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Ytterbium triflate catalyzed synthesis of chlorinated lactones

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ABSTRACT

The direct synthesis of chlorolactones from differently substituted alkenoic acids, using either sodium hypochlorite or chloramine T as the source of electrophilic chlorine and ytterbium triflate hydrate as the Lewis acid is described. In both cases the reactions proceeded in good yields affording selectively five- or six-membered chlorolactones.

1. Introduction

Halolactones are very important building blocks in organic synthesis and natural product chemistry. Among the insofar reported procedures to obtain five- or six-membered halolactones, iodo- and bromolactonization are probably the most used methodologies.[1] Since the pioneering works by Bougalt at the beginning of the 20th century,[2] the preparation of bromo- and iodolactones[3] has been well documented. On the other hand the synthesis of chlorolactones has drawn minor attention and only few methods have been reported till now in the literature.

Damin et al. discovered that the use of chloramine T in conjunction with methanesulfonic acid is able to produce chlorolactones from the corresponding alkenoic acids.[4] Mellegaard and Tunge proposed the use of PhSeCl and *N*-chlorosuccinimide (NCS), and β,γ-unsaturated acids as the way to prepare butenolides, but the reaction afforded mixtures of allyl chlorides and chlorolactones.[5] These authors also demonstrated the capacity of arylselenides to enhance the electrophilicity of halogen sources.[6] More recently, Massanet et al. reported the synthesis of chlorinated β- and γ-lactones from unsaturated acids with sodium hypochlorite under the catalysis of cerium trichloride heptahydrate.[7] This system produced efficiently electrophilic chlorine and constituted an alternative to chlorine gas, avoiding the use of harsh conditions, in agreement with the current concerns of green chemistry. Unfortunately many of these processes suffer major or minor drawbacks such as drastic reaction conditions, low yields, tedious work-up procedures, low selectivity leading to mixture of differently sized rings, co-occurrence of several side reactions, and need of chromatography for purification of adducts.[6,7] Moreover, in the case of transition metals catalyzed reactions (e.g., Ce^{+3}) there is a need of more than stoichiometric amounts of the Lewis acids to efficiently promote the process.

During the last 20 years, rare earth metal triflates have been found as unique Lewis acids in that they are water tolerant reusable catalysts.[8] In continuation of our ongoing studies aimed to develop mild and practical protocols for the synthesis of useful building blocks of biologically active natural compounds using $Yb(OTf)_3$ as the catalyst, it was speculated that this lanthanide salt, which has recently been shown to catalyze a variety of valuable and good yielding carbon–carbon and carbon–heteroatom bond forming reactions,[8,9] might be ideal for effecting the transformation of alkenoic acids into the corresponding chlorolactones starting from cheap sources of electrophilic chlorine like sodium hypochlorite or chloramine T. So, as a part of our studies aimed to explore the utility of lanthanide triflates catalyzed reactions under solvent free conditions,[10] we decided to investigate the use of $Yb(OTf)_3$ as a promoter of the preparation of differently substituted chlorolactones. To this aim herein, we report a simple method to transform unsaturated acids into the corresponding β-, γ- or δ-lactones by the action of electrophilic chlorine generated from sodium hypochlorite or chloramine T and $Yb(OTf)_3$ hydrate as the Lewis acid.

In a preliminary experiment, (*E*)-styrylacetic acid (entry 1) (2 mmol) was dissolved in a 1:1 biphasic mixture of CH_2Cl_2/H_2O (10 mL) and $Yb(OTf)_3$ was added (0.2 mmol).

The medium was vigorously stirred and an aqueous solution of NaClO (2 mmol; 10–13% available electrophilic chlorine) was

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added dropwise along a period of 30 min. After 24 h, work-up and crystallization from *n*-hexane the desired adduct, 4-chloro-5-phenyl-dihydrofuran-2-(3*H*)-one (**2**) was obtained in 48% yield.

Encouraged by results recorded using (*E*)-styryl acetic acid as the substrate, we applied the same reaction conditions, to several differently substituted alkenoic acids. The corresponding chlorolactones were selectively obtained in good yields. Results are reported in the Table 1.

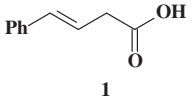
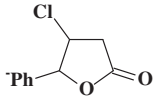
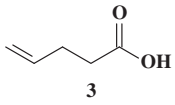
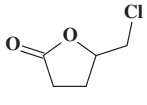
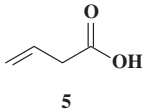
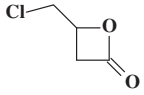
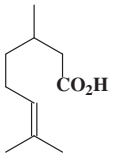
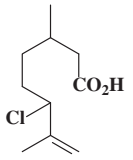
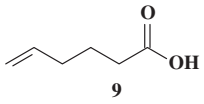
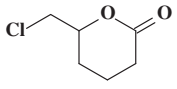
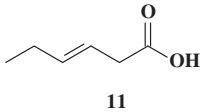
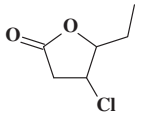
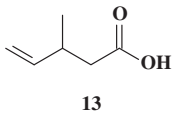
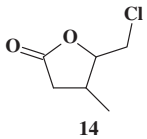
It should be put in evidence that the reaction is effective leading selectively to the formation of five- and six-membered rings. Moreover, it is interesting to note that the treatment of the (*E*)-3-esenoic acid under the above described experimental conditions afforded selectively 4-chloro-5-ethyl-dihydrofuran-2(3*H*)-one (**12**) instead of the two different reaction products, resulting also from the formation of a chlorobutenolide, as describe by Lopez and coworkers.[7] As stated above in any case a chromatographic separation was needed to isolate the adducts that were purified after the work-up by crystallization. In agreement with reported literature data in the same field, citronellic acid failed to furnish the lactone ring. For products (**2**), (**12**), and (**14**) only the *trans* isomers were obtained. Finally at the end of each reaction the catalyst was recovered as previously described[9a] and recycled without any significant loss of its catalytic activity. For example the reaction leading to compound (**2**) was repeated three additional times with the recovered Lewis acids with yields of 43%, 45%, and 46%, respectively.

From a mechanistic point of view we can hypothesize that, due to its high oxophilicity, the role of Yb^{+3} could be first to enhance the electronwithdrawing effects coordinating the oxygen atom in the ClO^- anion leading to a more electrophilic chlorine. The latter could in turn be more easily entrapped by the olefinic double bond leading to the formation of the corresponding chloronium ion and subsequent lactone ring closure.

As anticipated in the introductive remarks, Damin et al. discovered that the use of chloramine T in conjunction with methanesulfonic acid is able to produce chlorolactones from the corresponding alkenoic acids.[4]

On this basis we thought also about verifying the capacity of $Yb(OTf)_3$ to activate the conversion of olefinic acids using chloramine T as an alternative source of electrophilic chlorine, but avoiding the use of strong acids. For this reason, we decided exploring

Table 1
$Yb(OTf)_3$ promoted chlorolactonizations using sodium hypochlorite or chloramine T

Acid	Product	Reactant			
		NaClO (aq)		Chloramine T	
		Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
 **1**	 **2**	24	48	18	64
 **3**	 **4**	22	45	17	68
 **5**	 **6**	20	48	20	68
 **7**	 **8**	24	49	18	65
 **9**	 **10**	22	52	20	69
 **11**	 **12**	23	55	20	69
 **13**	 **14**	24	47	21	70

[a] Yields of pure isolated products, characterized by IR, GC/MS, ^1H NMR, and ^{13}C NMR.

the use of chloramine T as the source of chloronium ion in place of NaClO, performing the reaction using the same conditions as described above. Results are summarized in Table 1.

Also employing chloramine T in our procedure is safe, clean, and not expensive in practical and economical terms, and provides a valuable alternative to the method developed by Damin et al.[4] In fact our yields are significantly improved and the use of toxic solvents such as benzene as well as any kind of chromatographic purification is not required. It is noteworthy that our synthetic process is characterized by better yields than that developed using $CeCl_3{\cdot}7H_2O$[7] as the Lewis acid. Moreover, only 0.2 equiv of the catalyst, instead of a 1:3 ratio between the substrate and the lanthanide, is needed to efficiently promote the conversion of acids into lactones.

When comparing results obtained with the use of chloramine T and NaClO under $Yb(OTf)_3$ catalysis, it is evident that better yields were obtained employing the first reactant. This could be due to the fact that chloramine T has by far a greater solubility in CH_2Cl_2 than NaClO, being at the same time soluble in H_2O, thus facilitating its reaction with alkenoic acids. So it may be hypothesized that an effective reaction occurring at the interface between H_2O and the chlorinated solvent could be claimed as the key step leading to the desired adducts. The same mechanistic considerations given above could explain the formation of chloronium ion and ring closure, while the enhancement of the electrophilic features of the chlorine atom linked to the sulfonamide moiety of chloramine T, may be due to a strong coordination of Yb^{+3} on the oxygen atoms of the $-SO_2-$ moiety which could account for the great reactivity of alkenoic acids employed in this second methodology.

Also in the latter case $Yb(OTf)_3$ was recovered and recycled in the same way as described above. The reaction affording compound (**2**) employing chloramine T was repeated three more times leading to the desired product in 61%, 61%, and 63%, respectively.

In conclusion, in the present work we disclosed an easy and environmentally sound method for the synthesis of chlorinated lactones starting from differently unsaturated acids and a different source of chloronium ion effectively promoted by $Yb(OTf)_3$.The simple work-up procedure, mild reaction conditions, and from good to satisfactory yields make our methodology a valid and alternative contribution to the existing processes in the field of the synthesis of chlorinated lactones.

Further investigation into the scope and other applications of $Yb(OTf)_3$ promoted reactions are now in progress in our laboratories and will be reported in due course.

2. Experimental

2.1. Synthesis of chlorinated lactones with sodium hypochlorite. General procedure

To a stirred solution of alkenoic acid (2 mmol) in a 1:1 CH_2Cl_2/H_2O mixture (10 mL), 0.2 mmol of $Yb(OTf)_3$ (0.2 mmol) was added. The resulting mixture was vigorously stirred for 10 min at room temperature. A solution of NaClO (2 mmol, 10–13% available chlorine) was then added dropwise for 30 min. The reaction was monitored by TLC. After the appropriate time (see Table 1) the reaction mixture was washed with a saturated solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated to dryness. The desired product was then obtained after crystallization from *n*-hexane.

2.2. Synthesis of chlorinated lactones with chloramine T. General procedure

The same procedure as above was done but with the use of chloramine T (2 mmol) instead of NaClO.

2.2.1. 4-Chloro-5-phenyldihydro-2(3*H*)-furanone (2)

Yellow solid (mp: 65–66 °C); IR (neat, cm^{-1}): 1727, 1180; ^1H NMR;[4] ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 24.86, 28.36, 46.69, 78.72, 177.10; GC/MS: $M^+ = 134$, $M^{+2} = 136$. Anal. Calcd for $C_5H_7ClO_2$: C, 44.63; H, 5.24; O, 23.78. Found: C, 44.58; H, 5.27; O, 23.77.

2.2.2. 5-(Chloromethyl)-dihydro-2(3*H*)-furanone (4)

Pale yellow solid (mp: 122–124 °C); IR (neat, cm^{-1}): 1792, 1142; ^1H NMR;[5] (200 MHz, $CDCl_3$) δ 2.89 (dd, $J = 5.5$, 18.1 Hz, 1H), 3.17 (dd, $J = 7.2$, 18.1 Hz, 1H), 4.45 (ddd, $J = 5.3$, 7.2, 4.9 Hz, 1H), 5.59 (d, $J = 4.4$ Hz, 1H), 7.43 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 38.0, 57.7, 87.4, 125.1, 129.0, 129.2, 135.7, 172.7; GC/MS: $M^+ = 197$, $M^{+2} = 199$. Anal. Calcd for $C_{10}H_{10}ClO_2$: C, 61.08; H, 4.61; O, 16.27. Found: C, 61.09; H, 4.56; O, 16.21.

2.2.3. 4-(Chloromethyl)-2-oxetanone (6)

White–yellow solid (mp: 39–40 °C); IR(neat, cm^{-1}): 1750, 1730; ^1H NMR;[11] ^{13}C NMR (200 MHz, $CDCl_3$) δ 41.3, 45.7, 69.8, 167.2; GC/MS: $M^+ = 120$, $M^{+2} = 122$. Anal. Calcd for $C_{10}H_{10}ClO_2$: C, 39.86; H, 4.18; Cl, 29.41; O, 26.55. Found: C, 39.84; H, 4.23; O, 26.51.

2.2.4. 6-Chloro-3,7-dimethyl-7-octenoic acid (8)

Pale yellow solid (mp: 112–114 °C); IR (neat, cm^{-1}): 3500, 1710; ^1H NMR;[7] ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.13, 20.09, 29.05, 34.30, 40.73, 64.30, 115.15, 142.08, 178.33; GC/MS: $M^+ = 204$, $M^{+2} = 206$. Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.37; O, 15.63. Found: C, 58.60; H, 8.35; O, 15.65.

2.2.5. 6-(Chloromethyl)-tetrahydro-*2H*-pyran-2-one (10)

Yellow solid (mp: 85–87 °C); IR (neat, cm^{-1}): 1740, 1170; ^1H NMR;[4] ^{13}C NMR (200 MHz, $CDCl_3$) δ 18.10, 25.21, 29.51, 46.41, 79.12, 171.25; GC/MS: $M^+ = 148$, $M^{+2} = 150$. Anal. Calcd for $C_6H_9ClO_2$: C, 48.50; H, 6.11; O, 21.54. Found: C, 48.56; H, 6.13; O, 21.57.

2.2.6. 4-Chloro-5-ethyldihydro-2(3*H*)-furanone (12)

White solid (mp: 78–80 °C); IR (neat, cm^{-1}): 1772, 1168; ^1H NMR;[7] ^{13}C NMR (200 MHz, $CDCl_3$) δ 10.0, 26.6, 39.7, 42.7, 89.4, 173.5; GC/MS: $M^+ = 148$, $M^{+2} = 150$. Anal. Calcd for $C_6H_9ClO_2$: C, 48.50; H, 6.11; O, 21.54. Found: C, 48.57; H, 6.09; O, 21.51.

2.2.7. 5-(Chloromethyl)-4-methyldihydro-2(3*H*)-furanone (14)

Yellow solid (mp: 78–79 °C); IR (neat, cm^{-1}): 1722, 1185; ^1H NMR;[7] ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.1, 32.1, 32.9, 41.7, 80.9, 175.6; GC/MS: $M^+ = 148$, $M^{+2} = 150$. Anal. Calcd for $C_6H_9ClO_2$: C, 48.50; H, 6.11; O, 21.54. Found: C, 48.52; H, 6.09; O, 21.59.

The degree of purity of each product listed in the Table 1 was analyzed by GC/MS with a Hewlett Packard 6890 gas chromatograph equipped with a 12.5 mm $\times$ 0.25 mm MetSil column couplet to HP Chem Station Software. The carrier gas was helium at a pressure of 3.5 kg/cm^2, and the column temperature was programed from 50 to 270 °C at 10 °C/min. The chromatogram was obtained by using a reporting integrator. Mass spectra were obtained from a GC/MS system operating in the EI mode at 70 eV, equipped with a 12.5 mm $\times$ 0.25 mm MetSil column and an HP5973 Mass selective detector, by using the same chromatographic conditions reported above. The column was connected to the mass spectrometer insource through an open-split interface heated at 250 °C. ^1H and ^{13}C NMR spectra were recorded by using the same general procedure as already reported in Ref. 12.

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