m/z (relative intensity) 91 (77), 119 (100), 147 (11), 163 (4), 179 (4), and 191 (3).

2-Phenyl-1,3-propanediol. A 250-mL round-bottom flask with a side-arm was dried in an oven and cooled under a stream of dry nitrogen. The flask was fitted with a rubber syringe cap, a magnetic stirring bar, and a nitrogen outlet connecting tube. Then 1.80 g (10 mmol) of phenylmalonic acid was added followed by 52.0 mL of dry THF. The rapidly stirring solution was cooled to -30 °C, and 28.0 mL (80.0 mmol of hydride) of 0.95 M borane solution in THF was added slowly. The reaction mixture was maintained at -30 °C for 6 days. Then 40 mL of methanol was slowly added, and the solution was slowly warmed to room temperature overnight. The solvents were removed at reduced pressure, and the residue was dissolved in 125 mL of diethyl ether. The ethereal solution was washed with saturated potassium carbonate  $(2 \times 30 \text{ mL})$ , which was then extracted with diethyl ether  $(2 \times 100 \text{ mL})$ . The combined organic phases were dried with potassium carbonate and concentrated at reduced pressure to give 1.38 g (91%) of a white oily material, which was reprecipitated from a mixture of diethyl ether-hexane-toluene (5:150:30) to give the purified diol, 1.29 g (85%), mp 51-53 °C (lit.<sup>16</sup> mp 51-53 °C).

Registry No. 1a, 2613-89-0; 1b, 510-20-3; 1c, 141-82-2; 1d, 601-75-2; 1e, 534-59-8; 1f, 118459-48-6; 1g, 118459-49-7; 1h, 53181-45-6; 2a, 109306-89-0; 2b, 118459-50-0; 2-phenyl-1,3propanediol, 1570-95-2; benzoic acid, 65-85-0; phenylacetic acid, 103-82-2.

(16) Choi, Y. M.; Kucharczyk, N.; Sofia, R. D. J. Labeled Compd. Radiopharm. 1986, 23, 785.

## Notes

## A Simple Conversion of Diethyl Phenylmalonate with Metal Hydride to the Corresponding **Primary Diol: A Competing Reaction between Reduction and Metalation**

Yong M. Choi\* and Robert W. Emblidge

Wallace Laboratories, Division of Carter-Wallace, Inc., Cranbury, New Jersey 08512

Received August 26, 1988

2-Phenyl-1,3-propanediol (2) has been used as an important intermediate in the synthesis of 2-phenyl-1,3propanediol dicarbamate (felbamate), an antiepileptic drug under development in our laboratories.<sup>1,2</sup> The preparation of 2 from diethyl phenylmalonate (1) by reduction with excess lithium aluminum hydride (LAH) in refluxing ethyl ether has been described.<sup>1</sup> However, the procedure was not detailed, and the reported yield of 2 was only 30-50%.<sup>1,3</sup> Furthermore, we observed hydrogen evolution during the reaction,<sup>3</sup> probably due to  $\alpha$ -proton abstrac $tion^{4,5}$  (metalation) by the reagent, with formation of the malonic enolate 3 (Scheme I).

Enolizable 1,3-dicarbonyl compounds have frequently been reported to afford products of both reduction and metalation upon treatment with LAH.<sup>6-9</sup> Ketone enolates were found to resist reduction by the reagent.<sup>8,10</sup> Marshall and co-workers studied the reduction of malonic enolates with LAH in refluxing 1,2-dimethoxyethane.<sup>11</sup> However,

 Berger, F. M.; Ludwig, B. J. U.S. Patent No. 2,884,444, 1959.
 Swinyard, E. A.; Sofia, R. D.; Kupferberg, H. J. Epilepsia 1986, 27, 27

(3) These are "unpublished results".

Table I. Rates of Reduction of Diethyl Phenylmalonate						
with Metal Hydrides in Tetrahydrofuran at Room						
Temperature <sup>a</sup>						

		remperat	ure	
metal hydride	time, h	H <sub>2</sub> evolved, mmol/mmol of compd	total H <sup>-</sup> consumed, mmol/mmol of compd	H <sup>-</sup> used for reduction, mmol/mmol of compd
LiAlH4 <sup>b</sup>	0.25	0.05	2.05	2.00
•	0.50	0.05	2.05	2.00
	1.0	0.05	2.05	2.00
LiAlH <sub>4</sub>	0.25	0.18	3.51	3.33
	0.50	0.18	3.69	3.51
	1.0	0.18	3.81	3.63
	2.0	0.18	3.81	3.63
LiBH₄	0.25	0.57	2.27	1.70
	0.50	0.67	2.98	2.31
	1.0	0.67	3.34	2.67
	2.0	0.67	3.34	2.67
$AlH_3$	0.25	0.17	3.57	3.40
	0.50	0.17	3.69	3.52
	1.0	0.17	3.82	3.65
$BH_3-SMe_2$	0.25	0.01	0.01	0.00
	0.50	0.01	0.06	0.05
	1.0	0.01	0.06	0.05
	4.0	0.01	0.12	0.11
	8.0	0.01	0.16	0.15
	24.0	0.01	0.30	0.29
(i-Bu) <sub>2</sub> AlH	0.25	0.01	2.56	2.55
	0.50	0.01	2.98	2.97
	1.0	0.01	3.53	3.52
	2.0	0.01	4.02	4.01

<sup>a</sup>1.0 M in hydride in metal hydride and 0.17 M in substrate (compd). <sup>b</sup>Reduction of ethyl phenylacetate, 1.0 M in hydride in metal hydride and 0.33 M in compd.

the reduction gave a mixture of aldehydes and saturated or unsaturated alcohols as major products without formation of 1,3-propanediol.<sup>11</sup>

Accordingly, we undertook a detailed comparison of the behavior of representative Lewis basic reducing agents  $[LiAlH_4, LiBH_4]^{12a,c,13}$  with Lewis acidic ones  $[AlH_3, LiBH_4]^{12a,c,13}$ 

<sup>(4)</sup> Choi, Y. M.; Emblidge, R. W.; Kucharczyk, N.; Sofia, R. D. J. Org. Chem. 1987, 52, 3925.

<sup>(5)</sup> Choi, Y. M.; Emblidge, R. W.; Kucharczyk, N.; Sofia, R. D. J. Org. Chem., in press.

<sup>(6)</sup> Drieding, A. S.; Hartmann, J. A. J. Am. Chem. Soc. 1953, 75, 939. (7) Romann, E.; Frey, A. J.; Stadler, P. A.; Eschenmoser, A. Helv. Chim. Acta 1957, 40, 1900.

<sup>(8)</sup> Bailey, W. J.; Hermes, M. E.; Klein, W. A. J. Org. Chem. 1963, 28, 1724.

<sup>(9)</sup> Soai, K.; Oyamada, H. Synthesis 1984, 605.

<sup>(10)</sup> Dauben, W. G.; Eastham, J. F. J. Am. Chem. Soc. 1953, 75, 1718. (11) Marshall, J. A.; Anderson, N. H.; Hochstetler, A. R. J. Org. Chem. 1967. 32, 113.

<sup>(12) (</sup>a) Hudlicky, M. Reductions in Organic Chemistry; Ellis Horwood Limited: Chichester, England, 1984; pp 147-164. (b) Brown, H. C.; Yoon, N. M. J. Am. Chem. Soc. 1966, 88 1464. (c) Yoon, N. M.; G. J. Schull, J. J. M. B. Hull, Chem. Soc. 1968, 90, 2027.
 (13) (a) Yoon, N. M.; Cha, J. S. J. Kor. Chem. Soc. 1977, 21, 108. (b)

Brown, H. C.; Narasimhan, S.; Choi, Y. M. J. Org. Chem. 1982, 47, 4702.





 
 Table II. Reduction of Diethyl Phenylmalonate with Metal Hydrides at Room Temperature<sup>a</sup>

metal hydride	H <sub>2</sub> evolved, <sup>b</sup> mmol/mmol of time, h compd yield, <sup>c</sup> %			
LiAlH <sub>4</sub>	1.0	0.18	71	
AlH <sub>3</sub>	1.0	0.17	75	
BH <sub>3</sub> -SM $e_2^d$	2.0	0.14	85	
(i-Bu)-AlH	2.0	0.01	100	

<sup>a</sup> 30 mmol of diethyl phenylmalonate (compd) and 165 mmol of hydride in metal hydride in sufficient tetrahydrofuran to make the reaction 0.96 M in hydride and 0.18 M in 1, except for entry 3. <sup>b</sup> Hydrogen evolved during entire reaction under described conditions. <sup>c</sup> Isolated yield after further purification. <sup>d</sup> Reaction carried out distillation of SMe<sub>2</sub>.

BH<sub>3</sub>-SMe<sub>2</sub>, and  $(i-Bu)_2AlH$ <sup>12,14,15</sup> for two substrates containing reactive  $\alpha$ -hydrogen, ethyl phenylacetate and 1.

With LAH, a reactive reducing agent,<sup>12a,c</sup> addition of ethyl phenylacetate to hydride solution in THF resulted in the evolution of only 0.05 equiv of hydrogen and led to complete reduction in 0.25 h (Table I); thus, reduction successfully competes with metalation for this substrate. The corresponding reaction of 1, however, was found to be relatively slow. It essentially stopped in 1 h, showing a 91% uptake of hydride for reduction with 18% of metalation. Indeed, the hydride balance for the compound corresponding to metalation and reduction was found to be excellent. The material balance was also reasonable, showing a 71% isolated yield of 2 and 18% of the metalation (Table II). As indicated by the case of ethyl phenylacetate with LAH in Table I, both reduction of the free ester to diol 2 and the  $\alpha$ -hydrogen abstraction to give 3 are quite fast (ca. 0.25 h). The relatively slow reduction of enolate 3 (ca. 1 h) is presumably due to strong anion delocalization on the two carbonyl functional groups, as depicted in Scheme I.

A model experiment was carried out by LAH reduction of the lithium enolate of diethyl phenylmalonate prepared by addition of *n*-butyllithium to 1. With use of  $6.0 \text{ H}^-$  and 3.0 H<sup>-</sup> equiv of LAH, the reduction of the anion required 4 and 8 h, respectively, with approximately 2.0 H<sup>-</sup> consumption in both reactions (Table III). Treatment of a stoichiometric amount of hydride (2.2 H<sup>-</sup> equiv) with the anion resulted in the consumption of only 2 H<sup>-</sup> in 24 h, assuming a possible reduction of only one ester functional group (Table III). However, the isolated crude product was found to correspond to 1 along with unidentified side products.

A similar reaction mechanism is confirmed by the corresponding reaction with lithium borohydride (LiBH<sub>4</sub>) in THF.<sup>13</sup> The initial reaction proceeded rapidly (0.25 h) with 0.57 equiv evolution of the  $\alpha$ -hydrogen and 43% of 2, followed by the slow reduction of 3, requiring 1 h for completion (Table I). Although the metalation was faster than the reduction, the overall reaction pathway was still very similar to that of the LAH reduction.

With utilization of aluminum hydride (AlH<sub>3</sub>) as a Lewis acidic type reducing agent,<sup>12</sup> the reaction of 1 was carried out in THF at room temperature (~25 °C). It proceeded at a similar rate to that with the LAH reduction, yielding 85% of hydride uptake for reduction of two ester groups (2) in 0.25 h and 13% uptake for mono ester reduction (4) in 1.0 h; related to 0.17 equiv of the  $\alpha$ -hydrogen evolved (Table I). The isolated yield was found to be 75% of 2 (Table II), and the remaining material recovered corresponded to a mixture of 1 and side products.

With another representative acidic reducing agent, borane dimethyl sulfide  $(BH_3-SMe_2)$ ,<sup>4</sup> this reaction proceeded sluggishly under similar conditions, requiring 24 h to yield only 7% of reduction without any hydrogen evolution (Table I). However, the yield was enhanced when the reaction was conducted at ~40 °C with distillation of the dimethyl sulfide.<sup>14a,b</sup> The mass balances between isolated product and the  $\alpha$ -hydrogen evolution by metalation were excellent, showing 14% metalation and 85% reduction product in 2 h (Table II). Apparently, the reduction with the Lewis acidic reducing agents competes reasonably with metalation for the substrate.

To even further prohibit metalation, the use of a highly hindered reducing agent, diisobutylaluminum hydride [(i-Bu)<sub>2</sub>AlH],<sup>15</sup> was chosen for the experiment. Treatment of a hydride solution with 1 gave no evolution of hydrogen after 2 h at room temperature (Table I). After further purification, the yield of the desired product was quantitative (Table II). The reduction was extremely clean and with no competing formation of 3 through  $\alpha$ -proton abstraction.

In previous publications, the coordination of borane with carbonyl groups has been proposed as an explanation for the rates of reduction of ketones, carboxylic acids, esters, and aldehydes with borane.<sup>14,16,17</sup> Similarly, aluminum hydride has also been reported to be coordinated with the carbonyl group<sup>12c</sup> or tetrahydrofuran to form a 1:1 adition compound.<sup>12b,17,11</sup> In addition, a simple four-center transition state has been proposed for the hydroboration reaction, with the direction of the addition being controlled primarily by the polarization of the boran-hydrogen bond.<sup>19</sup> Other electrophillic metal hydrides of group IIIA of the periodic table, as well as their alkyl derivatives, were

<sup>(14) (</sup>a) Brown, H. C.; Choi, Y. M. Synthesis 1981, 439. (b) Brown,
H. C.; Choi, Y. M.; Narasimhan, S. J. Org. Chem. 1982, 47, 3153. (c) Braun, L. M.; Braun, R. A.; Crissman, H. R.; Opperman, M.; Adams, R. M. J. Org. Chem. 1971, 36, 2388. (d) Lane, C. F. Aldrichimica Acta 1975, 8, 20. (e) Krishnamurthy, S.; Thompson, K. L. J. Chem. Ed. 1977, 54, 778.

<sup>(15)</sup> Yoon, N. M.; Gyoung, Y. S. J. Org. Chem. 1985, 50, 2443.

<sup>(16)</sup> Brown, H. C.; Schlesinger, H. I.; Burg, A. J. Am. Chem. Soc. 1939, 61, 673.

 <sup>(17)</sup> Brown, H. C.; Stocky, T. P. J. Am. Chem. Soc. 1977, 99, 8218.
 (18) Wilberg, E.; Gosel, W. Z. Naturforsch 1956, 90, 2927.

<sup>(19) (</sup>a) Brown, H. C.; Zweifel, G. J. Am. Chem. Soc. 1959, 81, 247. (b)
Allred, E. L.; Sonnenberg, J.; Winstein, S. J. Org. Chem. 1960, 25, 26. (c)
Brown, H. C. Boranes in Organic Chemistry; Cornell University Press:
Ithaca, 1972; pp 263-269. (d) Jones, P. R. J. Org. Chem. 1972, 37, 1886.
(e) Pasto, D. J.; Lepeska, B.; Cheng, T. J. Am. Chem. Soc. 1972, 94, 6083.

Table III. Reduction of the Lithium Enolate of Diethyl Phenylmalonate with Lithium Aluminum Hydride in Tetrahydrofuran at Room Temperature

ratio of hydride to compd	time, h	H <sub>2</sub> evolved, mmol/ mmol of compd	total H <sup>-</sup> consumed, mmol/ mmol of compd	H <sup>-</sup> used for reduction, mmol/mmol of compd	
6.0 <sup>a</sup>	0.25	0.00	0.54	0.54	
	0.50	0.00	0.84	0.84	
	1.0	0.00	1.26	1.26	
	4.0	0.00	1.99	1.99	
	8.0	0.00	2.04	2.04	
	24.0	0.00	2.41	2.41	
3.0 <sup>b</sup>	0.25	0.00	0.43	0.43	
	0.50	0.00	0.74	0.74	
	1.0	0.00	1.05	1.05	
	4.0	0.00	1.66	1.66	
	8.0	0.00	2.09	2.09	
2.2°	0.25	0.00	0.46	0.46	
	0.50	0.00	0.74	0.74	
	1.0	0.00	1.02	1.02	
	4.0	0.00	1.54	1.54	
	8.0	0.00	1.73	1.73	
	24.0	0.00	2.00	2.00	

 $^{\circ}1.0$  M in hydride in lithium aluminum hydride and 0.17 M in compound (compd).  $^{b}0.5$  M in hydride and 0.17 M in compd.  $^{\circ}0.37$  M in hydride and 0.17 M in compd.

found to react with double bonds to give organometallic compounds through a four-centered cyclic transition state.  $^{\rm 20}$ 

Two transition states are proposed by the molecular models based on the data and literature, either reduction via a four-center transition state (6) or  $\alpha$ -hydrogen abstraction via a six-membered ring transition state (5). We have shown in all cases that reduction is more predominant than metalation. Furthermore, in our study using (i-Bu)<sub>2</sub>AlH, the formation of 5 is not favored, and as indicated by molecular models, this is presumably due to a steric congestion.



In conclusion, it appears clear that the reduction with all of the acidic and basic reducing agents used competes reasonably with the  $\alpha$ -proton abstraction (metalation) for the substrate except for the lithium borohydride reduction case. The compound 3, however, is found to be more slowly reduced to the corresponding undesired products. With acidic type metal hydrides, the isolated yields of 2 are higher than those with basic metal hydrides, especially for diisobutylaluminum hydride reaction, which provides a clean reduction with no metalation.

## **Experimental Section**

All glassware was dried thoroughly in a drying oven and cooled under a stream of dry nitrogen. All reduction experiments were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer solutions. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) was dried with excess lithium aluminum hydride and distilled under nitrogen immediately prior to use. All metal hydrides were the commercial products and were standardized by hydrolyzing a 1-mL aliquot of the solution with a glycerine-water-THF mixture and measuring the hydrogen evolved. Carboxylic acid esters were the commercial product of the highest purity.

Procedure for the Rate Study. The procedure for aluminum hydride is representative. Two 50-mL round-bottom side-arm flasks were dried in an oven and cooled down in a dry nitrogen atmosphere. The first flask was equipped with a rubber syringe cup, a magnetic stirring bar, and a reflux condenser connected to a gas buret. Then 13.7 mL (18 mmol of hydride) of a 0.44 M solution of aluminum hydride in tetrahydrofuran (THF) was injected into the flask, followed by 3.65 mL of dry THF. The flask was immersed in an ice bath and cooled to 0 °C. Then 0.65 mL (3.0 mmol) of diethyl phenylmalonate (1) was slowly added to the hydride solution (the resulting solution was 1.0 M in hydride in aluminum hydride and 0.17 M in starting material). The flask was immediately warmed to room temperature, and the rate of hydrogen evolution was followed with time. The results are summarized in Tables I and II.

The second reaction flask was prepared in the same manner. Aliquots (2.0 mL) were withdrawn at various time intervals and analyzed by hydrolysis. A blank experiment was performed in which THF was substituted for diethyl phenylmalonate. From the difference, the number of millimoles of hydride used for reduction per millimole of compound and hence the percentage of reaction was calculated. The results are summarized in Table I.

General Experimental Procedure. The detailed procedure for using borane dimethyl sulfide has been described previously.<sup>10</sup> The procedures utilizing aluminum hydride, lithium aluminum hydride, and lithium borohydride were the same as that described for diisobutylaluminum hydride with the exception that 42 mL of water replaced the methanol used to quench the excess reagent.

**Reduction of 1.** The reduction utilizing diisobutylaluminum hydride is representative. The reaction was carried out under a nitrogen atmosphere in a predried 250-mL round-bottom flask with a side-arm and a nitrogen outlet connecting tube. To the flask was added 165 mmol of hydride in diisobutylaluminum hydride solution (1.0 M) in THF under nitrogen. The rapidly stirring solution was cooled to 0 °C, and 6.4 mL (30 mmol) of 1 was slowly added, making the solution 0.96 M in hydride and 0.18 M in 1. No hydrogen evolution was observed. The solution was then allowed to warm to room temperature and stirred for 2 h at which time the reaction was complete (TLC monitoring). The reaction mixture was cooled to 0 °C and carefully quenched with 42 mL of methanol followed by 83 mL (165 mmol) of 2 N hydrochloric acid. The homogeneous solution was extracted twice with ether. The aqueous phase was then made alkaline (pH 9-10) with saturated potassium carbonate solution and extracted with ether. The combined organic phases were washed with saturated potassium carbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to yield the crude diol. The purified diol (mp 51-53 °C) was isolated in a quantitative yield (4.62 g, 29.8 mmol) by recrystallation from a mixture of hexane-toluene-ether (10:5:1). The results are summarized in Table II.

Reduction of the Lithium Enolate of Diethyl Phenylmalonate. The reduction utilizing 3 H<sup>-</sup> equiv in LAH is representative. To a dry 100-mL round-bottom flask with a side-arm and a nitrogen inlet connecting tube were added 1.07 mL (5.0 mmol) of 1 and 22.8 mL of dry THF. The solution was cooled to 0 °C, and 2.37 mL (5.25 mmol) of a 2.2 M solution of *n*-butyllithium in hexane was slowly added. After the pale yellow solution was stirred for 30 min at 0 °C, 3.75 mL (15.0 mmol H<sup>-</sup>) of a 1.0 M solution of lithium aluminum hydride was added, and the resulting solution was stirred at room temperature. Aliquots were removed at various times and checked for residual hydride by hydrolysis. The results are summarized in Table III.

**Registry No.** 1, 83-13-6; 2, 1570-95-2; LiAlH<sub>4</sub>, 16853-85-3; LiBH<sub>4</sub>, 16949-15-8; AlH<sub>3</sub>, 7784-21-6; BH<sub>3</sub>-SMe<sub>2</sub>, 13292-87-0; DiBAH, 1191-15-7; C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>·Li, 2422-04-0.

<sup>(20) (</sup>a) Eisch, J. J. The Chemistry of Organometallic Compounds; Macmillan: New York, 1967; pp 107-111. (b) Eisch, J. J.; Fichter, K. C. J. Organomet. Chem. 1983, 250, 63.