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HIGHLY REGIOSELECTIVE REDUCTION OF UNSYMMETRICAL CYCLIC ANHYDRIDES TO LACTONES WITH HINDERED TRIALKYLBOROHYDRIDES+

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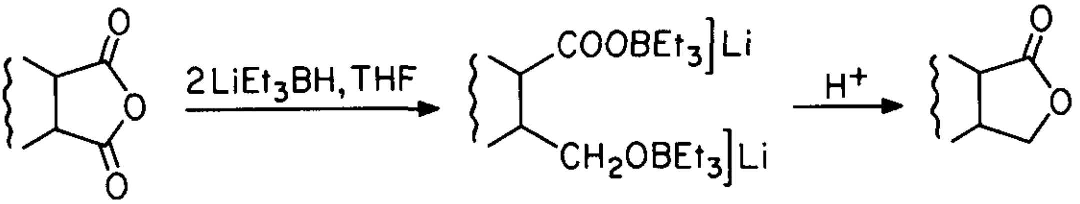
Abstract – Lithium trialkylborohydrides reduce cyclic anhydrides to the corresponding lactones in good to excellent isolated yields. With unsymmetrical anhydrides, increasing the steric requirements of the trialkylborohydride dramatically enhances the regioselectivity of the reduction of the less hindered carbonyl group of the anhydride.

The presence of γ-lactone functions in a number of natural products of biological interest such as sesquiterpenes, steroids, alkaloids, and sugars and their potential cytotoxic activity have elicited intense synthetic interest.[1] Further, γ-lactones themselves are key intermediates in the synthesis of molecules of medicinal interest such as prostaglandins[2] and antitumor agents.[3] An efficient and simple methodology for the construction of the γ-lactone moiety involves the selective reduction of cyclic anhydrides to the corresponding lactones with complex metal hydrides. Lithium aluminum hydride and sodium borohydride have been used extensively for this conversion.[4]

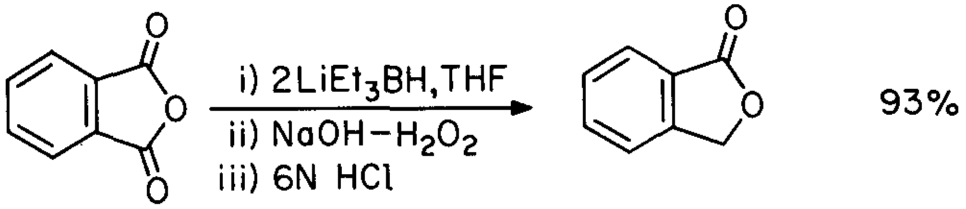
Recently, a number of lithium trialkylborohydrides have emerged as exceptionally powerful regio- and stereoselective reducing agents for organic functional groups.[5] A recent exploratory study[6] of the reduction characteristics of lithium triethylborohydride (Super Hydride) with organic compounds containing representative functional groups showed that carboxylic acids are essentially inert to this reagent. However, cyclic anhydrides (succinic and phthalic anhydride) rapidly consumed 2 equiv of Super Hydride, indicating clean and quantitative reduction to the corresponding hydroxy acids, which can be lactonized (eq 1).

+Dedicated to Professor Herbert C. Brown on the occasion of his 70th birthday.



(1)

Accordingly, it was of interest to explore the effectiveness of lithium triethylborohydride for the direct conversion of cyclic anhydrides to lactones. The remarkable applicability of this reagent for this transformation is shown by the selective reduction of symmetrical cyclic anhydrides such as cis-1,2-cyclohexanedicarboxylic anhydride, phthalic anhydride, and cis-4-cyclohexene-1,2-dicarboxylic anhydride to the corresponding lactones in excellent isolated yields (eq 2 and 3).



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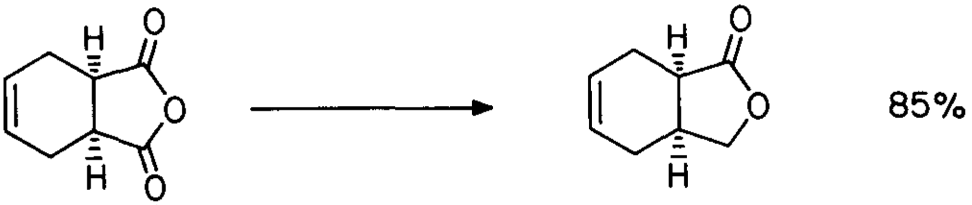
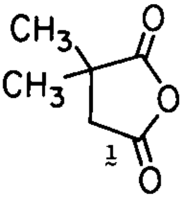
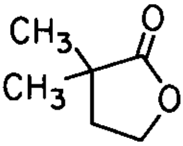
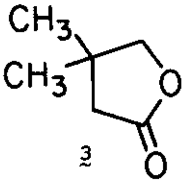
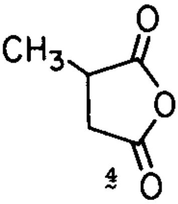
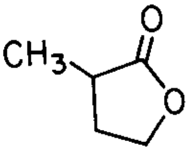
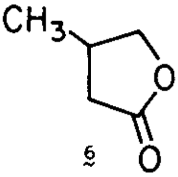
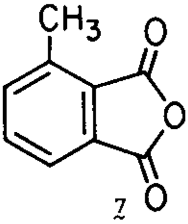
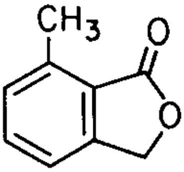
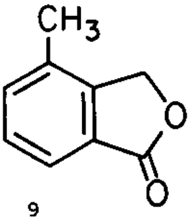


(3)

More important, the reduction of unsymmetrical cyclic anhydrides can potentially yield two different lactones. Complex metal hydride reduction of such unsymmetrical anhydrides usually (but not always) occurs predominantly at the more hindered carbonyl group.[4] Increasing the steric requirements of the alkyl group of trialkylborohydride dramatically enhances the stereoselectivity in cyclic ketone reductions.[5e,h] Consequently, it was desirable to examine the effect of steric requirements of the hydride reagent on the regioselectivity of the anhydride reduction. Accordingly, three representative unsymmetrical anhydrides, 2,2-dimethylsuccinic anhydride, 2-methylsuccinic anhydride, and 3-methylphthalic anhydride, were examined for their reactions with lithium triethylborohydride, lithium tri-sec-butylborohydride (L-Selectride), and lithium trisiamylborohydride (LS-Selectride). The ratio of isomeric lactones formed was determined

Table I. Reduction of Representative Cyclic Unsymmetrical Anhydrides with Lithium Trialkylborohydrides in Tetrahydrofuran at 0°C

Anhydride	Reagent	Products, ratio %	
 1		 2	 3
	$LiAlH_4$ [a]	5	95
	$NaBH_4$ [b]	0	100
	$LiEt_3BH$ [c]	25	75
	Li-<u>sec</u>-Bu_3BH [c]	75	25
	$LiSia_3BH$ [c]	92	8
 4		 5	 6
	$LiAlH_4$ [d]	31	69
	$LiEt_3BH$ [e]	49	51
	Li-<u>sec</u>-Bu_3BH [e]	62	38
	$LiSia_3BH$ [e]	68	32
 7		 8	 9
	$NaBH_4$ [f]	43	57
	$LiEt_3BH$ [g]	50	50
	Li-<u>sec</u>-Bu_3BH [g]	79	21
	$LiSia_3BH$ [g]	88	12

[a] Ref. 4g. [b] Ref. 4c. [c] Analysis by ^1H NMR at 90 MHz and by GLC. [d] Ref. 4a. [e] Analysis by GLC. [f] Ref. 4h. [g] Analysis by ^1H NMR at 270 MHz.

by gas chromatography[8] (GLC) and/or by ^{1}H NMR (90 or 270 MHz).[9] The lactonic products were isolated in excellent yields. The results are summarized in Table I.

Lithium aluminum hydride[4g] reduced 2,2-dimethylsuccinic anhydride (1) with high regioselectivity at the more hindered carbonyl group (95% attack), yielding β,β-dimethyl-γ-butyrolactone (3) as the major product. With sodium borohydride,[4c] reduction occurred exclusively at the more hindered carbonyl group to yield 3 as the only product. Lithium triethylborohydride gave a mixture of α,α-dimethyl-γ-butyrolactone (2) and β,β-dimethyl-γ-butyrolactone (3) in a ratio of 25:75. However, with lithium tri-*sec*-butylborohydride, a hindered reagent, a major shift in the regioselectivity was observed. The reagent reduced predominantly the less hindered carbonyl group (75% attack), yielding 2 as the major product. The highly hindered reagent lithium trisiamylborohydride showed even greater regiodiscrimination, yielding a mixture of 2 and 3 in a ratio of 93:7.

The presence of even a single α-methyl substituent (2-methylsuccinic anhydride, 4) is sufficient to direct the reagents towards the less hindered carbonyl group as the steric hindrance of the trialkylborohydride anion is increased.

With 3-methylphthalic anhydride (7), sodium borohydride showed considerable preference for the reduction of the hindered carbonyl (ortho to the methyl group), giving a mixture of 7-methylphthalide (8) and 4-methylphthalide (9). Here again, with hindered trialkylborohydrides we observed a remarkable preference for the reduction of the less hindered carbonyl group. Thus, LS-Selectride yielded 7-methylphthalide in 88% isomeric purity.

The following procedure for the reduction of 2,2-dimethylsuccinic anhydride with LS-Selectride is representative. An oven-dried 500-ml three-necked flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, and a reflux condenser connected to a mineral-oil bubbler was flame dried and cooled to room temperature under a stream of dry nitrogen. The flask was charged with 6.4 g (50 mmol) of 2,2-dimethylsuccinic anhydride and 35 ml of dry THF and cooled to 0°C (ice bath). Then 135 ml (135 mmol) of a 1.0 M solution of LS-Selectride in THF was added over 0.5 h with vigorous stirring. After 2 h at 0°C, the mixture was stirred for 2 h more at 25°C. Water (5 ml) was slowly added to destroy the excess hydride. The organoborane was oxidized (60 ml each of 3 N NaOH and 30% H_2O_2, 0°C; 60°C, 1 h), and the mixture was acidified (90 ml of 6 N HCl, 0°C). The resulting mixture was gently refluxed for 1 h. The organic phase was separated, and the aqueous phase was extracted with two 50-ml portions of ether. The combined extracts were washed once with cold dilute aqueous sodium bicarbonate and then with saturated brine and dried ($MgSO_4$). GLC analysis of the extracts on a 50-m fused-silica capillary column (Carbowax 20M) showed the presence of α,α-dimethyl-γ-butyrolactone (93%) and β,β-dimethyl-γ-butyrolactone (7%). The volatile solvents were distilled off, and the residue was fractionally distilled under reduced pressure to separate the siamyl alcohol, giving 4.35 g (76%) of lactonic products. ^{1}H NMR (90 MHz, $CDCl_3$) showed the product was a mixture of **2** and **3** in a ratio of 92:8.

In summary, the present study has clearly demonstrated the importance of steric requirements of the reducing agent in controlling the regioselectivity of the cyclic anhydride reductions. Further, such a variability in steric control has great potential for regio- and stereoselective design and synthesis of lactone moieties in natural products.

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7. Catalytic reduction of anhydrides generally produced lactones arising from the reduction of the less hindered carbonyl group; see ref. 4f.

8. GLC analyses were performed on a Hewlett-Packard 5880A series gas chromatograph equipped with a flame ionization detector and a 50-m Carbowax 20M fused-silica capillary column.

9. ^{1}H NMR spectra were recorded either on a Perkin-Elmer R-32 (90 MHz) or on a JEOL FX-270 (270 MHz) spectrometer, with $CDCl_3$ as the solvent and Me_4Si as the reference.

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