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An effective method for the preparation of chlorolactones

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Abstract

The effective chlorolactonization of alkenoic acids with (diacetoxyiodo)benzene and lithium chloride under mild conditions have been studied. Experiments show that various 4-pentenoic acids react with (diacetoxyiodo)benzene and lithium chloride fluently in CH_3OH at room temperature, obtaining five-membered chlorolactones in good yields in short times. Other alkenoic acids, such as 3-butenoic acid and *trans* 3-hexenoic acid give some more complicated results, and 4-pentynoic acid provides a chloroenol lactone with *Z* configuration in 40% of yield.

Keywords: Chlorolactone; (Diacetoxyiodo)benzene; Alkenoic acid; Preparation

Halolactonization have been studied extensively, and this type of transformation serves as an important key reaction in a variety of syntheses [1–3]. Whereas bromo- and iodolactonization are generally well documented, there are relatively few examples of the preparation of chlorolactones. The conversion of unsaturated carboxylic acids into chlorolactones is the classical process by adding of chlorine to the salts of unsaturated acids. However, molecular chlorine is a highly toxic, difficult to handle gas and dichlorocompounds are generally formed as byproducts [4]. To improve the chlorolactonization, chloramine T and sodium hypochlorite with Lewis acids were used to replace Cl_2 for the reaction have been successful [5,6]. Diphenyl diselenide and catalyst $(DHQD)_2PHAL$ catalyzed the chlorolactonization of unsaturated acids with *N*-chlorosuccinimide under mild conditions provided newer methods [7,8]. The conversion of alcohols into their corresponding chlolides was another method [9–11], but usually it needed multi-step reaction sequences. Recently, a convenient method for the bromolactonization of 4-pentenoic acid using hypervalent iodine reagent (diacetoxyiodo)benzene (DIB) and lithium bromide has been reported [12,13]. In order to extend the scope and develop a simple, mild and efficient chlorolactonization, we have investigated the cyclization of alkenoic acids with DIB and LiCl. Herein we report a novel and efficient chlorolactonization of unsaturated acids and a series of five-membered chlorolactones are obtained in good yields.

At the beginning, we select 4-pentenoic acid (**1a**) as the representative of alkenoic acids and mix it with equal equivalent of DIB and three equivalents of LiCl in THF at room temperature, we find that the reaction proceeds smoothly and only in 1 h it is compeled, a product of 5-(chloromethyl)-γ-butyrolactone (**2a**) is obtained in 56% of yield. Then, a series of experiments are performed on the reaction of 4-pentenoic acid with DIB and chlorides in 1 h in

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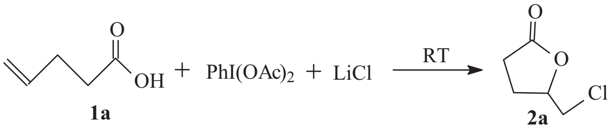
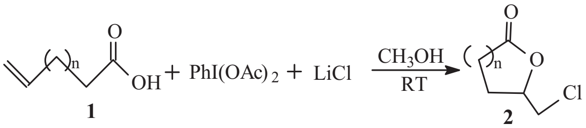


Scheme 1.

Table 1
Optimization of the chlorolactonization of 4-pentenoic acid.

Entry	DIB (equiv.)	LiCl (equiv.)	Solvent	Yield (%)[a]
1	1.0	3.0	CH_2Cl_2	21
2	1.0	3.0	THF	56
3	1.0	3.0	CH_3CN	42
4	1.0	3.0	DMF	22
5	1.0	3.0	CH_3OH	73
6	1.0	NaBr (3.0)	CH_3OH	20
7	1.0	KBr (3.0)	CH_3OH	8
8	1.0	NH_4Br (3.0)	CH_3OH	23
9	0.5	3.0	CH_3OH	33
10	0	3.0	CH_3OH	0

[a] Isolated yield.



Scheme 2.

order to determine the optimum reaction conditions (Scheme 1), the results are summarized in Table 1. It is shown that CH_3OH is the most preferred solvent (entries 1–5). Among chlorides, LiCl is the best chioce and others, such as KCl, NaCl and NH_4Cl are not effective in the reaction (entries 5–8). When the amount of DIB is one equivalent and LiCl is three equivalents, the yield reaches the highest of 73% (entries 5, 9, 10).

Under the optimum reaction conditions, the reaction of a series of alkenoic acids (**1**) with lithium chloride and (diacetoxyiodo)benzene in CH_3OH at room temperature is investigated (Scheme 2), and several chlorolactones (**2**) are provided in good yields, which are characterized by ^1H NMR, ^{13}C NMR, IR, MS, HRMS spectra and melting points, the good results are summarized in Table 2.

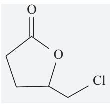
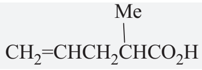
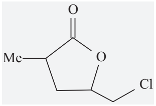
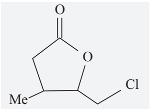
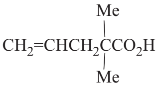
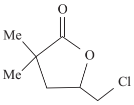
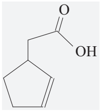
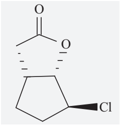
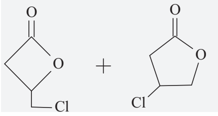
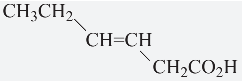
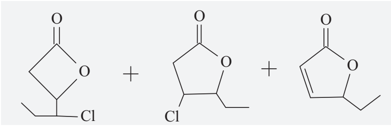
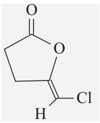
It is shown from Table 2 when a series of 4-pentenoic acids are used in the reaction, the desired products of 5-(chloromethyl)-γ-butyrolactones are obtained in good yields (entries 1–4); while 2-cyclopentene-1-acetic acid (**1e**) is used, the reaction provides the corresponding product in middle yield due to the restrictive effect of the ring (entry 5). Similar treatment of 3-butenoic acid and *trans* 3-hexenoic acids, the reactions give more complicated results: a four-membered ring chlorolactone and a five-membered ring chlorolactone are obtained from 3-butenoic acid with a ratio of 3:2; *trans* 3-hexenoic acids also provides a four-membered ring chlorolactone and a five-membered ring chlorolactone with the same ratio, besides both of them, an unsaturated lactone (**2j**) is found by ^1H NMR technique (entries 6, 7). When 4-pentynoic acid is used in the protocol, a chloroenol lactone with *Z* configuration is provided in 40% yield (entry 8). Efforts for preparation of the six-membered chlorolactone using 5-hexenoic acid are not successful, it means that this reaction is in favor of five-membered ring lactones and four-membered ring lactones.

The proposed mechanism for the chlorolactonization of alkenoic acids is similar to the literature procedure [14], which includes the electrophilic addition of (diacetoxyiodo)benzene on the double bond, then an intramolecular nucleophilic displacement is happened, following another nucleophilic displacement to give the chlorolactone.

A typical procedure for the chlorolactonization of alkenoic acids is as follows:

4-Pentenoic acid (**1a**) (0.3 mmol), (diacetoxyiodo)benzene (0.3 mmol) and lithium chloride (0.9 mmol) are added in CH_3OH (2 mL). The mixture is stirred at room temperature for 1 h and then separated on a silica gel plate using (3:2

Table 2
The result of the chlorolactonization of alkenoic acids.

Entry	Alkenoic acids (**1**)	Chlorolactones (**2**)	Yield (%)[a]
1	$CH_2{=}CH(CH_2)_2CO_2H$ **1a**	 **2a** [5]	73
2	 $CH_2{=}CHCH_2\overset{Me}{C}HCO_2H$ **1b**	 **2b** [15]	81
3	 $CH_2{=}CH\overset{Me}{C}HCH_2CO_2H$ **1c**	 **2c** [6]	80
4	 $CH_2{=}CHCH_2\overset{Me}{\underset{Me}{C}}CO_2H$ **1d**	 **2d** [16]	87
5	 **1e**	 **2e**	55
6	$CH_2{=}CHCH_2CO_2H$ **1f**	 **2f** [6] + **2g** [17]	(37 + 23)[b]
7	 $CH_3CH_2CH{=}CHCH_2CO_2H$ **1g**	 **2h** [6] +**2i** [6] + **2j** [18]	(30 + 20 + 20)[b]
8	$CH{\equiv}C(CH_2)_2COOH$ **1h**	 **2k** [19]	40

[a] Isolated yield.

[b] Determined by the 1H NMR.

hexane:ethyl acetate) as eluant, giving 5-(chloromethyl)-γ-butyrolactone (**2a**) in 73% of yield. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.80–4.76 (m, 1H), 3.76–3.68 (m, 2H), 2.70–2.61 (m, 1H), 2.60–2.54 (m, 1H), 2.46–2.39 (m, 1H), 2.22–2.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.10, 78.72, 46.69, 28.36, 24.86; IR (film, cm^{-1}) 1775, 1182; MS (EI, *m/z*, %): 136 (^{37}Cl M$^+$, 2.3), 134 (^{35}Cl M$^+$, 5.8), 85 (100).

In summary, we have successfully developed an effective chlorolactonization of pentenoic acids with (diacetoxyiodo)benzene and lithium chloride, several 5-(chloromethyl)-γ-butyrolactones are obtained in good yields. This method has some advantages such as mild reaction conditions, simple procedure and good yields. Furthermore, the scope of hypervalent iodine reagents in organic synthesis could be extended.

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