: 332.12126.

4.6 Synthesis of 3b through one pot Nazarov cyclization/Michael reaction

To a mixture of $Fe(ClO_4)_3 \cdot Al_2O_3(19 \text{ mg}, 5.0 \text{ mol}\%$ for Fe^{3+} , 0.01 mmol) in [bmim][NTf₂] (0.4 mL) was added **1b** (62 mg, 0.20 mmol) at rt and the mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled to rt after confirmation that the starting **1b** had been consumed and **2b** produced, then 2 eq. of 1-buten-3-one (0.03 mL, 0.40 mmol) was added to the reaction mixture at rt and stirred for 6 h at 60 °C. After being cooled to rt, the reaction was extracted with a mixed solvent of hexane and ether (2:1). The combined organic layers were evaporated to dryness and silica gel thin layer chromatography (TLC) (hexane:ethyl acetate = 3:2) gave **3b** (59.5 mg, 0.156 mmol) in 78% yield as a white solid. Ionic liquid layer was dried under reduced pressure at 60 °C for 30 min, feeding of substrate **1b** (62 mg) and conducted next reaction.

3b: mp: 139–142 °C; Rf = 0.11(hexane/ethyl acetate = 2/1); ¹H NMR (500 MHz, CDCl₃): δ 0.73(t, *J*=7.3 Hz, 3H), 0.97 (dt, *J*=15.3, 4.1 Hz, 2H), 1.14 (m, 4H), 2.09 (s, 3H), 2.35 (m, 1H), 2.52 (m, 2H), 2.75 (m, 1H), 3.31 (ddt, *J*=68.6

Hz, 12.7, 5.3, 2H), 4.26 (s, 1H), 6.05 (t, J=1.8 Hz, 1H), 7.08 (dd, J=7.6, 1.6 Hz, 2H), 7.18 (m, 3H), 7.34 (t, J=2.5 Hz, 1H), 10.9 (br, 1H); ¹³C NMR (125 MHz, CDCl₃) : δ 13.8, 22.0, 27.5, 27.8, 28.7, 29.9, 38.5, 50.9, 64.9, 71.3, 107, 127, 128.0, 128.6, 129, 134, 134, 138, 153, 170, 189, 208; IR (KBr): 3292, 2957, 1718(CO), 1676(CO), 1406, 1375, 1271, 1203, 765.7 cm⁻¹; HRMS(ESI): m/z: calcd for [MH]⁺ C₂₃H₂₈NO₄⁺: 382.20194, found: 382.20126.

We succeeded in obtaining **2b** in 87% yield when the reaction was stopped at Nazarov cyclization and isolated from the reaction mixture.

2b: mp: 99–103 °C; R*f* = 0.34 (hexane/ethyl acetate = 2/1); ¹H NMR (500 MHz, CDCl₃): δ 0.91 (t, *J*=7.1 Hz, 3H), 1.35 (dt, *J*=11.5, 4.2 Hz, 4H), 1.71 (dd, *J*=6.9, 7.3 Hz, 2H), 3.82 (d, *J*=3.2 Hz, 1H), 4.22 (m, 2H), 4.78 (d, *J*=3.2 Hz, 1H), 6.13 (t, *J*=2.1 Hz, 1H), 7.22 (d, *J*=8.2 Hz, 2H), 7.26 (td, *J*=6.6, 1.7 Hz, 1H), 7.33 (t, *J*=7.3 Hz, 2H), 7.39 (t, *J*=2.7 Hz, 1H), 11.1 (brs,1H); ¹³C NMR (125 MHz, CDCl₃): δ 13.9, 22.2, 27.9, 28.2, 44.1, 65.7, 68.3, 106.5, 127.1, 127.2, 128.8, 132.8, 134.4, 141.6, 155.2, 169.4, 184.4; IR (KBr):3221, 2956, 2872, 1726(CO), 1685(CO), 1450, 1400, 1319, 1161, 777cm⁻¹; HRMS(ESI): *m/z*: calcd for [MH]⁺ C₁₉H₂₂NO₃⁺: 312.16006, found: 312.15912.

Benzyl ester 3c and 2c were obtained using the same protocol.

3c: mp: 155–160 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.95 (s, 3H), 2.43–2.48 (m, 1H), 2.56–2.65 (m, 2H), 2.80–2.85 (m, 1H), 4.30 (d, *J*=15.0 Hz, 1H), 4.37 (s, 1H), 4.49 (d, *J*=15.0 Hz, 1H), 6.11 (s, 1H), 7.01–7.03 (m, 2H), 7.15–7.16 (m, 2H), 7.22–7.25 (m, 6H), 7.33–7.35 (m, 1H), 11.0 (s, NH,1H): ³C NMR (125 MHz, CDCl₃): δ 28.7, 30.0, 38.4, 51.0, 66.2, 71.4, 106.5, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 128.5, 128.9, 129.2, 134.0, 134.1, 135.2, 138.1, 152.6, 170.1, 188.2, 207.8; IR (KBr): 3244, 3030, 2955, 1734(CO), 1681(CO), 1495, 1456, 1402, 1371, 1259, 1220, 1155, 744 cm⁻¹; HRMS(ESI): *m/z*: calcd for [MH]⁺ C₂₅H₂₄NO₄⁺: 402.17062, found: 402.17126.

2c: 155–160 °C; ¹H NMR (400 MHz, CDCl₃): ^{TM3}.88 (d, J=3.25 Hz, 1H), 4.78 (d, J=3.2 Hz, 1H), 5.27 (d, J=3.6 Hz, 2H), 6.20–6.30 (brs, 1H), 7.16 (d, J=7.3 Hz, 1H), 7.23–7.45 (m, 10H), 11.1 (s, NH, 1H); ¹³C NMR (125 MHz, CDCl₃): ^{TM44.04}, 67.09, 68.09, 106.5, 127.20, 127.23, 127.38, 128.00, 128.05, 128.10, 128.30, 128.40, 128.77, 129.0, 132.7, 134.6, 135.6, 141.4, 155.2, 169.2, 184.1; IR(KBr): 3244, 2955, 1734(CO), 1681(CO), 1495, 1402, 1371, 1259, 1220, 1155, 744 cm⁻¹; HRMS(ESI): m/z: calcd for [MH]⁺ C₂₁H₁₈NO₃⁺: 332.12874, found: 332.12826.

The present work was supported by a Grant-in-Aid for Scientific Research in a Priority Area, "Science of Ionic Liquids", from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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