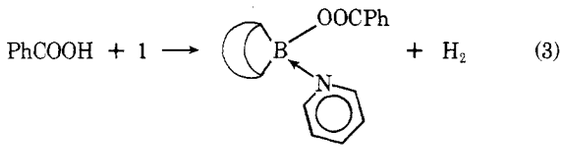
nitrile, alkyl halide, benzylic halide, epoxide, alkene, alkyne, and nitroalkane, are not affected by **1**. Carboxylic acids, alcohols, and water react relatively rapidly, liberating hydrogen (eq 3).[8] However, no further reaction of the initially formed

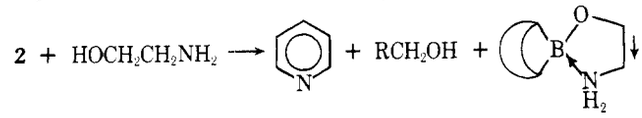


(3)

3

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.[2-7]

The isolation of the primary alcohol product from the *B*-alkoxy-9-BBN·py (**2**) intermediate is quite simple, requiring only addition of β-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.



4

(4)

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_2O under nitrogen was added a solution of **1** in Et_2O (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 β-aminoethanol (10 mmol, 0.61 mL) was added to precipitate **4**. The supernatant liquid was analyzed by GLC[11] (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_2O 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 β-aminoethanol (165 mmol, 9.97 mL) were added. The precipitate of **4** was filtered off and the Et_2O–pentane extract was washed with dilute HCl to remove pyridine and dried over anhydrous Na_2SO_4. 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.[12]

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.

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(8) H. C. Brown and S. U. Kulkarni, *Inorg. Chem.*, in press.
(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 × 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.[1] Dauben has recently shown that pressures in the 8–20-kbar range are useful in effecting cycloaddition reactions of enamines, dienamines, and furans.[2] The requisite apparatus for executing large-scale high-pressure syntheses is only moderately expensive,[3] making its use practical in preparative chemistry.

Highly negative (−25 to −45 cm^3/mol) volumes of activation have been measured for both 4 + 2 and polar 2 + 2 cycloadditions.[1,4] 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_2 and N_2 from neutral organic compounds should be retarded by pressure both on kinetic ($\Delta V^{\ddagger} > 0$) and thermodynamic ($\Delta V_{rxn} > 0$) 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_2 under conventional (100–200 °C) Diels–Alder conditions (Scheme I).[5,6] In the event of 100% regioselectivity

Scheme I

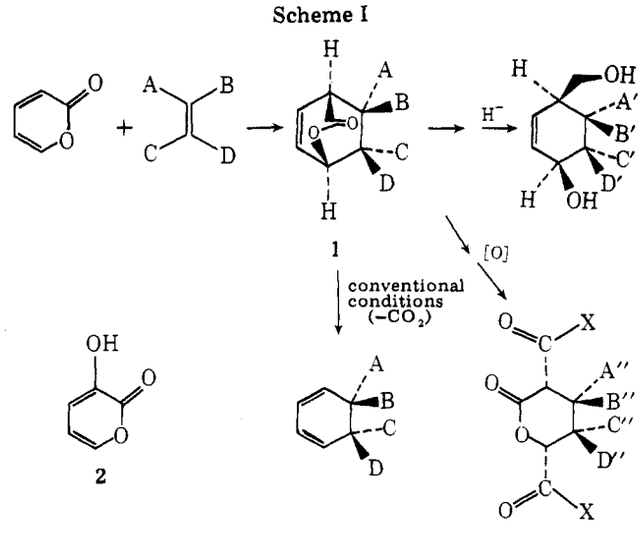
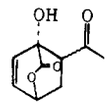
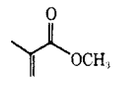
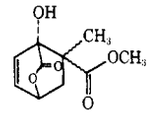
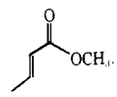
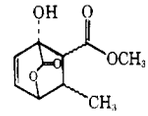
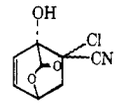
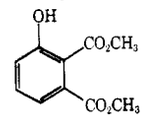


Table I. High-Pressure Cycloadducts of 3-Hydroxy-2-pyrone

Dienophile reacted with 2	Pressure, kbar	Product	Endo/exo ratio[10]	IR ($CHCl_3$), cm^{-1}	NMR ($CDCl_3$), Me_4Si internal standard[a]
	17	 3	>10:1	1752 (s) 1710 (s)	^1H: δ 1.85–2.61 (2 H, complex m), 2.28 (3 H, s), 3.17 (1 H, d of d, J = 5.0, 9.5 Hz), 5.34 (1 H, m), 6.15–6.63 (2 H, complex m) ^{13}C: 205.5, 175.0, 134.2, 130.1, 76.0,[b] 74.3, 47.7, 3.20, 30.6 ppm
	32	 4	3:1	1740 (s, br)	^1H: δ 1.37 and 1.31 (2 s, 3 H total area, relative area 3:1, assigned to endo and exo isomers), 1.76–2.93 (2 H, complex m) 3.71 (3 H, s), 5.28 (1 H, m), 6.48 (2 H, m) ^{13}C:[c] 174.5, 173.5, 137.5, 129.5, 78.7,[b] 73.7, 52.9, 46.5, 40.4, 21.9 ppm
	40	 5	3:2	1760 (s) 1737 (s)	^1H: δ 1.00 and 1.33 (2 d, J = 7 Hz, total area 3 H, relative area 3:2, assigned to endo and exo isomers), 2.07–2.45 (2 H, m), 3.73 (3 H, s) 4.97 (1 H, m), 6.47 (2 H, pseudo d, J = 4 Hz) ^{13}C endo:[b] 174.1, 171.6, 135.1, 130.1, 79.0, 52.6, 50.3, 40.1, 18.3 ppm ^{13}C exo:[b] 173.2, 172.5, 137.8, 129.1, 77.3, 53.8, 50.3, 39.4, 18.9 ppm
	30	 6	2:1	1775 (s)[d]	^1H:[e] 5 d (total area 2 H) at δ 2.40 (J = 2 Hz), 2.66 (J = 2), 3.00 (J = 3), 3.21 (J = 4), and 3.48 (J = 4), 5.43 (1 H, m), 6.35–7.00 (2 H, complex splitting) ^{13}C:[c,e] 169.6, 134.6, 131.9, 117.3, 71.9, 67.3,[b] 56.8, 46.1 ppm
	20	 7[12]	—	1723 (s) 1674 (s)	^1H: δ 3.92 (3 H, s), 3.88 (3 H, s) 6.90–7.65 (3 H, complex m) 10.47 (1 H, br, from authentic sample) ^{13}C: 169.4, 161.0,[f] 135.3, 134.4, 120.0, 119.3, 110.7, 52.8, 52.6 ppm

[a] The –OH group in adducts 3–6 is deuterated under the reaction conditions. [b] The bridgehead carbon bearing the –OH group is weak in intensity, even in the presence of $Cr(acac)_3$. In 3 and 4, its chemical shift assignment is tentative due to overlap with $CDCl_3$. In 5, the resonance is completely obscured, and in 6 it is upfield from $CDCl_3$ but still considered tentative due to its low intensity. [c] For the major (endo) isomer only. [d] The absence of $\nu_{C\equiv N}$ in α-chloronitriles has been previously noted: R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds", 3rd ed, Wiley, New York, N.Y., 1974, p, 110. [e] Obtained in $CDCl_3$/acetone. [f] An apparent degeneracy of the two carbonyl groups or a carbonyl group and the –OH carbon exists. In the presence of $Cr(acac)_3$, the 169.4 peak is ca. twice the 161.0 peak. Compare with methyl salicylate and methyl benzoate in L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, N.Y., 1972.

and endo cycloaddition, a single adduct of structure 1 would be obtained which contains two asymmetric carbons of fixed relative configuration otherwise lost upon CO_2 elimination. Possible reductive and oxidative elaborations of 1 to highly functionalized monocycles are also illustrated in Scheme I.

We report herein that the initial step in Scheme I can be realized at *room temperature* by the application of pressures in the 20–40-kbar range. All cycloadditions examined were quantitative, regiospecific, and to varying degrees, stereoselective. 3-Hydroxy-2-pyrone (2) was utilized to enable comparison with the recent work of Corey and Kozikowski.[6]

Reactions were conducted in a 0.3 mL Teflon screw-top vial in acetone-d_6 utilizing approximately a 10% excess of dienophile.[7] The filled capsule was placed inside a graphite–talc sleeve and fitted into a cylindrical high-pressure vessel of sintered tungsten carbide. Pressure was generated by forcing a carbide piston into the sample vessel with the aid of a 600-ton hydraulic ram.[8] Pressure was calculated from a master ram Heise gauge. Workup consisted merely of opening the vial and blowing off solvent and any excess dienophile, after which only product remained.[7b]

The cycloadducts obtained and supporting spectral data are summarized in Table I. Reactions were allowed to run overnight at the pressure indicated. Compounds 3–5 partially decomposed upon attempted silica gel chromatography,[9] so the products were characterized as a mixture of endo/exo stereoisomers. The stereoisomer ratios were determined by ^{13}C NMR and ^1H NMR.[10] The absence of regioisomers was established by decarboxylation (pyrolysis at 150–200 °C) of each stereoisomeric mixture to a single compound; in the cases of 4–5, the decarboxylation products had been previously characterized by Corey and Kozikowski.[6] Authentic samples were prepared by their method for comparison. Although the highest molecular weight ions in the mass spectra of 3–6 were $M^+ - 44$ peaks, IR and ^{13}C NMR data clearly indicate the presence of lactone functionality. The hydroxyl hydrogen of 2 was found to exchange with acetone-d_6 under the reaction conditions. Based upon data with other weak proton acids,[1] acetone would be expected to be a much stronger acid under pressure.

The high-pressure reactions of 2 with methyl methacrylate and methyl crotonate occur at temperatures 180 °C lower than those employed by Corey and Kozikowski. Adducts 4 and 5 are instantly destroyed under their conditions, which precludes observation of the effect of pressure on the endo/exo ratio.[10,11] When 3-hydroxy-2-pyrone was reacted with α-chloroacrylonitrile by conventional thermal means, only *o*-cyanophenol was produced.[6] Utilization of high pressure blocks CO_2 and HCl loss and enables isolation of 6. The bicyclic adduct of 2 and dimethyl acetylenedicarboxylate rapidly evolves CO_2 when the sample capsule is opened at room temperature, affording the known diester 7.[12] Since this decarboxylation involves breaking bonds at two doubly allylic positions and formation of an aromatic ring, its activation

energy is understandably lower. In related work, Pirkle has noted the low-yield endo dimerization of 2-pyrone at 7 kbar and 70 °C.[5d]

In conclusion, a series of highly functionalized organic compounds which would be difficult or impossible to synthesize by conventional methods have been made available in a single step by the application of high-pressure technology. As a corollary, we note that portions of C_mH_n energy surfaces normally inaccessible due to thermal small molecule extrusion might be studied by high-pressure techniques. Further exploratory high-pressure chemistry will be the subject of forthcoming publications from this laboratory.

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(3) See supplementary material cited in ref 2c for typical designs.
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(6) E. J. Corey and A. P. Kozikowski, *Tetrahedron Lett.*, 2389 (1975).
(7) (a) Usually ~175 mg total reactants. (b) A typical isolated yield is 145 mg of **6** from 89.1 mg of **2** and 82.9 mg of α-chloroacrylonitrile (20% excess); 10% loss due to capsule leakage is commonly encountered with our apparatus.
(8) The general design of the press and sample assembly employed has been described in detail: G. C. Kennedy and P. Lamori in "Progress in Very High Pressure Research", F. B. Bundy, W. R. Hibbard, and H. M. Strong, Ed., Wiley, New York, N.Y., 1961; H. A. Katzman, Ph.D. Dissertation, University of California, Los Angeles, 1970; R. B. Murphey, Ph.D. Dissertation, University of California, Los Angeles, 1975.
(9) The bridgehead, β-carbonyl, hydroxy group in **3–5** likely facilitates a retro-Aldol condensation.
(10) We consider our assignment of the endo configuration to the major isomer of **3–6** tentative.
(11) See K. Seguchi, A. Sera, and K. Maruyama, *Tetrahedron Lett.*, 1585 (1973).
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