

(7) Satisfactory analytical and spectroscopic data were obtained for all new compounds.

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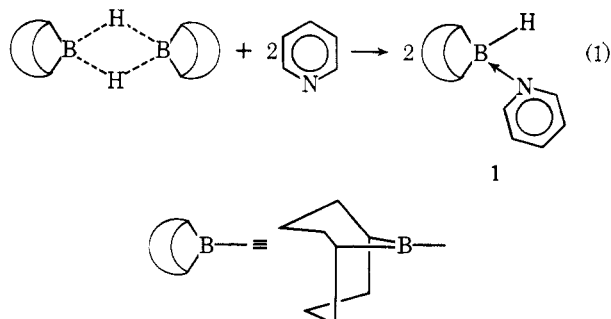
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### A New Reagent, 9-Borabicyclo[3.3.1]nonane-Pyridine, for the Selective Reduction of Aldehyde Groups in the Presence of Keto and Other Functional Groups

**Summary:** The exceptionally mild, highly selective, new reducing agent, 9-borabicyclo[3.3.1]nonane-pyridine (9-BBN-py), cleanly reduces the aldehyde group in the presence of keto and many other functional groups, making possible the clean, selective reduction of aldehyde groups in complex molecules.

**Sir:** The selective reduction of one carbonyl group in the presence of other such groups is a frequent synthetic problem. It has been solved in various ways.<sup>1</sup> A difficult, yet commonly encountered, problem in organic synthesis is the clean reduction of aldehyde in the presence of keto groups. Although aldehydes are reduced faster than ketones, the absolute rates are often too fast to take advantage of the favorable difference in the relative reduction rates. Consequently, in recent years, various reagents have been developed for such selective reductions. These include tetrabutylammonium cyanoborohydride,<sup>2</sup> sodium triacetoxyborohydride,<sup>3</sup> lithium tri-*tert*-butoxyaluminumhydride,<sup>4</sup> 9-borabicyclo[3.3.1]nonane (9-BBN),<sup>5</sup> and Li-*n*-Bu<sub>2</sub>-9-BBN "ate" complex.<sup>6</sup> More recently, diisopropylcarbinol on dehydrated alumina has been reported to be superior to all of these earlier reagents in its ability to distinguish effectively between an aldehyde and unhindered cyclohexanone.<sup>7</sup> However, this method requires large amounts of alumina with a tedious workup procedure resulting from the presence of both diisopropylcarbinol and diisopropyl ketone in the reaction mixture.

In this communication, we report application of the newly synthesized reagent, 9-borabicyclo[3.3.1]nonane-pyridine (9-BBN-py, 1),<sup>8</sup> for the selective reduction of aldehydes in the presence of ketones. The reagent 1 is conveniently prepared by a simple reaction between the readily available 9-BBN dimer<sup>9</sup> and pyridine in pentane solution (eq 1).<sup>8</sup> The product



thus obtained is a stable crystalline solid, indefinitely stable under nitrogen.<sup>10</sup>

The selectivity in reduction and the functional group tolerance exhibited by 1 is quite remarkable, far better than that

**Table I. Reduction of Aldehydes and Ketones by 9-BBN-py in THF Solutions<sup>a</sup> at 25 °C**

Compd	Time, h	% reduced <sup>b</sup>
Benzaldehyde	1.0	95
	1.5	100
Cinnamaldehyde	1.0	86
	1.5	98
Cyclohexylcarboxaldehyde	1.0	91
	3.0	100
Octanal	1.0	91
	2.0	99
Hexanal	1.0	94
	2.0	100
Propanal	1.0	85
	1.5	97
Cyclohexanone	1.0	0
	1.5	3
2-Methylcyclohexanone	2.0	0
2-Hexanone	1.0	5
	12.0	43
Dicyclopropyl ketone	1.5	8
3-Pentanone	1.0	5
	7.0	10
Acetophenone	1.0	3
	9.0	5
Phenylacetone	1.0	6
	8.0	46

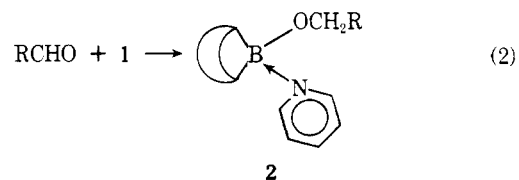
<sup>a</sup> The reaction mixture was 0.25 M in the substrate and 0.25 M in 9-BBN-py. <sup>b</sup> Progress of the reaction was followed by the measurement of residual hydride in the aliquot; for details of the procedure, see H. C. Brown, "Organic Syntheses via Boranes", Wiley, New York, N.Y., 1975, Chapter 9.

**Table II. Relative Reactivities of Aldehydes with Respect to Ketones toward 9-BBN-py in Et<sub>2</sub>O at 25 °C. Competition Experiments**

Compd used	Product	Mol % <sup>a</sup>
Cyclohexanone	Cyclohexanone	98.5
+	Cyclohexanol	1.5
Benzaldehyde	Benzaldehyde	6.0
	Benzyl alcohol	93.0
Acetophenone	Acetophenone	96.0
+	1-Phenylethanol	2.0
Benzaldehyde	Benzaldehyde	4.0
	Benzyl alcohol	94.0
3-Pentanone	3-Pentanone	96.0
+	3-Pentanol	2.5
Octanal	Octanal	4.5
	1-Octanol	94.5

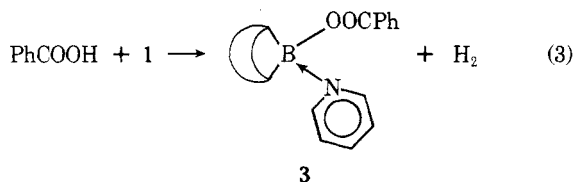
<sup>a</sup> Determined by GLC (ref 11) from the response ratios determined for authentic samples.

exhibited by the parent 9-BBN itself.<sup>5</sup> Thus a wide variety of aldehydes are reduced almost completely in 2 h at 25 °C in THF or Et<sub>2</sub>O solutions (eq 2), whereas, under similar exper-



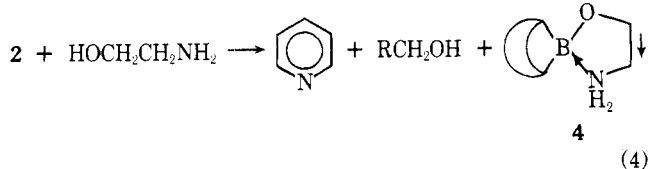
imental conditions, even unhindered ketones are not reduced significantly (Table I). Competition experiments carried out by adding 10 mmol of 1 to a mixture of 10 mmol of aldehyde and 10 mmol of ketone in Et<sub>2</sub>O reveal that 1 is highly selective toward aldehydes (Table II).<sup>11</sup> Also, various representative functional groups, such as ester, lactone, *N,N*-dialkylamide,

nitrile, alkyl halide, benzylic halide, epoxide, alkene, alkyne, and nitroalkane, are not affected by 1. Carboxylic acids, alcohols, and water react relatively rapidly, liberating hydrogen (eq 3).<sup>8</sup> However, no further reaction of the initially formed



*B*-acyloxy-9-BBN-py (3) occurs with excess 1. On the other hand, acid chlorides and anhydrides are reduced rapidly. Consequently, with the exception of these groups, the reagent permits the selective reduction of aldehyde groups in the presence of nearly all other functional groups. Such a remarkable inertness toward most of the functional groups, combined with a high selectivity for the reduction of aldehydes, has not been realized with any of the reagents previously described.<sup>2-7</sup>

The isolation of the primary alcohol product from the *B*-alkoxy-9-BBN-py (2) intermediate is quite simple, requiring only addition of  $\beta$ -aminoethanol. This displaces the alcohol with precipitation of the ethanolamine complex (4) of 9-BBN (eq 4). The latter can be removed by filtration in air.



The following experiment is representative for the determination of relative reactivities of aldehydes with respect to ketones. To a mixture of benzaldehyde (10 mmol, 1.02 mL), acetophenone (10 mmol, 1.17 mL) and *n*-tetradecane (5 mmol, 1.23 mL; an internal standard for GLC analysis) in 30 mL of Et<sub>2</sub>O under nitrogen was added a solution of 1 in Et<sub>2</sub>O (10 mmol, 6.7 mL of 1.5 M solution). After stirring for 2 h at 25 °C, the mixture was diluted with 30 mL of pentane, and  $\beta$ -aminoethanol (10 mmol, 0.61 mL) was added to precipitate 4. The supernatant liquid was analyzed by GLC<sup>11</sup> (Table II).

The reduction of hexanal is representative for the isolation of alcohols. To a well-stirred solution of hexanal (150 mmol, 18.5 mL) in 100 mL of Et<sub>2</sub>O under nitrogen was added an ether solution of 1 (165 mmol, 110 mL of 1.5 M solution). After stirring for 2 h at 25 °C, pentane (300 mL) and  $\beta$ -aminoethanol (165 mmol, 9.97 mL) were added. The precipitate of 4 was filtered off and the Et<sub>2</sub>O-pentane extract was washed with dilute HCl to remove pyridine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was pumped off and the product distilled: 11.8 g of 1-hexanol (77% yield), bp 80–82 °C (25 mm). Similarly, benzyl alcohol and cyclohexylmethanol were isolated in yields of 74 and 78%, respectively.<sup>12</sup>

In conclusion, the present study reveals that 9-BBN-py complex is a highly selective, unique reducing agent which should find application in situations requiring the selective reduction of aldehydes in the presence of other functional groups. The full scope and limitations of such reductions are being examined.

### References and Notes

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- (7) G. H. Posner, A. W. Runquist, and M. J. Chapdelaine, *J. Org. Chem.*, **42**, 1202 (1977); see Table III in this paper for comparison.
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- (9) Available from Aldrich Chemical Co., Milwaukee, Wisc.
- (10) Although 9-BBN-py is reasonably stable in air, it was used under nitrogen and exposure to air and moisture minimized.
- (11) A 14 ft  $\times$  1/8 in. column packed with 5% Carbowax 20M deposited on Varaport-30 was used for separation of the complex mixture.
- (12) The yields are not optimized. The isolated alcohols contain trace amounts of aldehydes.
- (13) Graduate research assistant on Grant GM 10937-14 from the National Institutes of Health.

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### High-Pressure Cycloadditions of Pyrones: Synthesis of Highly Functionalized Six-Membered Rings by Inhibition of Carbon Dioxide Loss

**Summary:** A series of highly functionalized bicyclic adducts (3–6) have been prepared via the high-pressure (20–40 kbar) cycloaddition of 3-hydroxy-2-pyrone (2) with various dienophiles at room temperature.

**Sir:** The application of pressure accelerates the rates of chemical reactions which have a negative volume of activation and retards the rates of those which have a positive volume of activation.<sup>1</sup> Dauben has recently shown that pressures in the 8–20-kbar range are useful in effecting cycloaddition reactions of enamines, dienamines, and furans.<sup>2</sup> The requisite apparatus for executing large-scale high-pressure syntheses is only moderately expensive,<sup>3</sup> making its use practical in preparative chemistry.

Highly negative (–25 to –45 cm<sup>3</sup>/mol) volumes of activation have been measured for both 4 + 2 and polar 2 + 2 cycloadditions.<sup>1,4</sup> Under thermodynamically ideal conditions, transition state stabilization of such reactions should be on the order of 1 kcal/mol per kilobar of pressure applied. Also, the thermal extrusion of small, stable molecules such as CO<sub>2</sub> and N<sub>2</sub> from neutral organic compounds should be retarded by pressure both on kinetic ( $\Delta V^\ddagger > 0$ ) and thermodynamic ( $\Delta V_{\text{rxn}} > 0$ ) grounds. We reasoned that this combination of factors would enable the preparation of highly functionalized six-membered rings from pyrone derivatives, which usually extrude CO<sub>2</sub> under conventional (100–200 °C) Diels–Alder conditions (Scheme I).<sup>5,6</sup> In the event of 100% regioselectivity

