High Yield Reduction of 2-O-Trifluoromethanesulphonate Esters of α–Hydroxylactones to the Corresponding 2-Deoxylactones by Lithium Iodide Trihydrate

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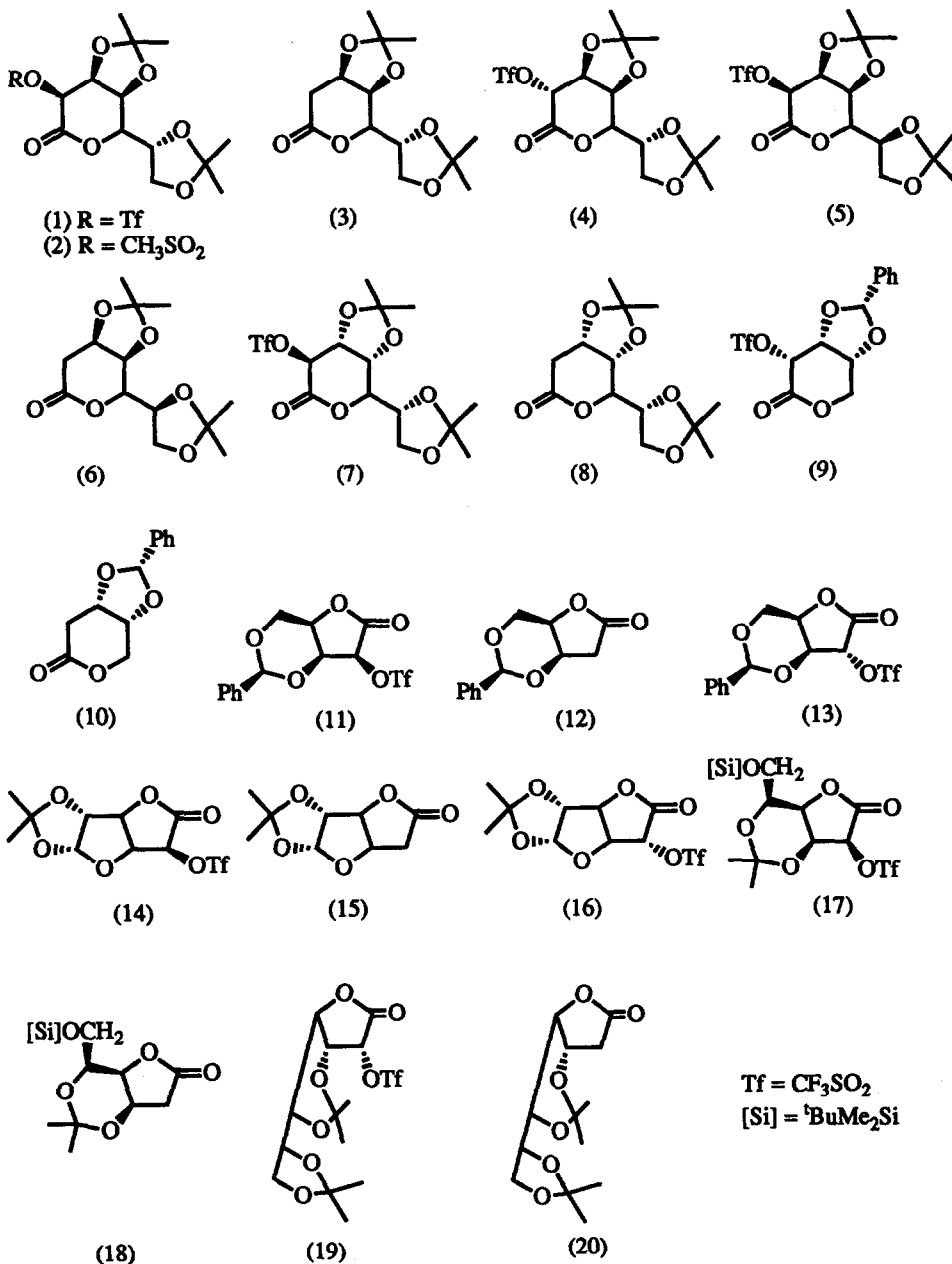[#]Glaxo Group Research, Greenford Road, Greenford, Middlesex, UB6 0HE

Reaction of 2-O-trifluoromethanesulphonate esters of 1,4- and 1,5-α-hydroxy lactones with lithium iodide trihydrate in tetrahydrofuran gives good to excellent yields of the corresponding 2-deoxy lactones.

This paper describes the efficient reductions of triflate esters of α-hydroxylactones by lithium iodide trihydrate to the corresponding 2-deoxygenated lactones in 72-95% yield. A plausible mechanism for the reduction (Scheme) involves initial S_N2 displacement of the triflate by iodide ion, followed by nucleophilic attack by iodide on the iodine atom of the iodolactone affording the equivalent of the lithium enolate of the lactone; subsequent capture of the lithium enolate by protonation by water gives the deoxygenated lactone. The stoicheiometry of the reaction results in the production of both iodine and lithium hydroxide in the course of the reduction. It is particularly noteworthy that, although in all cases in this paper there are β-leaving groups in the enolate ion equivalents, no significant fragmentation occurs; this may have major implications for the use of such anions for reaction with other electrophiles than protons.

n = 1,2
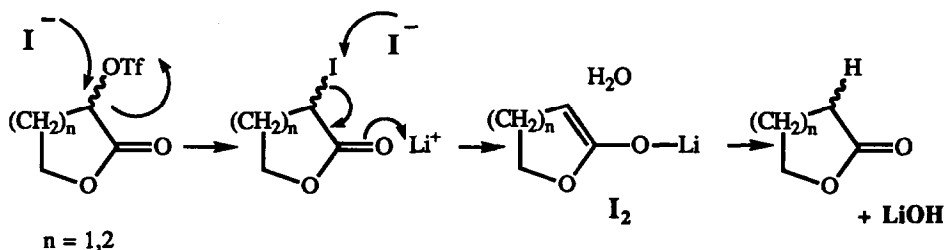
SCHEME

There are many readily available sugar lactones and it is frequently easy to obtain derivatives of such lactones that have only the α-hydroxyl group unprotected; subsequent esterification of the remaining free hydroxyl group by treatment with triflic anhydride usually leads to triflates in excellent [90-100%] yield which are kinetically stable and easily crystallised. Such triflates have been used in the synthesis of a number of highly functionalised amino acids[1,2,3] and amino sugar derivatives,[4] and in the formation of chiral oxetanes.[5] In a project in which the initial objective was the displacement of the triflate (1) with iodide, we observed that the major product was the deoxygenated material (3).[6] Accordingly, the iodide reductions of α-triflates of 5 δ-lactones and of 6 γ-lactones were investigated.

(1) R = Tf
(2) R = CH₃SO₂

(3)

(4)

(5)

(6)

(7)

(8)

(9)

(10)

(11)

(12)

(13)

(14)

(15)

(16)

(17)

(18)

(19)

(20)

Tf = CF₃SO₂
[Si] = ᵗBuMe₂Si

When the protected δ-lactone triflate[7] (1) was treated with lithium iodide trihydrate at room temperature in tetrahydrofuran, the sole organic product after 12 hours was the deoxygenated lactone (3) isolated in 85% yield. The epimeric triflate (4)[7] gave the same product (3), but rather more slowly; this reduction does not proceed by prior epimerisation of (4) to (1). In contrast, the mesylate[8] (2) gave no deoxygenated product (3) under these or more vigorous conditions; this demonstrates that it is necessary to use the excellent triflate leaving group in this reaction in order to obtain the nucleophilic displacement by iodide in the initiating step.

Table: 2-DEOXY LACTONES FROM LITHIUM IODIDE TRIHYDRATE REDUCTION OF THE CORRESPONDING TRIFLATES IN TETRAHYDROFURAN

Triflate	Temp	Time	Isolated Yield of Reduced Lactone (%)		Analytical Data on 2-Deoxylactones m.p. $[\alpha]_D^{20}$
(2)	R.T.	12h	85	(3)	123-124 °C; +67.8° (c, 1.01 in CHCl₃)
(4)	Reflux	48h	80	(3)	
(5)	R.T.	16h	83	(6)	182-184 °C; +72.4° (c, 0.96 in CHCl₃)
(7)	R.T.	16h	81	(8)	72-74 °C; +5.9° (c, 0.65 in CHCl₃)
(9)	Reflux[a]	0.5h	95	(10)	140-141 °C; +171.7° (c, 0.60 in CHCl₃)[c]
(11)	Reflux	12h	90	(12)	152-153°C; +27.1 (c, 0.95 in acetone)
(13)	Reflux	16h	80	(12)	
(14)	Reflux[a]	0.5h	92	(15)	89-90°C; +102.3° (c, 1.00 in CHCl₃)[d]
(16)	Reflux[a]	0.5h	90	(15)	
(17)	Reflux	10h	72	(18)	100-101°C; -75.6° (c, 0.25 in CHCl₃)
(19)	Reflux[b]	10h	89	(20)	71-73°C; -87.9° (c, 1.00 in CHCl₃)

[a] In 10:1 v/v ratio tetrahydrofuran:acetic acid. [b] Acetone was used as solvent .
[c] Lit.[10] 139-139.5°C; +171.3° (c, 1.71 in CHCl₃). [d] Lit.[12] 90.5-91.5°C; +93.9° (c, 1.3 in CHCl₃).

The δ-lactone triflate (5),[9] epimeric at C-6 with (2), gave clean reduction to the deoxyheptonolactone (6) in 83% yield. The triflate (7)[9] with the relative stereochemistry of the isopropylidene unit *trans* to the C-5 side chain also gave efficient reduction to (8). During the course of the reduction, an equivalent of base is liberated so that lactones which are particularly sensitive to base catalysed fragmentation decompose under the reaction conditions; thus only around 40% of the 2-deoxyribonolactone (10)[10] could be isolated from the reaction of the ribonolactone triflate (9)[2] with lithium iodide hydrate in tetrahydrofuran. When the reduction was carried out in a mixture of tetrahydrofuran and acetic acid, the deoxygenated δ-lactone (10) was isolated in 95% yield.

α–Triflates of γ-lactones are also smoothly converted to the corresponding deoxygenated lactones. Thus, the *lyxono*lactone triflate (11)[11] and the *arabinono*lactone triflate (13)[11] react with lithium iodide trihydrate in tetrahydrofuran to afford the deoxygenated lactone (12)[12] in isolated yields of 90% and 80% respectively. Again, in the cases of γ-lactones which are particularly sensitive to base, good yields may be obtained by using a mixture of tetrahydrofuran and acetic acid as solvent. Thus, although poor yields of the deoxylactone (15) resulted from the reduction of the epimeric lactones (14)[3,13] and (16),[3] treatment of (14) and (16) with hydrated lithium iodide in tetrahydrofuran in the presence of acetic acid gave the lactone (15) in 92% and 90% respective yields. Silyl protecting groups are stable to these reductions conditions; thus, the triflate (17) [prepared from L-gulonolactone by sequential treatment with *tert*-butyldimethylchlorosilane, acetonation and esterification with triflic anhydride] afforded lactone (18) in 72% yield. Iodine, which is produced during the reaction, is a well established catalyst for the formation and hydrolysis of ketals, so that lactones containing acetonides which are particularly prone to hydrolysis may also partially lose an acetonide protecting during the reduction; this problem may be readily overcome by the use of acetone as a solvent. Although the hydrated iodide reduction of the heptonodiacetonide triflate (19) [m.p. 119° - 120°C, $[\alpha]_D^{20}$ = -85.2° (c, 1.04 in CHCl₃), prepared in 98% yield by esterification of the corresponding alcohol[14] with triflic anhydride] gave only a moderate yield of the lactone (20) in tetrahydrofuran, the lactone (20) was isolated in 89% yield when acetone is used as the solvent.

Representative procedures for the reductions are:

2-Deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-1,5-lactone (3). Lithium iodide trihydrate (0.9 g, 4.8 mmol) was added to a solution of the triflate (2) (300 mg, 0.71 mmol) in tetrahydrofuran (20 ml) and the reaction stirred at room temperature for 12 h by which time t.l.c. (hexane:ethyl acetate, 1:1) showed no starting material (R_f 0.6) and one product (R_f 0.3). The solvent was removed and purification by flash chromatography (hexane:ethyl acetate, 1:1) yielded the title compound (3) as a colourless crystalline solid (164 mg, 85%).

5-Deoxy-glucuronolactone (15). The triflate (14) (193 mg, 0.55 mmol) and lithium iodide trihydrate (622 mg, 3.33 mmol) were refluxed in a mixture of tetrahydrofuran (10 ml) and acetic acid (1 ml) for 30 min. Evaporation of the solvent, followed by flash chromatography of the residue (ethyl acetate:hexane, 1:4), afforded 5-deoxy glucuronolactone (15) as a crystalline solid (101 mg, 92%).

All these reductions proceed via intermediate iodides which can be formed, usually in excellent yield, by the reaction of the triflates with tetra-*n*-butylammonium iodide; just as the mesylate (2) is not reduced readily to the lactone (3) by hydrated lithium iodide, (2) does not undergo reaction with tetra-*n*-butylammonium iodide to give an iodolactone. The stereochemical features of the formation of the iodides are currently being studied.

The α-deoxygenation of derivatives of heptonic acids has been recognised[15] as a promising approach for the synthesis of 2-deoxy sugars. Although several methods have been reported for the deoxygenation of 2-hydroxylactones,[16] the reaction of α-triflates of lactones with hydrated lithium iodide appears to be a very mild and generally high yield procedure for such a functional group transformation. The lack of fragmentation indicated by this work of the intermediate enolate equivalents by loss of the β-oxygen substituents may have major consequences in the potential of such lactones as chiral starting materials.[17]

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