Study on the bromolactonisation of alkenoic acids with (diacetoxyiodo)benzene

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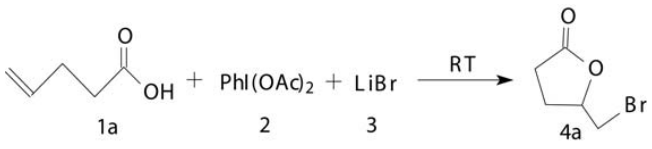
A study on the bromolactonisation of alkenoic acids is reported. When various pent-4-enoic acids reacted with (diacetoxyiodo)benzene (DIB) and lithium bromide in CH_3OH at room temperature, most of the five-membered bromolactones were obtained in good to excellent yields in short times. Some had two diastereoisomers. When but-3-enoic acid and *trans*-hex-3-enoic acid were treated under the same conditions, only unsaturated lactones were found after workup. When hex-5-enoic acid was subjected to the same conditions, however, the desired six-membered bromolactone was not successfully separated.

Keywords: bromolactonisation, alkenoic acids, (diacetoxyiodo)benzene

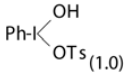
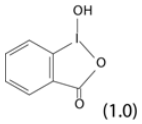
Lactonisations have been studied extensively, and this type of transformation serves as an important key reaction in a variety of syntheses.[1–3] Among them, halolactonisation and phenylselenolactonisation are general used methods.[4–7] Usually, alkenoic acids are used to construct lactones by halolactonisation, which involves the electrophilic addition of molecular halogens to the double bond followed by an intramolecular nucleophilic cyclisation.[8,9] Iodolactonisation is the most widespread applied halolactonisation as molecular iodine is a less toxic and easy to handle solid. Bromolactonisation has the restriction of molecular bromine is a toxic, difficult to handle, low-boiling lachrymatory liquid and also a strong oxidant.[10,11] To improve the bromolactonisation, *N*-bromosuccinimide (NBS) in combination with catalysts has been used successfully to replace Br_2.[12–16] Bis(2,6-disubstitutedpyridine)bromonium triflates and dibromodiarylselenium (IV) species have been reported to be efficient sources of positive bromine[17,18] and NaBr and H_2O_2 with selenoxide, arylseleninic acids and organotelluride as catalysts were found to be effective.[19–22] Recently, Braddock *et al*. reported a convenient method for the bromolactonisation of pent-4-enoic acid using the hypervalent iodine reagent (diacetoxyiodo)benzene (DIB) and lithium bromide; however, there was only one example.[23] Therefore, in order to extend the scope and develop a simple, mild and efficient bromolactonisation, we have investigated the cyclisation of alkenoic acids with DIB and LiBr, and found that the reaction was suitable for a series of pent-4-enoic acids, most of which gave good to excellent yields of 5-(bromomethyl)-γ-butyrolactones.

At the beginning, we mixed equal equivalents of pent-4-enoic acid (1a), DIB (**2**) and LiBr (**3**) in THF at room temperature, and found that after 25 min the reaction was completed as indicated in Braddock *et al*.'s report. [23] A product of 5-(bromomethyl)-γ-butyrolactone (**4a**) was obtained in 68% yield. Then, a series of experiments was performed on the reaction of pent-4-enoic acid with hypervalent iodine reagents and bromides in order to determine the optimum reaction conditions. The results are summarised in Table 1. It is shown that

Table 1 Optimisation of the bromolactonisation of pent-4-enoic acid



1a 2 3 4a

Entry	DIB (equiv reagent)	LiBr (equiv reagent)	Solvent	Time	Yield/%[a]
1	1.0	1.0	CH_2Cl_2	16 h	54
2	1.0	1.0	THF	25 min	68
3	1.0	1.0	CH_3CN	1 h	58
4	1.0	1.0	DMF	120 h	22
5	1.0	1.0	CH_3OH	20 min	74
6	1.0	NaBr (1.0)	CH_3OH	30 min	74
7	1.0	KBr (1.0)	CH_3OH	20 min	49
8	1.0	NH_4Br (1.0)	CH_3OH	40 min	66
9	PhI=O(1.0)	1.0	CH_3OH	1 h	68
10	$PhI(OCOCF_3)_2$ (1.0)	1.0	CH_3OH	1 h	47
11	 (1.0)	1.0	CH_3OH	1 h	34
12	 (1.0)	1.0	CH_3OH	1 h	67
13	2.0	2.0	CH_3OH	1 h	69
14	2.0	1.0	CH_3OH	1 h	80
15	1.0	2.0	CH_3OH	1 h	89

[a] Isolated yields.

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the yield of the product depended on solvent and CH_3OH was found to be preferred (entries 1–5). LiBr as well as NaBr were more active in the reaction than the other two bromides (entries 5–8). As a suitable hypervalent iodine reagent, DIB was the most effective one (entries 5, 9–12). When the amount of DIB was one equivalent and LiBr was two equivalents, the yield reached the highest, 89% (entries 5, 13–15).

Under the optimum reaction conditions, the reaction of a series of alkenoic acids (**1**) with DIB (**2**) and LiBr (3) in CH_3OH at room temperature were investigated. Table 2 shows that all the reactions were completed in 2 h. However, the corresponding products were quite different: when a series of pent-4-enoic acids was used in the reaction, the desired 5-(bromomethyl)-γ-butyrolactones were obtained, in good to excellent yields (entries 1–4); while 2-cyclopentene-1-acetic acid (**1e**) in the reaction gave the corresponding product only in 43% yield due to the restrictive effect of the ring (entry 5). On similar treatment of but-3-enoic acid and *trans*-hex-3-enoic acids, the reaction only provided the unsaturated lactones, not the desired bromolactones (entries 6 and 7). It was found by an ^{1}H NMR technique that the desired five-membered ring lactones and four-membered ring lactones were first formed, which were then transformed into the unsaturated lactones during workup procedure by elimination. Efforts for the preparation of the six-membered lactone 6-bromomethyltetrahydropyran-2-one using hex-5-enoic acid were only partially successful: the ^{1}H NMR spectrum of the crude product was indicative of it, but purification was not achieved.

Table 2 The result of the bromolactonisation of alkenoic acids

Entry	Alkenoic acids (**1**)	Bromolactones (**4**)	Time /h	Yield /%[a]
1	CH_2=CH$(CH_2)_2CO_2H$ **1a**	**4a**	1	89
2	CH_2=C(Me)CH_2CHCO_2H **1b**	**4b**	1	93
3	CH_2=CH(Me)$CHCH_2CO_2H$ **1c**	**4c**	1	87
4	CH_2=C(Me)CH_2CCO_2H (Me) **1d**	**4d**	1	95
5	**1e**	**4e**	0.5	43
6	CH_2=$CHCH_2CO_2H$ **1f**	**4f**	1	60
7	CH_3CH_2, CH=CH, CH_2CO_2H **1g**	**4g**	2	41

[a] Isolated yield.

Koser *et al*. in 1988 reported another lactonisation using the hypervalent iodine reagent, [hydroxyl((bis(phenyloxy)phosphoryl)oxy)iodo]benzene, and they found when 2-methylpent-4-enoic acid (**1b**) was treated with the hypervalent iodine reagent, the products were mixture of diastereoisomers, the ratios varied from 1.2 to 1.4:1.[24] In our reaction protocol, we also found when **1b** was used, the corresponding products were mixture of diastereoisomers and the ratio was 40:60, which was determined by examination of the ^{1}H NMR spectra of the bromolactones; while 3-methyl-pent-4-enoic acid (**1c**) was treated in the reaction, the ratio for the obtained mixture of diastereoisomers was 56:44.

A plausible mechanism is similar to the literature proposal,[23] which included the electrophilic addition of hypervalent iodine reagent **1** to the alkene, then an intramolecular nucleophilic displacement occurred, followed by another nucleophilic displacement to give the bromolactone.

In conclusion, we have successfully studied the bromolactonisation of alkenoic acids with (diacetoxyiodo)benzene, extended the application scope of the simple and efficient cyclisation and found that the reaction was suitable for a series of pent-4-enoic acids, most of which gave good to excellent yields of 5-(bromomethyl)-γ-butyrolactones. Other novel bromolactonisation reactions, such as using catalytic amounts of hypervalent iodine (III) reagents for bromolactonisations are being investigated, and will be reported in due course.

Experimental

IR spectra were recorded on a Thermo-Nicolet 6700 instrument, ^{1}H NMR spectra were measured on a Bruker AVANCE (500M) spectrometer, and mass spectra were determined on a Thermo-ITQ 1100 mass spectrometer. Diacetoxyiodo)benzene and all alkenoic acids are commercially available.

Bromolactonisation of alkenoic acids; general procedure

The alkenoic acid **1** (0.3 mmol), (diacetoxyiodo)benzene **2** (0.3 mmol) and lithium bromide **3** (0.6 mmol) were added to CH_3OH (2 mL). The mixture was stirred at room temperature for 1–2 h (shown in Table 2) and then separated on a silica gel plate using (3:2 hexane-ethyl acetate) as eluant to give **4** in good to excellent yields.

5-(Bromomethyl)-γ-butyrolactone **(4a)** [23]: Oil. ^{1}H NMR (500MHz, $CDCl_3$): 4.78–4.73 (m, 1H), 3.59–3.52 (m, 2H), 2.69–2.63 (m, 1H), 2.61–2.54 (m, 1H), 2.49–2.42 (m, 1H), 2.15–2.11(m, 1H). ^{13}C NMR (125MHz, $CDCl_3$): 176.1, 77.9, 34.0, 28.3, 26.2. IR (film): ν = 2962, 1777, 1168, 1023, 917 cm^{-1}. MS (EI, *m/z*, %): 179 (13), 181 (14), 99 (100).

2-Methyl-5-(bromomethyl)-γ-butyrolactone **(4b)** [25]: Oil. ^{1}H NMR (500MHz, $CDCl_3$): 4.78–4.73 (**3b$_1$**) and 4.61–4.55 (**3b$_2$**) (m, 1H), 3.60–3.57 (**3b$_1$**) and 3.54–3.50 (**3b$_2$**) (m, 2H), 2.86–2.81 (**3b$_1$**) and 2.78–2.71 (**3b$_2$**) (m, 1H), 2.66–2.60 (**3b$_1$**) and 2.44–2.38 (**3b$_2$**) (m, 1H), 2.13–2.07 (**3b$_1$**) and 1.75–1.68 (**3b$_2$**) (m, 1H), 1.31 (d, *J* = 7.0 Hz, 3H), ^{13}C NMR (125MHz, $CDCl_3$): 179.1, 178.4, 75.9, 75.8, 35.6, 35.5, 34.0, 33.8, 33.7, 33.5, 16.1, 15.0. IR (film): ν = 2975, 1775, 1182, 1157, 1016, 927 cm^{-1}. MS (EI, *m/z*, %): 193 (100), 195 (93).

3-Methyl-5-(bromomethyl)-γ-butyrolactone **(4c)** [26]: Oil. ^{1}H NMR (500MHz, $CDCl_3$): 4.72–4.69 (**3c$_1$**) and 4.30–4.27 (**3c$_2$**) (m, 1H), 3.63–3.44 (m, 2H), 2.84–2.50 (m, 2H), 2.34 (dd, *J* = 17.0, 3.5 Hz, **3c$_1$**) and 2.25 (dd, *J* = 18.0, 8.0 Hz, **3c$_2$**) (1H), 1.23 (d, *J* = 7.0 Hz, **3c$_1$**) and 1.17 (d, *J* = 7.0 Hz, **3c$_2$**) (3H). ^{13}C NMR (125MHz, $CDCl_3$): 175.6, 175.3, 84.5, 80.9, 37.2, 36.6, 34.1, 34.0, 32.5, 32.3, 28.6, 19.6, 18.3, 13.0. IR (film): ν = 2969, 1781, 1156, 998, 940 cm^{-1}. MS (EI, *m/z*, %): 193 (12), 195 (13), 71 (100).

2, 2-Dimethyl-5-(bromomethyl)-γ-butyrolactone **(4d)** [27]: Oil. ^{1}H NMR (500MHz, $CDCl_3$): 4.67–4.61 (m, 1H), 3.57 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.50 (dd, *J* = 11.0, 6.5 Hz, 1H), 2.28 (dd, *J* = 13.0, 6.5 Hz,

1H), 1.94 (dd, J = 13.0, 10.0 Hz, 1H), 1.30 (s, 3H), 1.10 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): 180.9, 74.6, 41.9, 40.5, 33.6, 24.9 (d, J = 3.8 Hz). IR (film): ν = 2971, 1773, 1206, 1139, 1111, 1026, 915 cm^{-1}. MS (EI, *m/z*, %): 207 (100), 209 (96).

6-Bromohexahydrocyclopenta[b]furan-2-one **(4e)** [16]: Oil. ^{1}H NMR (500 MHz, $CDCl_3$): 5.08 (d, J = 6.0 Hz, 1H), 4.54 (d, J = 4.0 Hz, 1H), 3.19–3.14 (m, 1H), 2.88 (dd, J = 18.5, 10.0 Hz, 1H), 2.50–2.00 (m, 4H), 1.63–1.58 (m, 1H). ^{13}C NMR (125MHz, $CDCl_3$): 176.4, 90.5, 52.8, 36.0, 35.9, 33.1, 31.3. IR (film): ν = 2968, 1778, 1159, 1014, 875. MS (EI, *m/z*, %): 205 (5), 207 (4), 79 (100).

2(5H)-Furanone [28]: Oil. ^{1}H NMR (500MHz, $CDCl_3$): 7.61–7.59 (m, 1H), 6.19–6.17 (m, 1H), 4.93–4.92 (m, 2H). IR (film): ν = 3100, 1780, 1750, 1600, 1450, 1350, 1330, 1150, 1090, 1030 cm^{-1}.

5-Ethyl-2(5H)-furanone [28]: Oil. ^{1}H NMR (500MHz, $CDCl_3$): 7.47–7.45 (m, 1H), 6.14–6.12 (m, 1H), 5.03–5.00 (m, 1H), 1.88–1.82 (m, 1H), 1.77–1.70 (m, 1H), 1.02 (t, J = 1.9 Hz, 3H). IR (film): ν = 3110, 2995, 1810, 1260, 1170, 1150, 1110, 920 cm^{-1}.

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