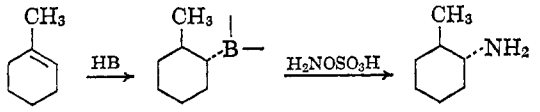
A Stereospecific Synthesis of Alicyclic and Bicyclic Amines *via* Hydroboration

Sir:

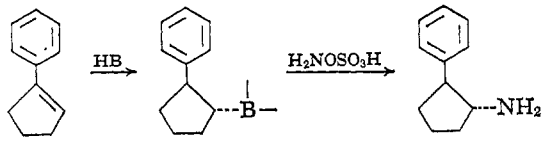
We previously reported that the comparatively reactive organoboranes from terminal olefins and relatively unhindered internal and alicyclic olefins could be converted into the corresponding amines by treatment with chloramine or hydroxylamine-O-sulfonic acid.[1] Unfortunately, the reaction was not satisfactory for organoboranes from relatively hindered olefins, such as 1-methylcyclohexene. Consequently, we were unable to take advantage of the highly stereospecific nature of the hydroboration of such derivatives to achieve a stereospecific synthesis of the corresponding amines.

We now wish to report that the reagent, hydroxylamine-O-sulfonic acid, is soluble in diglyme[2] and in this solvent converts the organoboranes from both unhindered and hindered olefins into the corresponding amines.

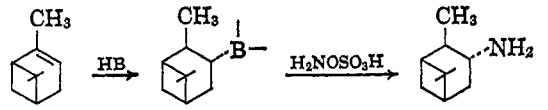
Thus, 1-methylcyclopentene, 1-methylcyclohexene, and 1-methylcycloheptene can be converted into the corresponding *trans*-2-methylcycloalkylamines.



Similarly, 1-phenylcyclopentene and 1-phenylcyclohexene are converted into the *trans*-2-phenylcycloalkylamines.



Finally, bicyclic olefins, such as norbornene and α-pinene, are successfully converted by this procedure into isomerically pure *exo*-norbornylamine and isopinocampheylamine.



The epimeric purity of the *trans*-2-methylcyclopentylamine and *trans*-2-methylcyclohexylamine was confirmed by glpc analysis on a 20 ft × 0.25 in. column of 2.5% silicone (Dow 200), 0.5% Armeen 18D on Chromosorb W, under conditions which achieved resolution of the two isomers. In the case of norbornylamine nmr examination revealed the absence of the *endo* isomer. Finally, the isomeric purity of the products is also indicated by the ready preparation of solid derivatives with sharp melting points.

Table I. Stereospecific Conversion of Alicyclic and Bicyclic Olefins into Amines by the Modified Hydroboration–Amination Reaction

Olefin	Amine	Yield, % Anal.	Yield, % Isol.	Properties Bp, °C (mm)	Properties n^{20}D	Derivative,[a] mp, °C Obsd	Derivative,[a] mp, °C Lit.
1-Methylcyclopentene	*trans*-2-Methylcyclopentylamine	56	45	121 (740)	1.4408	117.5–118	*trans* 116 *cis* 85.4
1-Methylcyclohexene	*trans*-2-Methylcyclohexylamine	58	45	148 (750)	1.4504	151.5–151.8	*trans* 151–153 *cis* 113.6–114.6
1-Methylcycloheptene	*trans*-2-Methylcycloheptylamine[e]	45	40	62 (8)	1.4687	165–166[e]	
1-Phenylcyclopentene	*trans*-2-Phenylcyclopentylamine	47	43	85 (1)	1.5548	162–162.5[e]	*cis* 154
1-Phenylcyclohexene	*trans*-2-Phenylcyclohexylamine	42	38	Mp 48–55		181–182	*trans* 181–182
Norbornene	*exo*-Norbornylamine	57	48	49 (10)	1.4838	143–144[b]	*exo* 144[b] *endo* 132[b]
(−)-α-Pinene	Isopinocampheylamine[c,e]	58	45	83 (10)	1.4878	129–130[e]	P[d] 144

[a] Benzamide, except where otherwise indicated. [b] Acetate. [c] α^{25}D +33.7° (neat). [d] Pinocampheylamine. [e] Analytical data within accepted limits were obtained for all new compounds.

The experimental results are summarized in Table I.

The following procedure for the conversion of 1-methylcyclohexene into *trans*-2-methylcyclohexylamine is representative. A dry 250-ml flask, equipped with a dropping funnel, condenser, and magnetic stirrer, was flushed with nitrogen. A solution of 0.78 g (20.6 mmoles) of borohydride in 25 ml of diglyme was introduced, followed by 4.8 g (50 mmoles) of 1-methylcyclohexene. The flask was immersed in an ice–water bath and hydroboration was achieved by the dropwise addition of 3.90 g (27.5 mmoles) of boron trifluoride etherate. The solution was then stirred at room temperature for 3 hr. Hydroxylamine-O-sulfonic acid,[3] 6.22 g (55 mmoles) in 25 ml of diglyme, was added and the solution heated to 100° for 3 hr. The solution was cooled, treated with 20 ml of concentrated hydrochloric acid, and then poured into 200 ml of water. The acidic aqueous phase was extracted with ether to remove diglyme and residual boronic acid. The solution was then made strongly alkaline with sodium hydroxide and the amine was extracted with ether. Titration of the ether extract indicated a 58% yield of amine. Distillation yielded 5.0 g, 45% of *trans*-2-methylcyclohexylamine.

Although the yields of amines realized are only in the range of 40–50%, this simple one-stage synthesis of a single epimeric derivative should provide a highly convenient synthetic route to such derivatives. We have also established that the hydroboration–amination reaction can tolerate the presence of many functional groups, thus making it possible to convert many un-

(1) H. C. Brown, W. R. Heydkemp, E. Breuer, and W. S. Murphy, *J. Am. Chem. Soc.*, **86**, 3565 (1964).

(2) The reagent is insoluble in tetrahydrofuran utilized in the earlier procedure.

(3) Hydroxylamine-O-sulfonic acid (Allied Chemical Co., Marcus Hook, Pa.) exhibited purities of 70–80%.[4] Reagent of better than 99% purity was obtained from this product by washing with several portions of dry tetrahydrofuran.

(4) H. J. Matsuguma and L. F. Audrieth, *Inorg. Syn.*, **5**, 122 (1957).

saturated natural products into the corresponding amines.

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Dialkylboranes as Consistent Reagents for Steric Control of Reduction in Both Monocyclic and Bicyclic Systems

Sir:

We wish to report that the dialkylboranes exhibit remarkable consistency in directing the reduction of both α-substituted cycloalkanones and bicyclic ketones from the less hindered direction to give predominantly the less stable of the two possible alcohols. Thus these reagents are highly promising both for achieving the preferred synthesis of a given isomer and for establishing the configurations of a pair of epimeric alcohols.

Since their introduction, the complex hydrides, such as lithium aluminum hydride and sodium borohydride, have been exceedingly valuable for the convenient conversion of ketones to alcohols. One aspect of this application, however, has resulted in frustrating ambiguities. The reduction of monocyclic ketones, such as 2-methylcyclopentanone and 2-methylcyclohexanone, appears to involve the attack of the reagent from the side of the methyl group, presumably the more hindered direction, to yield predominantly the more stable of the two possible alcohols (*trans*).[1,2] On the other hand, the reduction of bicyclic systems involves approach of the reagent from the less hindered side of the carbonyl group to yield the less stable of the two possible alcohols.[3]

These results have led to two different generalizations governing the course of such reductions.[1] In the case of relatively flexible monocyclic ketones the steric factor in the transition state will be relatively small and the course of the reduction will be controlled primarily by the stability of the product. On the other hand, in rigid bicyclic ketones, the steric factor will be far greater in the transition state and will exert a dominant role on the course taken by the reduction.[4]

Even in the case of the monocyclic ketones, reduction by lithium aluminum hydride is not consistent! Thus, 2-methylcycloheptanone[5] and the 2-methylcyclooctanone (Table I) yield the *cis* alcohol preferentially. There would be obvious advantages to a reagent which achieves the reduction of both monocyclic and bicyclic ketones with consistent stereochemistry.

Previously, we had observed that disiamylborane and diisopinocampheylborane reduced 2-methylcyclopentanone and 2-methylcyclohexanone to give the *cis* alcohol preferentially.[6] Extension of this study to representative monocyclic and bicyclic derivatives reveals that reduction to give predominantly the less stable of the two possible alcohols is of wide generality.[7]

The results are summarized in Table I.

The 1-methylcycloalkenes were subjected to hydroboration–oxidation to yield the pure *trans*-2-methylcycloalkanols.[8] A sample was retained for identification purposes and the remainder oxidized to ketone by the chromic acid–ether procedure.[9] The reduction procedures were similar to those previously described.[4,6] The products were analyzed by glpc using a temperature-programmed capillary instrument (Perkin-Elmer Model 226) to establish actual total yields (>85%), as well as the relative yields reported in Table I.

Table I. Reduction of Representative Ketones by Dialkylboranes at 0°

	Per cent alcohol involving reduction to form the less stable epimer				
Ketone	Lithium aluminum hydride in THF	Diborane in THF	Disiamylborane in THF	Dicyclohexylborane in diglyme	Diisopinocampheylborane in diglyme
2-Methylcyclobutanone[a]	25	41	74	71	83
2-Methylcyclopentanone[a]	21	25	78	80	94
2-Methylcyclohexanone[a]	25	26	79	94	94
2-Methylcycloheptanone[a]	73	74	64	97	98
2-Methylcyclooctanone[a]	73	82	*d*		
Norcamphor[b]	90	98	92	94	94
Camphor[c]	91	52	65[e]	93[e]	100[e]

[a] *cis*-2-Methylcycloalkanol. [b] *endo*-Norborneol. [c] Isoborneol. [d] Very slow reaction. [e] Slow reduction.

These results are quite promising. They suggest that the dialkylboranes should prove quite valuable in providing consistent steric control of reduction in both flexible monocyclic and in rigid bicyclic systems. We continue to explore the scope of this reduction.

(1) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, 78, 2579 (1956).
(2) For an alternative interpretation, see J. C. Richer, *J. Org. Chem.*, 30, 324 (1965).
(3) S. Beckmann and R. Mezger, *Ber.*, 89, 2738 (1956).
(4) H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, 87, 5620 (1965).
(5) W. Hückel and J. Wächter, *Ann.*, 672, 62 (1964).
(6) H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, 83, 3166 (1961).
(7) On the other hand, where the alkyl substituent is relatively remote from the reaction center, as in 3- and 4-methyl- and -*t*-butylcyclohexanones, the dialkylboranes exert only a minor influence on the direction taken by the reduction—in all cases the product is predominantly the more stable of the two possible epimers. Thus it is quite clear that the 2-methyl substituent in the 2-methylcycloalkanones must be exerting a dominant steric effect on the direction taken in the reductions involving the highly hindered dialkylboranes.
(8) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 83, 2544 (1961).
(9) H. C. Brown and C. P. Garg, *ibid.*, 83, 2952 (1961).
(10) Graduate research assistant on Grant DA-ARO(D)-31-124-117 supported by the Army Research Office (Durham).

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