COMMUNICATIONS

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Improved Procedure for Borane-Dimethyl Sulfide Reduction of Carboxylic Esters

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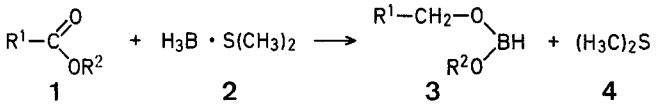
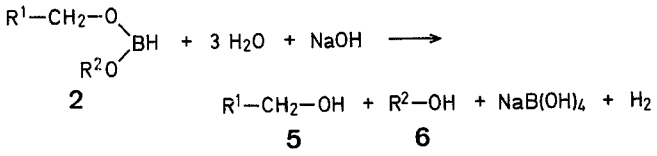
Sodium borohydride is an excellent reagent for the reduction of aldehydes and ketones, but it is generally too slow for a convenient reduction of carboxylic esters[1]. The reduction of such esters by diborane[2], borane-tetrahydrofuran[3], or by borane-dimethyl sulfide[4,5] is also relatively slow. Accordingly, lithium aluminium hydride[6,7], lithium borohydride[8,9], or calcium borohydride[10] have been the preferred reagents[11].

We describe here a simple procedure which makes it possible to reduce carboxylic esters **1** with borane-dimethyl sulfide (**2**) rapidly, in essentially quantitative yields. We have observed that **2** is stable in refluxing tetrahydrofuran for long periods of time. Under these conditions, the reagent reduces esters **1** to an intermediate, presumably the dialkoxyborane **3** at a reasonable rate.



1 **2** **3** **4**

Simple hydrolysis with water or, preferably, aqueous alkali, gives the corresponding alcohols **5** and **6**.

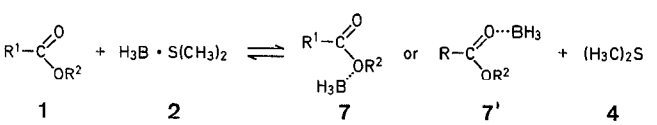


2 **5** **6**

When potassium carbonate is used, the tetrahydrofuran layer separates above the alkaline phase. The product is then readily recovered from the tetrahydrofuran phase by simple distillation.

In applying this procedure to ethyl benzoate, a relatively resistant ester[3], we noted that the reaction was 67% complete in 0.25 h, but then required more than 8 h to go to essential completion (98%). The data are summarized in the Table 1.

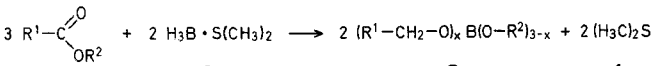
In reviewing the literature data, it appeared that the reduction of esters was fastest with uncomplexed diborane[2], slower with borane-tetrahydrofuran[3], and slowest with **2**[4,5]. Evidently, the more tightly coordinated the borane, the slower the reduction. This suggested that the reduction probably proceeds through a transfer of borane from its complexes to the ester group[3] (**7** or **7'**).



1 **2** **7** **7'** **4**

On this basis, the decrease of the rate of reduction of ethyl benzoate by **2** as the reaction proceeds could be attributed to a combination of two factors. First, the accumulation of dimethyl sulfide in the reaction mixture would repress the transfer of borane to the ester group to give the desired intermediate (**7** or **7'**). Second, the accumulation of dimethyl sulfide, b.p. 38 °C, would reduce the temperature of the refluxing reaction mixture (tetrahydrofuran, b.p. 67 °C).

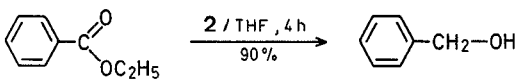
It appeared that a simple distillation of dimethyl sulfide from the reaction mixture, as it is liberated, would overcome the difficulty. Indeed, that proved to be the case. The reaction was complete (100%) in 1.0 h (Table 1). We then examined the possibility of reducing the amount of **2** from the 50% excess used in these experiments to essentially the stoichiometric (1.0 ester: 0.67 **2**).



1 **2** **8** **4**

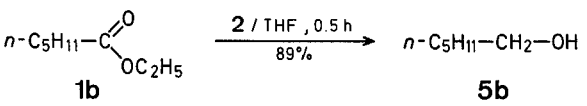
We used a slight excess of **2** (10%) to allow for small amounts of active hydrogen impurities (water, alcohol, acid) in the ester and in the apparatus. In order to minimize the solvent required, we also increased the concentration of each of the reactants, 3.0 molar for the ester **1** and 2.2 molar for **2**. Indeed, the reaction appeared to be complete in 4 h, since examination of the reaction mixture by G.L.C. revealed the absence of residual ester. Accordingly, we adopted this procedure and applied it to a number of representative esters.

As mentioned, the reduction of ethyl benzoate (**1a**) required approximately 4.0 h and we isolated a 90% yield of benzyl alcohol (**5a**) in 90% yield.

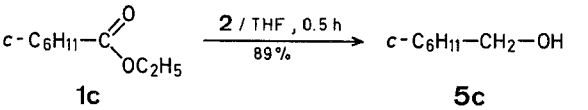


1a **5a**

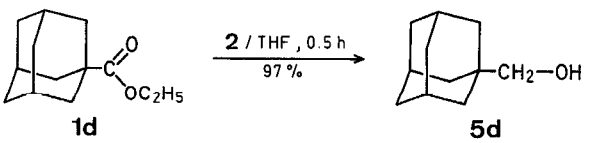
The reduction of aliphatic esters proceeded much more rapidly. Thus, ethyl *n*-hexanoate (**1b**) was converted into 1-hexanol (**5b**) in 0.5 h, and ethyl cyclohexanecarboxylate (**1c**) was reduced to hydroxymethylcyclohexane (**5c**) in the same time. Finally, even the highly hindered derivative, ethyl adamantane-1-carboxylate (**1d**), was reduced to 1-hydroxymethyladamantane (**5d**) in essentially quantitative yield (Table 2).



1b **5b**



1c **5c**



1d **5d**

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The presence of unsaturation limits the procedure. The reagent would hydroborate any double or triple carbon-carbon bonds[12]. Functional groups that are readily reduced by borane-tetrahydrofuran[3] or **2**[4,5] would undergo concurrent reduction of these groups. Finally, the presence of amino groups in the ester would require the introduction of additional reagent to compensate for the formation of amine-borane adducts[13]. With these restrictions, this reduction with **2** appears to be broadly applicable to the reduction of a wide variety of carboxylic esters.

Table 1. Reduction of Ethyl Benzoate (**1a**) with Borane-Dimethyl Sulfide (**2**) in Tetrahydrofuran at Reflux[a]

	Accumulation of $(H_3C)_2S$		With Distillation of $(H_3C)_2S$	
Reaction Time [h]	Hydride Used mmol/mmol **1a**	Reaction [%]	Hydride Used mmol/mmol **1a**	Reaction [%]
0.25	1.35	67	1.49	75
0.50	1.48	74	1.66	83
1.00	1.65	83	2.00	100
2.00	1.88	94		
4.00	1.95	97		
8.00	1.96	98		

[a] The initial concentrations were 2.0 molar in ethyl benzoate and 2.0 molar in borane-dimethyl sulfide.

Table 2. Reduction of Esters **1** by **2** in Tetrahydrofuran at Reflux with Distillation of Dimethyl Sulfide[a]

Ester	Alcohol	Reaction time [h]	Yield[b] [%]	m.p. [°C] or b.p. [°C]/torr	
				found	reported
1a	**5a**	4	90	96–98°/15	93°/10[14]
1b	**5b**	0.5	89	76–78°/15	158°/760[14]
1c	**5c**	0.5	89	84–86°/15	83°/14[14]
1d	**5d**	0.5	97	115–117°	115–118°[15]

[a] Ester **1** (30 mmol, 3.0 molar solution), **2** (22 mmol, 2.2 molar solution); ratio $H^{\ominus}$: ester = 2.2; volume of distillate collected: 1.6 ml.
[b] Yield of isolated product.

Reduction of Ethyl Benzoate (1a) by 2 with Accumulation of Dimethyl Sulfide:

Borane-dimethyl sulfide (**2**) is standardized before use as follows. An aliquot portion of **2** is hydrolyzed using 1:1:1 mixture of glycerine/water/tetrahydrofuran. From the volume of hydrogen liberated, the concentration of **2** is calculated (8.73 molar). In a typical experiment, a 50-ml flask equipped with a sidearm, magnetic stirring bar, and a reflux condenser connected to the nitrogen source through a mercury bubbler is cooled under nitrogen. The flask is charged with the 8.73 molar solution of **2** (5.73 ml, 50 mmol) and tetrahydrofuran (12.03 ml). The solution is stirred and ethyl benzoate (**1a**; 7.24 ml, 50 mmol) is added slowly at 25 °C. The reactants are heated on a oil bath to reflux. Samples are removed periodically for analysis of residual **2** by hydrolysis, as above. A blank experiment is performed under identical conditions, but without addition of the ester. Aliquots are withdrawn periodically for analysis of residual hydride. From the data (Table 1), the number of mmols of hydride used for reduction in the various time intervals could be calculated. At the conclusion of the reaction, the material is hydrolyzed by aqueous alkali and subjected to G.L.C. analysis (CW-20M, 6′ × 1/8″). This analysis reveals the absence of ester **1a** and the presence of benzyl alcohol (**5a**) in a yield of essentially 100%.

Reduction of Ethyl Benzoate (1a) by 2 with Distillation of Dimethyl Sulfide:

The procedure is identical to that described above with one exception. A 12″ Vigreux column, maintained at ~40 °C by a heating jacket, is attached to the reaction flask. Dimethyl sulfide is distilled off as fast as it is formed. A total of 2.1 ml (95%) is collected at the end of the reaction. The hydrolysis of aliquots reveals the progress of the reaction. The data are summarized in Table 1. Here also G.L.C. analysis (CW-20M, 6′ × 1/8″) of the completed reaction reveals the absence of ester **1a** and the presence of essentially an 100% yield of benzyl alcohol (**5a**) (following hydrolysis).

Reduction of Esters 1 by 2 with Distillation of Dimethyl Sulfide; General Procedure:

The experimental setup is identical with that described previously. In the reaction flask under nitrogen at 25 °C is placed the solution of **2** (2.52 ml, 22 mmol), tetrahydrofuran (~3 ml), and the ester **1** (30 mmol) to be reduced. The total volume is 10 ml (2.2 molar in **2** and 3.0 molar in ester **1**). The reaction mixture is heated to reflux and the dimethyl sulfide collected as it is distilled through the Vigreux column. A total of 20.8 mmol (95%) is obtained. When no more dimethyl sulfide distills, the reaction is over. The reaction mixture is brought to room tempature and water (15 ml) is added to the stirred reaction mixture. Then, anhydrous potassium carbonate (2 g) is added to hydrolyze the borate ester and to extract the boric acid. Additional potassium carbonate is added to saturate the aqueous phase. Ether (10 ml) is added and the ether/tetrahydrofuran extract is fractionally distilled to provide the corresponding alcohols in yields of 89–97% (Table 2).

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