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Lactones 30. Reaction of halolactones with trialkylphosphites☆

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Abstract—The reaction of halolactones with trialkylphosphites in the presence of water afforded dehalogenated lactones.

Halolactonization of γ,δ-unsaturated acids or esters is one of the most often applied methods for the synthesis of saturated and unsaturated γ- and δ-lactones.[2–6] In the synthesis of saturated lactones, halolactones are usually dehalogenated by reduction with tributyltin hydride,[7,8] or other organic tin hydrides.[9]

During attempts to synthesize lactones with alkyl phosphonate groups from iodolactones, via the Arbuzov reaction, we observed that in the presence of water some substrates were transformed into dehalogenated lactones.[10] This observation led to detailed studies on the conditions and scope of this reaction and also its mechanism.

Here we present the results of dehalogenation of racemic iodo-, bromo- and chloro-lactones **1**–**6**. Iodolactones **1**–**4** were obtained, mainly by iodolactonization of the corresponding γ,δ-unsaturated acids: iodolactone **1**, as a mixture of diastereoisomers, from 3-ethyl-4-methyl-4-pentenoic acid, lactone **2** as a diastereoisomeric mixture from 3-isobutyl-5-methyl-4-methylene-hexanoic acid,[11] lactone **3** from 3-phenyl-4-pentenoic acid,[10] and bicyclic iodolactone **4** from 1,5,5-trimethyl-(2-cyclohexen-1-yl)acetic acid.[7] Bromolactone **5** and chlorolactone **6** were obtained by bromo- and chloro-lactonization of ethyl (1,5,5-trimethyl-2-cyclohexen-1-yl)acetate with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS), respectively, according to the procedure described earlier.[12] The structures of iodo-, bromo- and chloro-lactones **1**, **5** and **6** were confirmed from their spectral (^{1}H NMR and IR) data.[13–15]

The reactions of halolactones with trialkylphosphites were carried out on the 3.5 mmol scale according to the following procedure: a mixture of halolactone (3.5 mmol) and triethylphosphite (10.5 mmol) was heated at 130 °C for 1 h. After that time, the reaction mixture was cooled to 70–80 °C. Next, distilled water (5 mmol) was added and the mixture was heated at 150–180 °C for 6–8 h. The reaction progress was monitored by TLC and GC. The products were isolated from the reaction mixture by column chromatography (silica gel, hexane–acetone, 4:1). The results of the experiments are presented in Table 1. Except for the reactions of chlorolactone **6**, the isolated yields are given in Table 1.

Taking into consideration the results in Table 1 presented it is apparent that slightly higher yields were observed in the experiments using triethylphosphite. Comparison of the reactivity of the lactones with different halogen atoms indicates that iodolactones and bromolactones exhibited similar, high reactivity in this dehalogenation process. GC analysis (HP-5, 30 m, 0.32 mm, 0.25 μm; detector FI 300 °C, initial temperature 100 °C, then 20 °C/min to 260 °C, then 50 °C/min to 300 °C, hold 1 min) indicated only a trace amount of saturated lactone **4a** in the product mixture obtained from the reaction of chlorolactone **6.**

All the lactones prepared are known compounds (**1a**,[16] **2a**,[11] **3a**[10] and **4a**[7]), the spectroscopic data of which corresponded with the literature.

Considering the mechanism of this reaction the results from earlier studies on the dehalogenation of organic halo compounds employing dimethyl phosphonate as a source of the hydrogen atom for radical reduction should be quoted.[17,18] The reaction was initiated with benzoyl peroxide or AIBN, and thus, a free radical

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☆ For Lactones 29, see Ref. 1.

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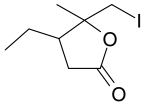
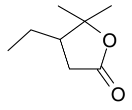
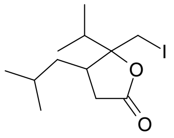
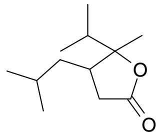
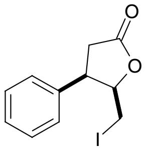
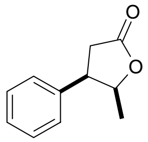
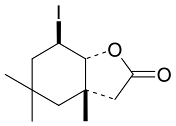
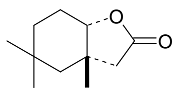
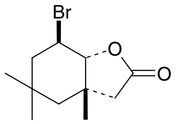
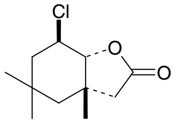
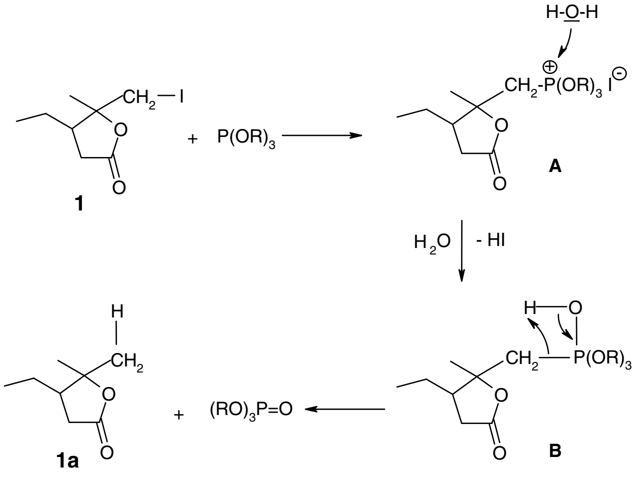
Table 1.

Substrate	Product	Time (h)	Trialkyl phosphite	Yield (%)
 **1**	 **1a**	6 8	P(OEt)$_3$ P(O*i*-Pr)$_3$	80 54
 **2**	 **2a**	6 8	P(OEt)$_3$ P(O*i*-Pr)$_3$	74 54
 **3**	 **3a**	6 7	P(OEt)$_3$ P(O*i*-Pr)$_3$	60 55
 **4**	 **4a**	6 8	P(OEt)$_3$ P(O*i*-Pr)$_3$	90 89
 **5**	**4a**	6 8	P(OEt)$_3$ P(O*i*-Pr)$_3$	92 75
 **6**	**4a**	10 12	P(OEt)$_3$ P(O*i*-Pr)$_3$	5 3

mechanism for this process was proposed. Triethylphosphite or diethyl phosphonate in combination with vanadium(III) chloride and zinc was applied for the dehalogenation of gem-dibromo-cyclopropanes.[19] All the above methods required an anhydrous reaction medium and an inert atmosphere.

The dehalogenation observed in the method presented here proceeds in the presence of water. Studies on this reaction led to the following observations. The reaction of halolactones with triethylphosphite without water led, as usual via Arbuzov reaction, to the corresponding phosphonates. No reaction of these phosphonates with water under the conditions of this method was observed. The formation of an alkyl iodide in the presence of water was also not observed. The signal at −0.321 ppm in the ^{31}P NMR spectrum of the reaction mixture confirms the formation of triethyl phosphate during the course of this reaction. Taking into consideration these observations the mechanism presented below can be proposed (Scheme 1).

The trialkoxyphosphonium salt (**A**) formed in the reaction of the halolactone with trialkylphosphite



Scheme 1.

is, in the presence of water, converted into trialkoxyhydroxyphosphonate (**B**). This unstable compound is converted into the corresponding lactone and trialkyl phosphate or its products of hydrolysis. Further studies on the mechanism of this reaction and its wider application are in progress.

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13. Data for **1**: oil, diastereoisomeric mixture (62% of diastereoisomer **a** and 38% of diastereoisomer **b**): diastereoisomer **a**, ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.97 (3H, t, $J = 7.3$, $\mathrm{C}H_3\mathrm{CH}_2$), 1.29–1.70 (2H, m, $\mathrm{CH_3C}H_2$), 1.57 (3H, s, CH$_3$), 2.37 (1H, dd, $J = 17.3$ and 10.1, one of H-3), 2.27–2.47 (1H, m, H-4), 2.66 (1H, dd, $J = 17.3$ and 8.3, one of H-3), 3.27, 3.34 (2H, 2 × d, $J = 11.1$, CH$_2$I); ^{13}C NMR (151 MHz, CDCl$_3$): δ 9.4, 12.9, 22.1, 27.3, 34.8, 46.5, 84.9, 174.8; diastereoisomer **b**, ^{1}H NMR (300 MHz, CDCl$_3$); δ 0.95 (3H, t, $J = 7.3$, $\mathrm{C}H_3\mathrm{CH}_2$), 1.29–1.70 (2H, m, $\mathrm{CH_3C}H_2$), 1.42 (3H, s, CH$_3$), 2.28 (1H, dd, $J = 16.8$ and 10.1, one of H-3), 2.27–2.47 (1H, m, H-4), 2.73 (1H, dd, $J = 16.8$ and 8.0, one of H-3), 3.36, 3.46 (2H, 2 × d, $J = 11.1$, CH$_2$I); ^{13}C NMR (150 MHz, CDCl$_3$): δ 12.7, 14.4, 20.7, 23.4, 35.0, 45.0, 85.1, 174.3; IR (film, cm^{-1}): 1775 (s), 1382 (m), 1255 (s), 1160 (s), 957 (s); Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 36.27; H, 5.13.
14. Data for **5**: crystals, mp 110–113 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.01; 1.17 (6H, two s, (CH$_3$)$_2$C), 1.19 (3H, s, CH$_3$-6), 1.36 (1H, d, $J = 14.9$, one of CH$_2$-5), 1.70 (1H, dd, $J = 14.9$ and 2.2, one of CH$_2$-5), 1.79 (1H, dd, $J = 13.8$ and 13.2, H-3 axial), 2.02 (1H, ddd, $J = 13.8$, 4.1 and 2.2, H-3 equatorial), 2.13; 2.76 (2H, 2 × d, $J = 17.5$, CH$_2$-7), 4.02 (1H, ddd, $J = 13.2$, 9.2 and 4.1, H-2), 4.22 (1H, d, $J = 9.2$, H-1); ^{13}C NMR (150 MHz, CDCl$_3$): δ 26.8, 30.7, 33.3, 33.5, 40.5, 40.9, 45.2, 46.4, 49.4, 90.8, 175.2; IR (KBr, cm^{-1}): 1784 (s), 1454 (m), 1143 (s), 1024 (s), 989 (s), 696 (m); Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.56. Found: C, 50.56; H, 6.87.
15. Data for **6**: crystals, mp 97–98 °C, ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.07, 1.12 (6H, two s, (CH$_3$)$_2$C), 1.26 (3H, s, CH$_3$-6), 1.40 (1H, d, $J = 15.0$, one of CH$_2$-5), 1.69 (1H, dd, $J = 13.7$ and 12.6, axial H-3), 1.70 (1H, dd, $J = 15.0$ and 2.2, one of CH$_2$-5), 1.95 (1H, ddd, $J = 13.7$, 4.1 and 2.2, equatorial H-3), 2.20; 2.60 (2H, 2 × d, $J = 17.5$, CH$_2$-7), 4.02 (1H, ddd, $J = 12.6$, 8.7 and 4.1, H-2), 4.14 (1H, d, $J = 8.7$, H-1); ^{13}C NMR (150 MHz, CDCl$_3$): δ 26.8, 30.5, 32.4, 33.4, 40.6, 41.1, 45.2, 45.3, 58.3, 90.4, 175.3; IR (KBr, cm^{-1}): 1786 (s), 1455 (m), 1157 (s), 991 (m), 742 (m); Anal. Calcd for $C_{11}H_{17}ClO_2$: C, 60.97; H, 7.91. Found: C, 61.08; H, 7.98.
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