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Tandem isomerization–lactonization of olefinic fatty acids using the Lewis acidic ionic liquid, choline chloride·$2ZnCl_2$

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ABSTRACT

The tandem isomerization–lactonization of unsaturated fatty acids to their corresponding γ-lactones was carried out for the first time in the presence of a Lewis acidic ionic liquid, choline chloride·$2ZnCl_2$. The ionic liquid initially catalyzes the stepwise migration of the double bond along the carbon chain toward the carboxyl group at the Δ4 position, which subsequently undergoes lactonization resulting in the formation of γ-lactones. This one step process allows the formation of γ-lactone in good yield with little or no formation of δ-lactones. The studied ionic liquid plays the dual role of solvent as well as catalyst.

Aliphatic γ-lactones are industrially important oleochemicals having applications as flavor and food additives.[1–3] They are also useful synthons for the development of novel biodegradable detergents and other organic intermediates.[4] The most sustainable method for the synthesis of aliphatic γ-lactone is from unsaturated fatty acid, derived from renewable fats and oils. Fatty acid lactones are usually prepared following a tandem isomerization–lactonization pathway. There are several literature reports for the preparation of γ-lactones of unsaturated fatty acids using catalysts such as perchloric acid, *p*-toluenesulfonic acid, sulfuric and trifluoroacetic acids, ion exchange resin[4–7] etc. However, poor yields, vigorous reaction conditions, and poor selectivity (δ vs γ) are some of the shortcomings of these reported methods. Moreover, in most of these cases stoichiometric quantity of mediators is required for the initial isomerization of double bonds over 5 or more carbon atoms. Even then there are possibilities of side reactions, like formation of di- and oligomerizations at the double bonds or intermolecular additions of carboxylate groups to double bonds.[7–9] Recently, Brønsted and Lewis acid catalysts are replaced with eco-friendly solid recyclable heterogeneous catalysts to conduct tandem isomerization–lactonization of fatty acids. Zhou et al.[8] studied the conversion of unsaturated fatty acids to γ-lactones, catalyzed by the Amberlyst-15 resin, Nafion NR-50 resin, and a nanocomposite of Nafion resin/silica, SAC-13. The reported methods are successful for short chain unsaturated fatty acids (C5–C7). However, with the increase in chain length as well as the position of the double bond, the tandem reactions are slow and afford a very poor yield. In recent times, silver triflate catalyzed synthesis of γ-lactones from fatty acids is reported by Goßen et al.[9] The method is regioselective, giving exclusively γ-lactone and only traces of δ-lactone. However, the reported yields are very poor; the highest yield (71%) was obtained only with the fatty acid containing a terminal double bond (10-undecylenic acid). There is no report so far on utilization of ionic liquid (IL) for conducting tandem isomerization–lactonization of unsaturated fatty acids for the synthesis of γ-lactone. The present work is an attempt to develop such a clean and environmentally friendly protocol.

Ionic liquids (IL) are an extensively used eco-friendly, non-conventional reaction medium for many chemical and biochemical transformations.[10] Abott et al. reported a new class of moisture insensitive Lewis acidic IL composed of choline chloride and $ZnCl_2$.[11] The Lewis acidic nature is due to the presence of complex zinc chloride ions, $[ZnCl_3]^-$, $[Zn_2Cl_5]^-$, and $[Zn_3Cl_7]^-$ as confirmed by ESI-MS. Compared to other IL, preparation of this IL is relatively easy. It has been extensively used as a Lewis acid as well as reaction medium in carrying out Diels–Alder reactions, Fischer indole annulation, O-acetylation of cellulose and monosaccharide and protection of carbonyls.[11–15] A liquid–liquid biphasic novel synthesis of long chain wax esters was also reported by us wherein the IL is playing the dual role of solvent as well as Lewis acid catalyst.[16] In continuation of our research on IL, we propose to synthesize γ-lactone by tandem isomerization–lactonization of unsaturated fatty acid catalyzed by the Lewis acidic IL choline chloride·$2ZnCl_2$. Two types of fatty acids are taken up in the present work, one with unsaturation at the terminal position (10-undecylenic acid) and

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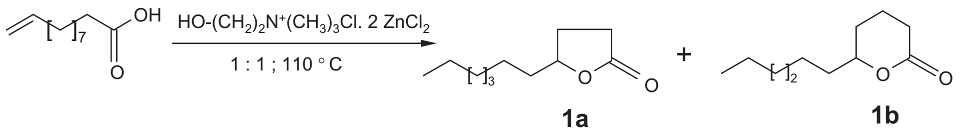
Table 1
Tandem isomerization–lactonization of UDA to undecalactone catalyzed by choline chloride·2ZnCl$_2$ [a]



Time (h)	Unreacted UDA + isomer of UDA (%)	γ-Undecalactone **1a** (%)	δ-Undecalactone **1b** (%)
2	56.3	27.6	16.1
4	19.7	56.8	23.5
6	13.5	71.8	14.7
8	9.6	79.4	11.0
10	–	93.2	6.8
12	–	94.5	5.5

[a] Compositions of products were determined by GC.

the other at the central position of the carbon chain (Δ9 for oleic acid and Δ13 for erucic acid).

The isomerization–lactonization of 10-undecylenic acid (UDA) was carried out initially for the formation of peach flavored γ-undecalactone catalyzed by the Lewis acidic IL, choline chloride·2ZnCl$_2$. The objective is to optimize the various reaction conditions such as molar ratio of IL to substrate, reaction temperature, and reaction time. Initially, UDA was taken in IL at 1:1 molar ratio of UDA: IL and stirred at 110 °C. Progress of the reaction was monitored by GC and GC–MS (see Supplementary data for chromatographic conditions). After 2 h, both γ- and δ-lactones are formed along with isomeric mixture of UDA (Table 1). However, as the reaction progresses, there is decrease in the concentration of isomeric mixture of UDA and increase in the formation of lactones. Among lactones, there is slow conversion of δ-lactone to thermodynamically stable γ-lactone. Zhou et al.[8] also reported such slow conversion of δ-lactone to γ-lactone during Nafion SAC-13 or Amberlyst-15 catalyzed tandem reactions of unsaturated fatty acids. After 10 h, about 93.2% formation of γ-lactones was observed along with 6.8% formation of δ-lactones and complete disappearance of UDA isomer.

Results obtained indicate that a raised temperature could possibly accelerate the reaction and favor the exclusive formation of γ-lactones. Accordingly, a set of reactions were conducted at 130 °C varying the molar ratio of UDA and IL. Progress of the reaction was monitored by GC and results obtained after 8 h are shown in Table 2. At a lower mole fraction of IL, less than 50% formation of lactones was observed. However, at 0.5:1.0 M ratio of IL: UDA, near-exclusive formation of γ-lactone was observed along with traces of formation of δ–lactone and isomeric UDA. Identical results were obtained at higher mole fraction of IL. At this optimized molar ratio of 0.5:1.0 of IL:UDA, a reaction was also conducted at 150 °C. After 2 h, 82.2% formation of γ-lactone was observed along with 1.8% of δ-lactone and 16% of isomeric UDA as per GC. However, GC chromatogram showed the appearance of additional ghost peaks after 3 h. Thus the optimized reaction conditions for exclusive formation of γ-undecalactone are: molar ratio of IL: UDA, 0.5:1.0 mol/mol; temperature, 130 °C and a reaction time of 8 h.

Lactonization of oleic acid and erucic acid was also conducted following the conditions optimized for UDA. But due to location of the double bond, very little reaction was observed. This indicates requirement of a bit drastic reaction conditions to achieve the necessary isomerization of Δ9 and Δ13 double bonds, respectively of oleic and erucic acids to their corresponding Δ4 position and their subsequent lactonization. Under this circumstance, it was planned to increase the molar equivalent of IL as well as reaction temperature. Accordingly, a reaction was carried out by taking equimolar ratio of IL and oleic acid at 150 °C. Progress of the reaction was monitored by GC and GC–MS and the composition of the reaction mixture after every 2 h of the reactions are given in Table 3. Within 4 h, about 86-87% formation of γ-stearolactone was observed, beyond that no further increase in product formation was observed. Thus, 86–87% formation of γ-stearolactone was observed when equimolar ratio of IL and oleic acid is reacted at 150 °C over a period of 4 h. Erucic acid, under similar reaction conditions afforded 42% formation of isolated γ-erucalactone. This is expected as the Δ13 double bond needs to be isomerized to Δ4 position over a much longer carbon network compared to oleic acid. However, prolonging the reaction time to 16 h afforded 52–55% formation of γ-erucalactone. Beyond 16 h, no appreciable increase in product formation was observed.

The mechanism of Brønsted acid catalyzed tandem isomerization–lactonization of unsaturated fatty acid involves initial protonation at the olefinic carbon. The resultant carbocation undergoes

Table 2
Optimization of molar ratio of IL and UDA during tandem isomerization–lactonization of UDA to undecalactone at 130 °C catalyzed by choline chloride·2ZnCl$_2$ [a]

Molar ratio of IL: UDA	Unreacted UDA + isomer of UDA (%)	γ-Undecalactone **1a** (%)	δ-Undecalactone **1b** (%)
0.125:1.0	73.7	20.6	5.7
0.25:1.0	44.0	46.4	9.6
0.5:1.0	1.0	98.5	0.5
0.75:1.0	1.0	98.2	0.8
1.0:1.0	1.0	98.3	0.7

[a] Compositions of products were determined by GC.

Table 3
Tandem isomerization–lactonization of oleic acid to stearolactone catalyzed by choline chloride·2ZnCl$_2$ (1:1, mol/mol of oleic acid: IL) at 150 °C [a]

Reaction time (h)	Unreacted oleic acid + isomer of oleic acid (%)	γ-Stearolactone (%)	δ-Stearolactone (%)
2	27.82	70.86	1.32
4	10.42	86.81	2.77
6	10.83	86.82	2.35
8	10.67	87.01	2.32

[a] Compositions of products were determined by GC.

stepwise migration of olefinic function vis-à-vis carbocation toward the carboxylate group till the Δ4 position, where the nucleophilic attack by the carboxyl moiety is facilitated.[17] Gooßen et al.[9] also proposed similar silver triflate catalyzed shifting of double bond followed by lactonization. We presume similar mechanistic pathway for the tandem reaction of unsaturated fatty acid catalyzed by IL, choline chloride·$2ZnCl_2$. In fact, it is the higher complex zinc chloride ions, $[Zn_2Cl_5]^-$ and $[Zn_3Cl_7]^-$ present in the IL which forms complex with the π-cloud of the double bond. The resultant complex undergoes a series of 1,2-H shift over the carbon chain toward the carboxylate group till Δ4 position followed by lactonization to give the desired lactone and releasing the complex zinc ions. In order to understand the role of complex zinc ions in IL, tandem isomerization–lactonization of UDA was also carried out in a solvent-free and IL-free medium by adding anhydrous $ZnCl_2$ at 1:1 molar ratio of UDA: $ZnCl_2$ at 130 °C. After 8 h, about 50% formation of γ-undecalactone was observed along with the formation of several other side products including δ-undecalactone. This indicates increased regiospecificity of the desired product achieved during the tandem reactions catalyzed by the complex zinc ions present in the IL compared to $ZnCl_2$.

The feasibility of any catalytic process depends on the reusability of the catalyst. In the present work, the IL plays the dual role of solvent as well as catalyst. Recyclability of the IL was studied for the preparation of γ-undecalactone under the optimized reaction conditions of 0.5:1.0 molar ratio of IL:UDA at 130 °C over a period of 8 h. In the first reaction conducted with recycled IL, the catalytic activity of the IL was found to decrease, resulting in the formation of 55% of γ-undecalactone. Earlier work carried out by us using the same Lewis acidic IL for the liquid–liquid biphasic novel synthesis of long chain wax esters, the recovered IL was found to be recyclable at least for 6 successive operations.[16] It is not clear at this stage the possible reason for loss of activity of the IL observed in the first recycled reaction for the tandem isomerization–lactonization of UDA to form γ-undecalactone.

In conclusion, a novel and efficient tandem isomerization–lactonization of unsaturated fatty acids to γ-lactones using the Lewis acidic IL, choline chloride·$2ZnCl_2$ as solvent/catalyst is reported.[18] The present method shows superior catalytic activity and enhanced regiospecificity than other reported hazardous catalytic systems. Moreover, lactonization of very long chain fatty acids as well as fatty acids with central double bond (like oleic and erucic acid) could be achieved at ease and the corresponding γ-lactones are obtained in high yields compared to any other reported methods. However, loss in activity of the recovered IL was observed which restricts their recyclability.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.112.

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18. *Preparation of γ-lactones*: (a) γ-undecalactone: A mixture of 10-undecenylic acid (2.0 g; 10.8 mmol) and IL (2.23 g; 5.4 mmol) was stirred at 130 °C. After 8 h, the product was separated from IL by extracting first with ethyl acetate then with hexane. The organic solvent was evaporated using rotary evaporator and dried under vacuum to get 1.88 g of peach flavored γ-undecalactone as clear oil (isolated yield, 94%). The structure of the product was confirmed by ^{1}H and ^{13}C NMR, ESI-Mass and matched well with literature report.[8] ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.46 (tt, 1H, CH–O), 2.51 (dd, 2H, α-CH_2), 2.31–2.26 (m, 1H, β-CH_2), 1.90–1.75 (m, 1H, β-CH_2), 1.75–1.60 (m, 1H, δ-CH_2), 1.60–1.50 (m,1H, δ-CH_2), 1.40–1.20 (m, 10H, $5CH_2$), 0.85 (t, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ):14.0–29.5 (CH_2), 31.8 (β-CH_2), 35.5 (α-CH_2), 81.1 (CH-O), 177.1 (C=O). ESI-Mass *m*/*z*: [m^++Na] 207, [m^++1+Na] 208. (b) *γ-stearolactone:* A mixture of oleic acid (2 g, 7.8 mmol) and IL (2.9 g, 7.8 mmol) was stirred at 150 °C. After 4 h, the product was separated from IL by extracting first with a binary mixture of ethyl acetate and hexane (30:70) and finally with hexane. The organic solvent was evaporated to get 1.73 g of crude product, which was crystallized from acetone at −20 °C to get 1.48 g of γ-stearolactone as white solid (isolated yield, 74%). The structure of the product was confirmed by ^{1}H and ^{13}C NMR, ESI-Mass and matched well with literature report.[4] ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.46 (tt, 1H, CH–O), 2.51 (dd, 2H, α-CH_2), 2.31–2.26(m, 1H, β-CH_2), 1.90–1.75 (m, 1H, β-CH_2), 1.75–1.60 (m, 1H, δ-CH_2), 1.60–1.50 (m, 1H, δ-CH_2), 1.40–1.10 (m, 24H, $12CH_2$), 0.85 (t, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ):14.0–29.5 (CH_2), 31.8 (β-CH_2), 35.5 (α-CH_2), 81.1 (CH–O), 177.1 (C=O). ESI-Mass *m*/*z*: [m^++Na] 305.3, [m^++1+Na] 306.3. (c) *γ-erucalactone:* A mixture of erucic acid (2 g, 5.9 mmol) and IL (2.42 g, 5.9 mmol) was stirred at 150 °C. After 4 h, the product was separated from IL by extracting first with ethyl acetate and then with hexane. The organic solvent was evaporated to get 1.86 g of crude product, which was crystallized from acetone at −20 °C to get 0.8 g of γ-erucalactone as white solid (isolated yield is 42%). The structure of the product was confirmed by ^{1}H NMR, ^{13}C NMR and ESI-Mass. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.46 (tt, 1H, CH–O), 2.51 (dd, 2H, α-CH_2), 2.31–2.26(m, 1H, β-CH_2), 1.90–1.75 (m, 1H, β-CH_2), 1.75–1.60 (m, 1H, δ-CH_2), 1.60–1.50 (m,1H, δ-CH_2), 1.40–1.10(m, 32H, $16CH_2$), 0.85 (t, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ):14.0–29.5 (CH_2), 31.8 (β-CH_2), 35.5 (α-CH_2), 81.1 (CH–O), 177.1 (C=O). ESI-Mass *m*/*z*: [m^++Na] 361.4, [m^++1+Na] 362.4.