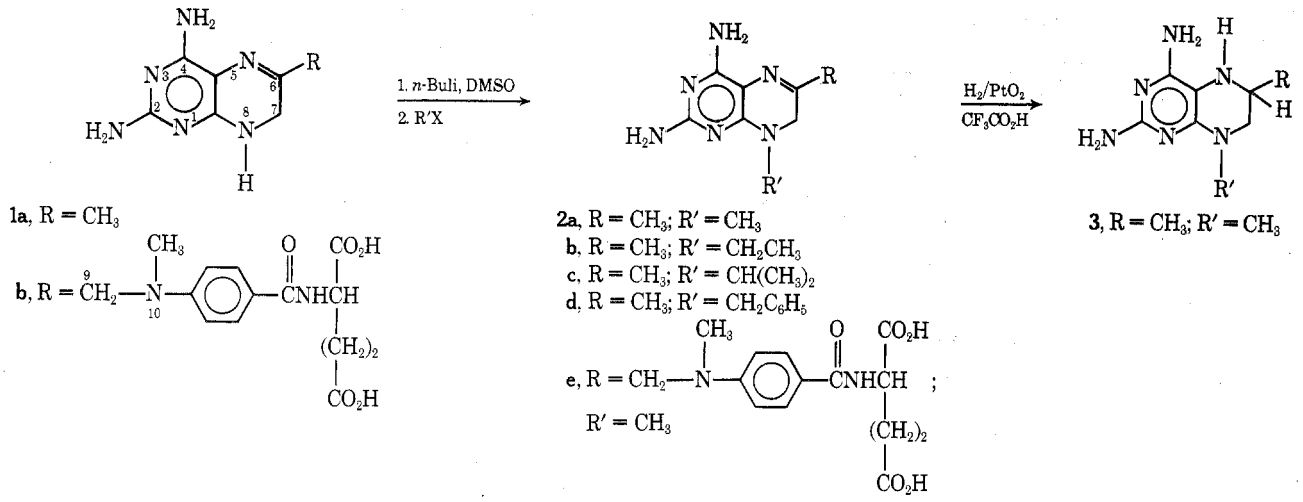

(m, 4 H, phenyl CH's). The nmr spectrum was essentially identical with that of **1b** except for the N^8 CH_3 singlet at δ 3.24, which also appears at this δ value in **2a.** To confirm alkylation at N^8, **2e** was treated with excess sodium dithionite in water at reflux for 45 min—conditions which lead to reductive cleavage at the 9,10 bond.[11] The reaction mixture was then made basic and extracted with $CHCl_3$ to give **2a** (46%).

These reactions make available some 7,8-dihydro- and 5,6,7,8-tetrahydropteridine derivatives which would otherwise require lengthier synthetic procedures. The biological properties of these and similar compounds are under investigation.

References and Notes

(1) This work was supported by Research Grant C6516 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.
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(8) E. C. Taylor, K. L. Perlman, Y. H. Kim, I. P. Sword, and P. A. Jacobi, *J. Amer. Chem. Soc.*, **95,** 6413 (1973).
(9) *n*-Butyllithium reacts with DMSO to form lithium methylsulfinyl carbanion, which is probably the actual nucleophile which causes deprotonation of the 7,8-dihydropteridine. Sodium methylsulfinyl carbanion may serve equally well in this reaction. See E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87,** 1345 (1965).
(10) For a review of the antitumor agent methotrexate (MTX), see D. G. Johns and J. R. Bertino in "Cancer Medicine," J. F. Holland and E. Frei, III, Ed., Lea and Febiger, Philadelphia, Pa., 1973, p 739.
(11) 7,8-Dihydromethotrexate has been prepared[12,13] by reduction of MTX with excess sodium dithionite at room temperature, in the presence of sodium ascorbate, according to the method used by S. Futterman [*J. Biol. Chem.*, **228,** 1031 (1957)] for the preparation of 7,8-dihydrofolic acid. In our hands, this procedure led to very low yields of 7,8-dihydro MTX, contaminated with unreacted MTX. We were able to prepare fairly pure 7,8-dihydro MTX in 80% yield by reduction of commercial disodium MTX (Ben Venue Laboratories, Inc., Bedford, Ohio) with 10 molar equiv of sodium dithionite in water at reflux for 15 min, in the presence of 5 equiv of sodium hydroxide. If less sodium hydroxide is used, the pH of the reaction mixture falls below 7 during the reaction and extensive reductive cleavage occurs at the 9,10 bond. The product is precipitated from solution by adjusting the pH to 3.5 with HCl and is obtained as a white solid, mp 180–185° dec, uv $\lambda_{max}^{0.1\ N\ HCl}$ 292 nm (ϵ 23,400). *Anal.* Calcd for $C_{20}H_{24}N_8O_5 \cdot H_2O$: C, 50.62; H, 5.52; N, 23.62. Found: C, 50.61; H, 5.06; N, 23.49.
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Received September 16, 1974

Conjugate Reduction and Reductive Alkylation of α,β-Unsaturated Cyclohexenones Using Potassium Tri-*sec*-butylborohydride

Summary: β-Unsubstituted cyclohexenones undergo 1,4 reduction and reductive alkylation to afford saturated ketones in high yield through the agency of potassium tri-*sec*-butylborohydride.

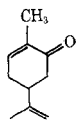
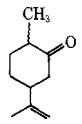
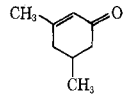
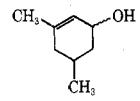
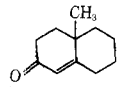
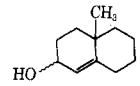
Sir: The reduction of cyclic ketones using hindered borohydrides, especially lithium and potassium tri-*sec*-butylborohydride,[1,2] has been shown to occur with a high degree of stereoselectivity for the less stable isomer. Similar selectivity has been reported in the preparation of allylic alcohols by reduction of acyclic α,β-unsaturated ketones.[3] In view of these facts we were encouraged to study the reaction of these borohydride reagents with cyclic enones. The potentially useful results we encountered prompts this preliminary communication.

We have observed that conjugated cyclohexenone systems which are unsubstituted at the β-vinylic carbon undergo exclusive 1,4-reduction in the presence of potassium tri-*sec*-butylborohydride (K-Selectride™, Aldrich Chemical Co.) to produce the corresponding saturated ketones in nearly quantitative yield.[4] No traces of allylic or saturated alcohol can be detected when 1 equiv of reducing agent is employed. If, however, an excess of 2 equiv of borohydride is present and the reaction is quenched at −78° with water, only saturated alcohols are obtained. Table I summarizes our results.

The reduction seems to occur equally well in pure tetrahydrofuran (THF) or in ether–THF mixtures and is quite rapid at −78°. 3,5-Dimethyl-2-cyclohexenone (**7**) cleanly affords a mixture of allylic alcohols and no saturated ketone or dimethylcyclohexanol whatsoever, thus demonstrating that the 1,4 addition of hydride is extremely sensitive to steric factors.[6] Not surprisingly, reduction of 10-methyl-$\Delta^{1,9}$-2-octalone (**9**) followed a similar course. Numerous attempts to effect the reduction of 2-cyclopentenone by direct or inverse admixture with Selectride™ led to a complex mixture which included cyclopentanol as a major product.

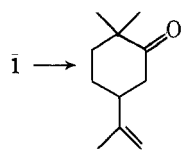
A survey of other conjugated functional groups seems to support the remarkable substrate specificity of this reagent. Ethyl crotonate, for instance, was recovered unchanged after exposure for 1 hr at −78° to an equimolar amount of K-Selectride™. This observation suggests that selective reductions may be feasible in complex polyfunctional structures containing a variety of electron-deficient olefins.

Table I

Enone	No.	Product[5]	No.	Yield,[b] %
	1		2	98
	3		4	99
	5		6	95
	7		8	83
	9		10	95

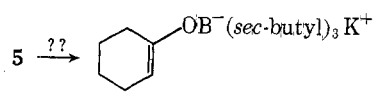
[a] This product was identical with an authentic sample. [b] Isolated yields of glc pure materials.

In those cases where conjugate enone reduction is successful, we have also been able to use the intermediate enolate in a second, alkylation, step.[7,8] For example, when carvone is treated with 1 mol equiv of K-Selectride™ followed by 1.3 equiv of methyl iodide, a 98% yield of 1-methyl-1,6-dihydrocarvone (11) can be realized.[5] A similar



11

experiment using cyclohexenone and 1.5 equiv of allyl bromide leads to a mixture of 2-allylcyclohexanone (55%), cyclohexanone (15%), and some dialkylated ketone (30%) in high yield.[9] The nature of the intermediate species, whether a simple potassium enolate or a borate such as 12, remains uncertain. If shown to be the former, this method



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would afford a facile and convenient access to reactive potassium enolates in unhindered systems. Work is being continued in an effort to learn whether other unsaturated moieties, particularly esters and nitriles, can also experience 1,4 reduction, reductive alkylation, and perhaps even intramolecular reductive cyclization. A typical experimental procedure follows.

To a dry THF solution (5 ml) of carvone (0.366 g, 2.44 mmol) under nitrogen at −78° was added 1 equiv of K-Selectride™ (0.5 *M* solution, 4.9 ml). After the mixture was stirred for 1 hr at −78°, methyl iodide (1.3 equiv, .20 ml) was injected and the low temperature bath removed. The contents of the flask were brought to 0° for 10 min, by which time a white precipitate had appeared. Addition of 10% NaOH solution (7 ml) and 30% H_2O_2 (5 ml) sufficed to oxidize the trialkylborane by-product after stirring for 3 hr at room temperature. Excess peroxide was destroyed with sodium bisulfite and three hexane extractions afforded 0.400 g (98%) of 11 as a water-white liquid.[10]

References and Notes

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(3) E. J. Corey, K. B. Becker, and R. K. Varma, *J. Amer. Chem. Soc.*, **94**, 8616 (1972)
(4) Sodium borohydride in pyridine has also been observed to effect 1,4 reduction of enones followed by carbonyl reduction thus affording saturated alcohols: W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965)
(5) All products exhibited ir and nmr data completely in accord with the assigned structures.
(6) This sensitivity may account for the apparently exclusive formation of allylic alcohol from the β-cyclopentyl-α,β-unsaturated ketone reported in reference 3.
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(9) Enolate equilibration during alkylation of enol borates has been observed by Pasto. *Cf.* ref 8a.
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Received October 3, 1974

Methylation of Prototropic Ambident Nucleophiles. The Proton as a Formal Directing Group

Summary: The fact that six different prototropic ambident nucleophiles react with methylfluorosulfonate and aqueous base to give, in high yields, the product resulting from methylation at the heteroatom which does not bear the proton in the major tautomer is taken to suggest a general regiospecific synthesis of potential synthetic value.

Sir: The mobility of an active hydrogen generally precludes its actually functioning as a blocking or directing group in the traditional sense. Nonetheless, the efficient alkylative conversion of monosubstituted amides to imidates[1] provides one of a number of precedents[2] which suggest, that under some conditions, the proton of a prototropic ambident nucleophile can formally direct alkylation away from its bonding site in the major tautomer. We wish to draw attention to the synthetic value of this prospect with the report that it applied to the reactions of at least six such nucleophiles with methylfluorosulfonate. Comment is also made on the mechanistic considerations which underlie such specificity.

The formation of 2-methoxy-6-methyl-4-pyrone (2) from 4-hydroxy-6-methyl-2-pyrone (1) has been reported after separation of isomers produced by reaction of 1 with diazomethane[3] or by multiple steps involving the trimethylsilyl blocking group[4] in <20% yields. Treatment of 1 with methylfluorosulfonate[5] followed by removal of excess methylating agent under reduced pressure and treatment of the resulting solid with 10% aqueous sodium hydroxide gives 2 in 90% yield. Similar reactions of 3–7 give 8–12,[1a,f,2a,b] in quantitative yields. In each case these products are the formal result of methylation at the heteroatom which does not bear the proton in the major tautomer. This sequence appears to be superior to alternative methods of preparation of these compounds.[1-5]