Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1749–1752

Synthesis of chlorinated β- and γ-lactones from unsaturated acids with sodium hypochlorite and Lewis acids

José A. López-López, Francisco M. Guerra, F. Javier Moreno-Dorado, Zacarías D. Jorge and Guillermo M. Massanet*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, Polígono Río San Pedro S/N, 11510 Puerto Real, Cádiz, Spain

Received 21 November 2006; revised 8 January 2007; accepted 9 January 2007
Available online 13 January 2007

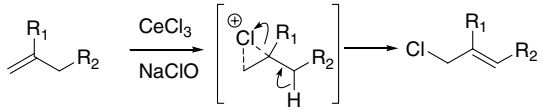
Abstract—The direct synthesis of several β- and γ-lactones used as electrophilic sources of chlorine, sodium hypochlorite and a Lewis acid is described. The scope and limitations of the method are discussed.

1. Introduction

Recently, we have reported the allylic chlorination of terminal double bonds by sodium hypochlorite promoted by cerium trichloride heptahydrate.[1] This system produces efficiently electrophilic chlorine and constitutes an easy and safe alternative to the use of chlorine gas, avoiding the use of harsh conditions, in agreement with the current concerns of green chemistry.

The mechanistic insights of the reaction point to a cerium-promoted formation of a chloronium ion and the subsequent loss of the adjacent proton (Scheme 1). We thought that this chloronium ion could be trapped intramolecularly by a nucleophilic group present in the molecule so as to give rise to a heterocyclic ring. If such a group resulted to be a carboxylic acid, the corresponding lactone should be formed (Scheme 2).[2]

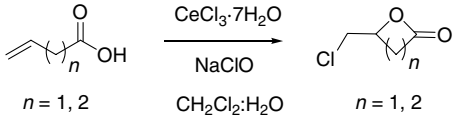
Since the pioneering works by Bougalt at the beginning of the twentieth century,[3] the preparation of bromo and



Scheme 1. Allylic chlorination with $CeCl_3{\cdot}7H_2O$/NaClO.

Keywords: γ-Lactone; β-Lactone; Lactonization; Sodium hypochlorite; Lewis acid.
* Corresponding author. Tel.: +34 956 016366; fax: +34 956 016193; e-mail: g.martinez@uca.es

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.043



Scheme 2. Chlorolactonization with $CeCl_3{\cdot}7H_2O$/NaClO.

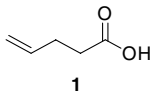
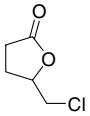
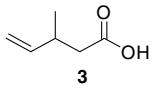
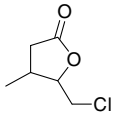
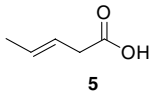
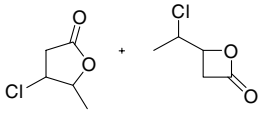
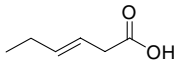
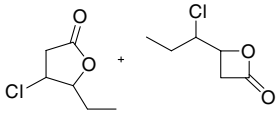
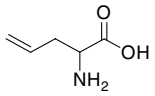
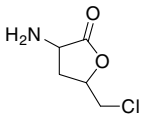
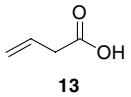
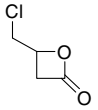
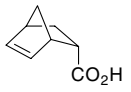
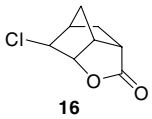
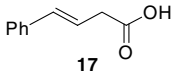
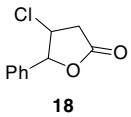
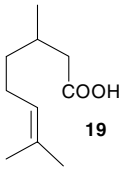
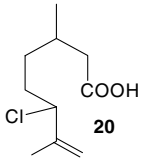
iodolactones[4] has been well documented. The synthesis of chlorolactones has drawn minor attention and only a few methods have been reported.

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.[5] Mellegaard and Tunge proposed the use of PhSeCl and NCS in β,γ-unsaturated acids as a way to prepare butenolides, but the reaction produced mixtures of allyl chlorides and chlorolactones.[6] These authors have also demonstrated the capacity of arylselenides to enhance the electrophilicity of halogen sources.[7]

2. Results and discussion

Herein, we report a simple method to transform β,γ- and γ,δ-unsaturated acids into the corresponding β- or γ-lactones by the action of electrophilic chlorine generated from sodium hypochlorite and a Lewis acid. The choice of the Lewis acid is a key point. Given our experience in the use of cerium trichloride, this metal was our first option, but as in the case of the allylic chlorination, we soon discovered that other metallic salts were also

Table 1. Chlorolactonization of unsaturated carboxylic acids with Lewis acid/NaClO[a]

Entry	Substrate	Products	Yield (%) γ-chlorolactone:β-chlorolactone ratio						
			$CeCl_3 \cdot 7H_2O$	$FeCl_3 \cdot 6H_2O$	$CuCl_2 \cdot 2H_2O$	$MgCl_2 \cdot 6H_2O$	$ZnCl_2$	$SnCl_2$	$Ce(NO_3)_3 \cdot 6H_2O$
1	 **1**	 **2**	95	96	94	100	94	40	95
2[b]	 **3**	 **4**	95	94	100	96	95	37	92
3[c]	 **5**	 **6** **7**	100 4:1	80 1:0	100 4:1	100 1:0	100 3:1	61 2:1	100 4:1
4[c]	 **8**	 **9** **10**	100 7:2	80 1:0	100 7:2	100 1:0	100 7:3	35 2:1	100 7:2
5[b]	 **11**	 **12**	89	92	91	100	97	100	86
6	 **13**	 **14**	93	0[d]	92	95	75	56	89
7	 **15**	 **16**	96	91	88	93	92	63	95
8	 **17**	 **18**	80	80	100	100	85	21	80
9	 **19**	 **20**	100	100	96	85	97	48	90

[a] All reactions were run at room temperature in a 1:1 CH_2Cl_2/H_2O mixture, with 3 equiv of $MCl_n \cdot mH_2O$ (1.5 equiv when $FeCl_3 \cdot 6H_2O$ is employed).
[b] The observed ratio *syn*/*anti* is in all cases 2:3.
[c] Only a single stereoisomer is observed for compounds **6**, **7**, **9** and **10**.
[d] Only dichlorination of the double bond was observed.

capable of promoting the transformation of pent-4-enoic acid into the corresponding γ-lactone **2** (Table 1, entry 1). This reaction was run in a biphasic system, employing a water/dichloromethane mixture as solvent and 3 equiv of Lewis acid and sodium hypochlorite in most cases. The results are summarized in Table 1.

The presence of a methyl group in the main chain of the carboxylic acid does not influence the outcome of the reaction. Thus, treatment of 3-methylpent-4-enoic acid **3** (entry 2) under the above described conditions produced 5-(chloromethyl)-4-methylfuranone **4** in high yields (except with $SnCl_2$, vide infra).

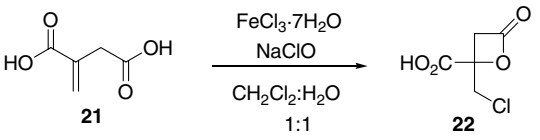
In all those cases in which regioselection is an issue, the formation of the most stable lactone is preferred. Interestingly, treatment of (*E*)-pent-3-enoic acid **5** (entry 3) provided β-lactone **7** in moderated yields. When the formation of the β-lactone was the only possibility, the yields resulted to be almost quantitative. Thus, treatment of but-3-enoic acid **13** with 3 equiv of $MgCl_2{\cdot}6H_2O$ produced the corresponding β-lactone **14** in 95% yield (entry 6).

It is also noteworthy the transformation of the amino-acid D,L-allylglycine into 3-amino-3-(chloromethyl)furanone **12** as a mixture of epimers. This reaction transcurred quantitatively when $MgCl_2$ or $SnCl_2$ was employed (entry 5).

The presence of an aromatic substituent as in styryl-acetic acid **17** (entry 8) is also tolerated and the reaction occurred in yields up to 80% of lactone **18**. The presence of chlorinated products in the aromatic ring was not observed.

The influence of the distance of the carboxyl group to the chloronium ion was also inspected. When the carboxyl group is too far apart from the chloronium ion, the reaction is not possible and other competitive reactions take place. In all those cases in which we attempted to get a δ-lactone, only addition of molecular chlorine to the double bond was observed. In the case of citronellic acid **19** (entry 9), only the product from the allylic chlorination was formed.

Regarding the nature of the metal, the best yields were observed by the employment of $MgCl_2{\cdot}6H_2O$, in high to quantitative yields. On the other side, $SnCl_2$ produced the poorest results, although surprisingly, this metal chloride was able to transform allylglycine quantitatively into the corresponding amino chlorinated γ-lactone **12** (entry 5). The behaviour of $FeCl_3$ was also different. First, when 3 equiv of this reagent was employed, only the addition of chlorine to the double bond was observed. When the amount of $FeCl_3$ was reduced to 1.5 equiv, the behaviour was similar to other metals, and more interestingly, it was able to transform itaconic acid into the highly functionalized lactone 4-carboxy-4-(chloromethyl) oxetanone **22** (Scheme 3). This transformation failed with the other different metals assayed.



Scheme 3. Transformation of itaconic acid into 4-carboxy-4-chloromethyl oxetanone.

Finally, in order to study the role of the anion chloride, we decided to run the reactions in the presence of cerium nitrate hexahydrate. The yields were in the same range as that in the other metallic chlorides, suggesting that a chloride as a counterion of the metal is not necessary, and that the sodium hypochlorite is able to provide the chlorine atoms needed for the reaction to proceed.

All the reactions were finished after 30 min. The transformation from the carboxylic acid to the lactone started immediately after the addition of the very first drop of sodium hypochlorite solution, so at the end of the addition of NaOCl, the reaction was almost finished. In order for the reaction to proceed, the carboxylic group must be located two or three bonds far from the double bond. The procedure is safe, clean and inexpensive, constituting an alternative to consider for the preparation of this type of valuable synthons.

3. General procedure

The following procedure can be considered as representative. The amount of metal should be reduced to 1.5 equiv in the case of $FeCl_3{\cdot}6H_2O$.

3.1. Synthesis of β- and γ-lactones with $CeCl_3{\cdot}7H_2O$/NaClO

The unsaturated acid (1 mmol) was dissolved in CH_2Cl_2/H_2O mixture (1:1, 10 mL) and $CeCl_3{\cdot}7H_2O$ was added (3 equiv). The mixture was vigorously stirred and diluted NaClO (10–13% available chlorine, 3 equiv) aqueous solution was added dropwise for 10 min. After stirring for 30 min, saturated aqueous Na_2SO_3 solution was added and the mixture was filtered through Celite. The filtered mixture was extracted with EtOAc (3×20 mL). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford the corresponding chlorolactone.

3.2. Selected spectroscopic data for novel compounds[8]

3.2.1. 5-Chloromethyl-4-methylfuranone 4. ^{1}H NMR ($CDCl_3$, 400 MHz, diasteromers mixture): trans-isomer: 4.6 (dt, 1H, H-5, $J = 6.28$ Hz), 3.62 (m, 1H, H-6), 2.73 (dd, 1H, H-3_a, $J = 13.4$, 8.4 Hz), 2.5 (m, 1H, H-4), 2.16 (dd, 1H, H-3_b, $J = 13.0$, 9.3, 4.1 Hz), 1.11 (d, 2H, H-7, $J = 6.87$ Hz). Cis-isomer: 4.22 (m, 1H, H-5), 3.68 (d, 2H, H-6, $J = 4.68$ Hz), 2.68 (dd, 1H, H-3_a, $J = 13.0$, 9.3 Hz), 2.28 (m, 1H, H-4), 2.15 (dd, 1H, H-3_b, $J = 13.0$, 9.3 Hz), 1.06 (d, 2H, H-7, $J = 6.87$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz). Trans-isomer: 175.8, 84.8, 44.5, 36.8, 36.5, 18.3. Cis-isomer: 175.6, 80.9, 41.7, 32.9, 32.1, 13.1.

3.2.2. 4-Chloro-5-methyl-dihydrofuran-2(3*H*)-one 6. ^{1}H NMR ($CDCl_3$, 400 MHz): 4.62 (dt, 1H, H-5, $J = 8.0$, 5.1 Hz), 4.15 (ddd, 1H, H-4, $J = 7.9$, 7.0, 5.6 Hz), 3.09 (dd, 1H, H-3_a, $J = 18.2$, 7.7 Hz), 2.75 (dd, 1H, H-3_b, $J = 18.3$, 6.9 Hz), 1.41 (d, 3H, H-6, $J = 7.5$ Hz). ^{13}C NMR: 172.6, 83.64, 56.35, 38.49, 18.48.

3.2.3. 4-(1-Chloroethyl)oxetan-2-one 7. ^{1}H NMR ($CDCl_3$, 400 MHz): 5.18 (ddd, 1H, H-4, $J = 8.8$, 5.6, 4.1 Hz), 4.43 (td, 1H, H-5, $J = 8.9$, 3.4 Hz), 3.56 (dd, 1H, H-3_a, $J = 16.7$, 5.7 Hz), 2.77 (dd, 1H, H-3_b, $J = 16.7$, 4.2 Hz), 1.55 (d, 3H, H-6, $J = 7.4$ Hz). ^{13}C NMR: 166.4, 72.1, 49.4, 41.6, 20.7.

3.2.4. 4-Chloro-5-ethyl-dihydrofuran-2(3*H*)-one 9. ^{1}H NMR ($CDCl_3$, 400 MHz): 4.60 (dt, 1H, H-5, $J = 8.0$, 5.1 Hz), 4.19 (ddd, 1H, H-4, $J = 7.9$, 7.0, 5.6 Hz), 3.20 (dd, 1H, H-3_a, $J = 17.9$, 8.0 Hz), 2.92 (dd, 1H, H-3_b, $J = 18.0$, 6.9 Hz), 1.86 (m, 1H, H-6_a), 1.71 (m, 1H, H-6_b), 1.10 (t, 3H, H-7, $J = 7.5$ Hz). ^{13}C NMR: 173.5, 89.4, 42.7, 39.7, 26.6, 10.0.

3.2.5. 4-(1-Chloropropyl)oxetan-2-one 10. ^{1}H NMR ($CDCl_3$, 400 MHz): 4.54 (ddd, 1H, H-4, $J = 8.8$, 5.6, 4.1 Hz), 3.99 (td, 1H, H-5, $J = 8.5$, 3.7 Hz), 3.65 (dd, 1H, H-3_a, $J = 16.7$, 5.7 Hz), 3.35 (dd, 1H, H-3_b, $J = 16.2$, 4.4 Hz), 2.13 (m, 1H, H-6_a), 1.83 (m, 1H, H-6_b), 1.14 (t, 3H, H-7, $J = 7.4$ Hz). ^{13}C NMR: 167.2, 71.7, 57.2, 44.2, 28.2, 11.9.

3.2.6. 4-Carboxy-4-(chloromethyl)oxetanone 22. ^{1}H NMR (DMSO-d_6, 400 MHz): 4.25 (dd, 2H, H-6, $J = 12.3$, 11.1 Hz), 3.82 (dd, 2H, H-3, $J = 26.9$, 16.9 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 175.8, 167.9, 94.6, 47.6, 31.9.

Acknowledgement

This investigation was supported by the Consejería de Medio Ambiente de la Junta de Andalucía.

References and notes

1. Moreno-Dorado, F. J.; Guerra, F. M.; Manzano, F. L.; Aladro, J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2003**, *44*, 6691–6693.
2. Van Tamelen, E. E.; Shamma, M. *J. Am. Chem. Soc.* **1954**, *76*, 2315.
3. (a) Bougault, M. J. *Ann. Chim. Phys.* **1908**, *14*, 145; (b) Bougault, M. J. *Ann. Chim. Phys.* **1908**, *15*, 296.
4. (a) Arnold, R. T.; Campos, M. M.; Lindsay, K. L. *J. Am. Chem. Soc.* **1953**, *75*, 1044; (b) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *38*, 800–802; (c) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; 1991; pp 363–421; (d) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2002**, 3099; (e) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273–5308; (f) Drake, M. D.; Bateman, M. A.; Detty, M. R. *Organometallics* **2003**, *22*, 4158–4162; (g) Mellegaard-Waetzig, S. R.; Wang, C.; Tunge, J. A. *Tetrahedron* **2006**, *62*, 7191–7198.
5. Damin, B.; Forestiere, A.; Garapon, J.; Sillion, B. *J. Org. Chem.* **1981**, *46*, 3552.
6. Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979–8981.
7. Wang, C.; Tunge, J. *Chem. Commun.* **2004**, 2694–2695.
8. Lactones **2**, **6**, **7**, **9**, **10**, **12**, **14**, **16** and **18** have been previously reported in the following articles. Lactone **2**: see Ref. 5; lactones **6**, **7**, **9** and **10**: Gauthier, P. M. F.; Le Moult, M. M. P.; Rochelle, J. C.; Senet, J. P. EU Patent FR2655334, 1991 (No spectroscopic data are provided in the patent); lactone **12**: Witkop, B.; Beiler, T. *J. Am. Chem. Soc.* **1956**, *78*, 2882–2893; lactone **14**: Iida, M.; Araki, T.; Teranishi, K.; Tani, H. *Macromolecules* **1997**, *10*, 275–284; lactone **16**: Hart, H.; Chloupek, F. J. *J. Am. Chem. Soc.* **1961**, *85*, 1155–1160, lactone **18**: see Ref. 6.