

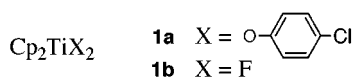
Convenient Two-Step Conversion of Lactones into Cyclic Ethers

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We recently developed a new method for the reduction of lactones that offers easy access to five- and six-membered ring lactols using a titanocene diphenoxide (**1a**)/tetrabutylammonium fluoride/alumina mixture or titanocene difluoride (**1b**) as the catalyst;¹ polymethylhydrosiloxane (PMHS) was used as the stoichiometric reductant (Scheme 1). A variety of lactones were reduced to the corresponding lactols in good to excellent yields.



During our studies of lactone hydrosilylation, we noted that one of the most general ways of transforming a lactone to the corresponding cyclic ether is through a two-step procedure involving initial reduction with DIBAL-H (forming the lactol), followed by treatment with $\text{Et}_3\text{SiH}/\text{BF}_3\cdot\text{OEt}_2$.^{2a} Both of these reactions occurred at low temperatures (-78°C) under an inert atmosphere. This method has been applied, in nearly unaltered form, in many syntheses.³ This silane reduction protocol has also been used to reduce lactols prepared via independent methods.⁴

We set out to determine whether we could combine our room-temperature protocol for lactone reduction with the deoxygenative reduction of lactols. We hoped to develop a procedure for converting lactones to cyclic ethers that would offer experimental simplicity and could be conducted at room temperature.

A (perfluoroalkyl)sulfonic acid resin, Nafion-H, has been reported to catalyze the reduction of simple nonaryl methylacetals in refluxing dichloromethane using triethylsilane to yield the corresponding ethers.⁵ With this precedent in mind, we examined Amberlyst 15, a commonly used sulfonic acid resin, as a catalyst in the deoxygenative reduction of lactols.

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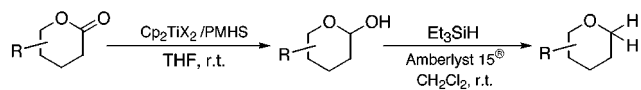
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Table 1. Two-Step Preparation of Cyclic Ethers from Lactones

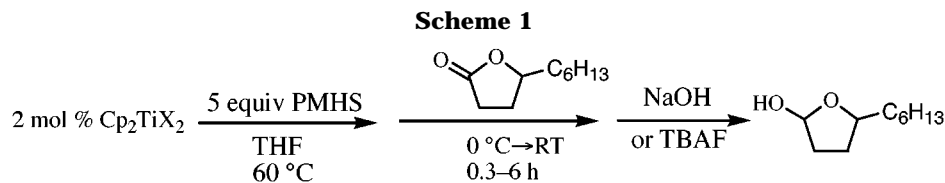


Entry	Lactone	Ether	Cp_2TiX_2	Yield ^a	Reference ^d
a			1a	67	8
b			1b	90	2a
c			1b	94	9
d			1b	74 ^b	6
e			1b	80	
f			1b	89	10
g			1a	83	11
h			1b	38 (99) ^c	12

^a Yields are based on amount of lactone used and refer to isolated products of >95% pure material based on ¹H NMR and GC analysis. All compounds were characterized by IR, ¹H NMR, and ¹³C NMR. ^b Rotation agreed with literature value. ^c Yield in parentheses refers to the use of isolated lactol and only to the second step. ^d Reference to a literature characterization of the compound.

We found that addition of the resin to a solution of the lactol and triethylsilane in CH_2Cl_2 at room temperature led to the rapid and clean formation of the cyclic ether. The combination of this procedure with the titanocene-catalyzed reduction of lactones constitutes a practical and novel way to effect the transformation of a lactone to its corresponding cyclic ether (see Table 1). It should be noted that both reductive steps take place at room temperature and the second does not necessitate the use of an inert atmosphere.

The methodology for the conversion of a lactone to a cyclic ether described herein (see Table 1) compares favorably with techniques currently employed for this transformation. A common alternative technique for this transformation proceeds via reduction of the lactone (to the diol), selective conversion of one of the hydroxyl groups to a leaving group, and finally, cyclization. LiAlH_4 is often used for the reduction step; a plethora of reagents have been employed for the cyclization step. For example, the reduction and cyclization sequence has been



reported several times for the cyclic ether (–)-ambroxide (Table 1, entry d) derived from the corresponding lactone using LiAlH_4 followed by treatment with POCl_3 , TsOH , or TsCl in overall yields of 88–90%;⁶ a comparable yield is obtained using our system. Using the DIBAL-H/ $\text{BF}_3 \cdot \text{OEt}_2/\text{HSiEt}_3$ method, Kraus prepared 2-phenyltetrahydrofuran in 75% yield;^{2a} using our procedure, a 90% yield is realized (Table 1, entry b).

In conclusion, we have developed a simple and practical method for the conversion of lactones into cyclic ethers. The first step reduces the lactone to the lactol using a readily available titanocene complex and an inexpensive stoichiometric reducing agent. After a brief workup, crude product can be further transformed into the corresponding cyclic ether using Amberlyst 15 and triethylsilane. The yields for this two-step procedure are good to excellent.

Experimental Section

General Methods. The titanocene bisphenoxide **1a** and the lactones used in entries a and g (Table 1) were prepared as previously described.^{1a} Tetrahydrofuran was distilled under argon from sodium/benzophenone ketyl before use. Titanocene difluoride was prepared via the literature procedure.⁷ All other compounds are commercially available and were used as purchased. All products were previously known (except 2-hexyltetrahydrofuran), and their ^1H NMR, ^{13}C NMR, and IR spectra

were consistent with literature spectral data. 2-Hexyltetrahydrofuran was also characterized by elemental analysis (E & R Analytical Laboratory, Inc.). References to known products are given in Table 1. ^1H NMR and ^{13}C NMR were taken in CDCl_3 at 300 and 75 MHz, respectively.

General Procedure. Titanocene difluoride (10.8 mg, 0.05 mmol) and dry THF (3 mL) are added to an oven-dried Schlenk flask under an argon atmosphere. To the yellow solution was added PMHS (0.75 mL, 12.5 mmol) via syringe. The reaction vessel was placed in a hot water bath (ca. 60 °C) for 0.5–2 min, resulting in a color change from yellow to dark blue, which was accompanied by bubbling. The flask was cooled in an ice bath, and lactone (2.5 mmol) was added dropwise via syringe. The reaction mixture was stirred at room temperature and monitored by TLC. After consumption of the starting material (0.1–6 h), the catalyst was deactivated by exposure to air. The reaction mixture was diluted with THF (10 mL), transferred to a 100 mL round-bottom flask, and treated with 1 M NaOH (15 mL). [CAUTION: vigorous bubbling!]. The two-phase mixture was stirred for 1 h or until the organic layer became clear. The organic phase was diluted with ether (20 mL), washed twice with 1 M NaOH (10 mL), washed with a saturated brine solution (10 mL), dried (MgSO_4), and concentrated *in vacuo*. Amberlyst 15 ion-exchange resin (1.25 g) was added to a stirred solution of dichloromethane (10 mL), triethylsilane (0.8 mL, 5 mmol), and the crude lactol product. The reaction was stirred at room temperature open to the air until TLC analysis indicated the reaction was complete (0.5–5 h). The Amberlyst 15 was removed by filtration and washed with CH_2Cl_2 . The resulting solution was concentrated *in vacuo*. Flash column chromatography was performed.

2-Hexyltetrahydrofuran (Entry c). The general procedure was used to convert 0.45 mL (2.5 mmol) of δ -decanolactone to the corresponding cyclic ether. The ether was purified via flash chromatography (SiO_2 , 2% ether in pentane) to give 0.74 g (94%) of a clear liquid. IR (film, cm^{-1}) ν_{max} : 2957, 2927, 2857, 1459, 1378, 1068. ^1H NMR (300 MHz, CDCl_3): δ 3.66–3.91 (m, 3H), 1.8–2.01 (m, 3H), 1.2–1.67 (m, 11H), 0.88 (t, 3H $J = 7$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 79.4, 67.5, 35.7, 31.8, 31.3, 29.4, 26.3, 22.5, 14.0. Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{O}$: C, 76.86; H, 12.90. Found: C, 76.83; H, 12.84.

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