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IMPROVED PROCEDURE FOR LITHIUM BOROHYDRIDE REDUCTION OF CYCLIC ANHYDRIDES TO LACTONES IN TETRAHYDROFURAN

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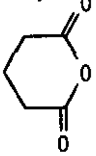
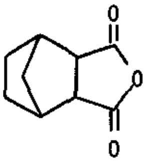
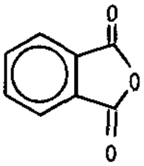
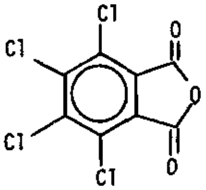
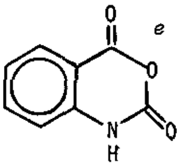
Abstract - The rate of reduction of several cyclic anhydrides by lithium borohydride in tetrahydrofuran at 25°C has been studied. The reaction has been utilized for the rapid and selective conversion of cyclic anhydrides to lactones.

The reduction of cyclic anhydrides to lactones is a reaction of considerable potential synthetic utility. In view of their chemical nature, the reaction of anhydrides should be studied only in aprotic solvents like tetrahydrofuran. Sodium borohydride has been used for the reduction of anhydrides in tetrahydrofuran, although it forms a heterogeneous mixture.[2-7] Unfortunately, lithium borohydride, which is more reactive and highly soluble in tetrahydrofuran, has not been utilized for this reaction.[8] Also, there is no systematic study of the rate and stoichiometry of the reaction leading to the development of a synthetic procedure. In the present study, the rate, stoichiometry and mechanism of reduction of cyclic anhydrides by lithium borohydride is described together with a versatile procedure for the lactone synthesis. In a typical rate study, 5 mmol of lithium borohydride was added to 5 mmol of the anhydride in sufficient tetrahydrofuran to give 5 ml of solution. This makes the reaction mixture 1.0 *M* in both the reactants. The solution was maintained at 25°C and aliquots were removed at appropriate intervals and analyzed for residual hydride. In this manner it was possible to establish both the rate at which reduction proceeds and the stoichiometry of the reaction, *i.e.*, the number of hydrides utilized per mole of compound when the reaction comes to an effective halt. Succinic anhydride and glutaric anhydride form heterogeneous reaction mixtures and in these cases the reactions for each time period were carried out separately and the whole reaction mixtures were hydrolyzed with 1:1 mixture of 2 *N*. hydrochloric acid-tetrahydrofuran. The results are given in Table 1.

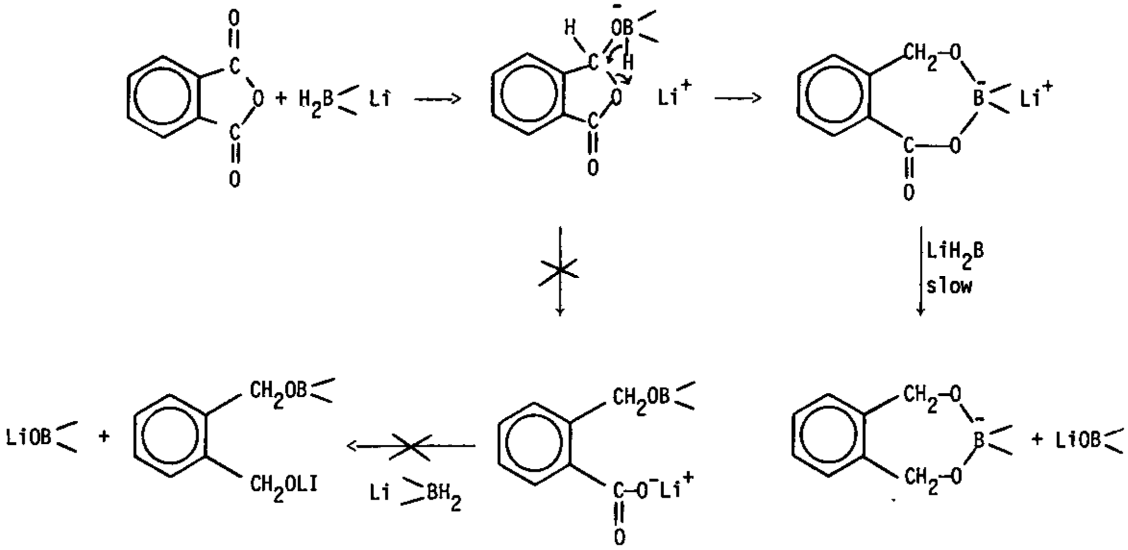
Table 1

Rate of Reduction of Anhydrides with Lithium Borohydride[a]

No.	Compound	Time (h) 0.25	Hydride Used for Reduction[b] 1.0	3.0	6.0
1		0.4 2.01[c]	0.5 *d*	0.6	0.68
2		0.82 1.96[c]	0.99 *d*	1.06	1.24
3		2.12	2.18	2.28	2.56
4		2,08	2,4	2,48	2,60
5		2,01	*d*		
6		1,17	1,74	1.96[f]	

[a] [Anhydride] = [$LiBH_4$] = 1.0 *M*. [b] Mmol/mmol of anhydride. [c] Reverse addition. [d] White precipitate formed. [e] 1 mmol of H_2 is evolved within 5 min. [f] 2, h.

The study indicates a rapid consumption of 2 mmol of hydride per mmol of anhydride, although excess hydride is used to reduce both the carbonyl groups. Further uptake of hydride is very slow. The results could be explained by the following scheme:

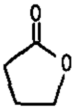
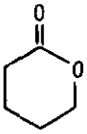
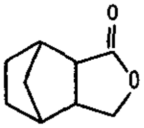
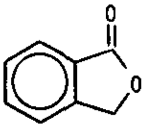
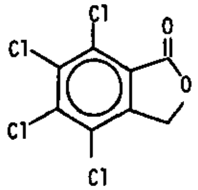
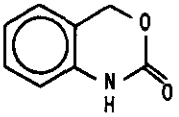


The formation of lithium carboxylate is quite unlikely, in view of the inertness of the carbonyl group for further reduction.[8]

The above study indicates the possibility of partial reduction of cyclic anhydrides by lithium borohydride using essentially theoretical amounts of the reagent (two hydrides per anhydride) in tetrahydrofuran at 25°C. Under these conditions, the reductions are complete in 15 min. Protonolysis of the product produced the lactones in good yields. The results are summarized in Table 2. However, isatoic anhydride contains an active hydrogen and hence requires three hydrides for complete reduction. The reaction proceeds with the evolution of a theoretical amount of hydrogen in 5 min. Further uptake of two hydrides is complete in two hours. Protonolysis of the reaction mixture produced the expected product, 2-oxodihydro-4,5-benzo-1,3-oxazine, since the amide carbonyl is inert towards borohydride reductions.[8]

Table 2

Reduction of Anhydrides with Lithium Borohydride to Lactones

No.	Product	Procedure	Yield %	mp or bp/mm of Hg, °C Found	Reported
1		B	68	105-107/20	202-203/760[11]
2		B	77	120-122/20	102-104/7[10]
3		A	76	150-152/20	[a]
4		A	91	70-72	72-73[9]
5		A	86	208-209	208.5[12]
6		A	73	120-122	119-120[13]

[a] IR and NMR spectra were consistent with the structures assigned.

A typical procedure is described in the following:

Reduction of Phthalic Anhydride with Lithium Borohydride to Phthalide. (Procedure A). To a solution of 2.96 g (20 mmol) of phthalic anhydride in 16.05 ml of tetrahydrofuran was added 3.95 ml (2.78 *M*, 11 mmol) of lithium borohydride in tetrahydrofuran in drops. After 15 min, the whole reaction mixture was hydrolyzed using 6 *N* hydrochloric acid (7 ml) and the liberated hydrogen was collected (100 ml, 3.9 mmol). The reaction mixture was heated on a steam bath for 30 min, cooled and saturated with sodium chloride. The organic layer was separated. The aqueous layer was extracted with tetrahydrofuran (3 x 10 ml). The combined organic layer was dried over anhydrous magnesium sulfate. Removal of solvent using aspirator vacuum produced 2.44 g (91%) of phthalide, mp 70-72°C [lit.[9] 72-73°C].

Reduction of Glutaric Anhydride with Lithium Borohydride to δ-Valerolactone. (Procedure B). Reverse addition was made in the case of reduction of glutaric anhydride. To a solution of 20 ml of lithium borohydride (11 mmol, 0.55 *M*) in tetrahydrofuran, 2.28 g (20 mmol) of glutaric anhydride was added under nitrogen atmosphere in small portions. After 15 min, the whole reaction mixture was hydrolyzed as before. 125 ml of hydrogen (4.86 mmol) was collected, indicating 98% completion of the reaction. The reaction mixture was heated on a steam bath for 30 min, cooled and saturated with sodium chloride. The lactone was extracted with ether (3 x 10 ml) and dried over anhydrous magnesium sulfate. Fractional distillation under vacuum produced 1.54 g (77%) of δ-valerolactone, bp 120-122°C/20 mm [lit.[10] 102-104°C/7 mm].

Dedication: This work is dedicated to Professor Herbert C. Brown on the occasion of his 70th birthday, in admiration of his pioneering work in the art of blending physical organic chemistry with the synthetic field.

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