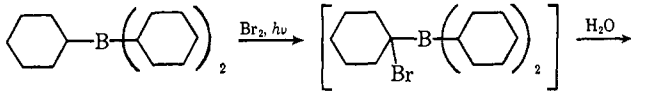
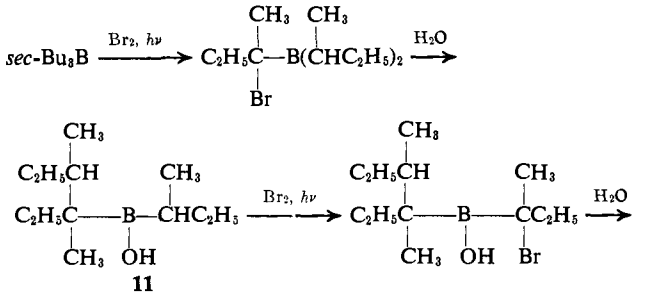
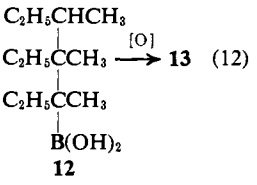
lowed by oxidation, gave an 89% yield of 1-cyclohexylcyclohexanol (**4**) (eq 11).



$$\mathbf{2} \xrightarrow{[O]} \mathbf{4} \qquad (11)$$

Similarly, tri-*sec*-butylborane is readily converted by an equimolar amount of bromine into 3,4-dimethyl-3-hexanol from oxidation of **11** in a yield of 86%. Use of 2 mol equiv of bromine produces 4-ethyl-





$$\xrightarrow{[O]} \mathbf{13} \qquad (12)$$

3,4,5-trimethyl-3-heptanol (**13**) (from oxidation of **12**) (eq 12). The results are summarized in Table I.

Table I. Dimerization and Trimerization of Olefins into Alcohols *via* Hydroboration–Bromination–Oxidation

Organoborane[a]	Bromine, mmol	Product	Yield[b] mmol	Yield[b] %
Triethylborane	10	3-Methyl-3-pentanol[d]	4.4	88[c]
Triethylborane	20	3-Methyl-3-pentanol[d]	8.5	85
Tri-*n*-butylborane	20	5-Propyl-5-nonanol[d]	7.6	76
Tri-*sec*-butylborane	10	3,4-Dimethyl-3-hexanol[d]	8.6	86
Tri-*sec*-butylborane	20	3,4-Dimethyl-3-hexanol[d]	4.4	44
		4-Ethyl-3,4,5-trimethyl-3-heptanol[e]	4.6	46
Tricyclohexylborane	10	1-Cyclohexylcyclohexanol[d]	8.9	89

[a] All reactions involve bromination of 10 mmol of R_3B in methylene chloride in the presence of a water phase. [b] By glpc analysis based on the maximum production of 1 mol of alcohol from 1 mol of R_3B, except where otherwise indicated. [c] Based on bromine used. [d] Structure assigned by comparison with an authentic sample. [e] Exhibited analytical data and spectra in accordance with assigned structure.

The lower yield realized in the case of **13** is evidently the result of a relatively sluggish migration of the bulky alkyl group in the last stage[6,7] (eq 12). Displacement of the α-bromo substituent by base appears to occur competitively. However, even yields of 50% must be considered quite satisfactory for the preparation of such highly branched structures.

Consequently, this new synthesis of carbon structures *via* α bromination of organoboranes appears to provide a convenient means of combining three molecules of a terminal olefin and either two or three molecules of an internal olefin to produce highly substituted tertiary alcohols.

(6) Removal of the water layer, followed by titration of the hydrogen bromide present, indicated that 90–94% of the calculated quantity of acid was present in all previous cases. Consequently, in these cases the alkyl transfers must have occurred prior to the treatment with sodium hydroxide and hydrogen peroxide. In the synthesis of **13**, only 28 mmol of acid was present in the aqueous phase. Only after sodium hydroxide was added did the last 10 mmol of acid appear. Consequently, in this case we believe that the transfer of the bulky alkyl group requires the base.[7]

(7) A similar reluctance to migrate has been observed for the bulky thexyl group in the carbonylation of organoboranes; see H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, **89**, 5285 (1967).

(8) Graduate research assistant on Grant No. GM 10937 from the National Institutes of Health.

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Site-Selective Geminal Alkylation of Ketones. Reduction–Alkylation of *n*-Butylthiomethylene Derivatives

Sir:

The α alkylation of ketones is often beset by undesired side reactions including aldol condensation, uncontrollable polyalkylation, and, with unsymmetrical ketones, isomer formation.[1] A number of synthetic methods—the use of blocking groups,[1c,2] enolate trapping followed by separation and regeneration,[1b,3] and reduction–alkylation[1c,4]—have been employed in order to avoid these difficulties. At present, however, there exists no general means for achieving selective geminal alkylation of an α,α,α'-trisubstituted acetone. We have found that the corresponding *n*-butylthiomethylene derivatives of such ketones[2] undergo a "double reduction" with lithium–ammonia solutions[5] affording a methyl-substituted enolate anion at the original methylene position which can be alkylated *in situ*.[6] This facile reduction–alkylation operation permits the direct introduction of one methyl group and a second, variable substituent at the ketone flank which condenses with ethyl formate. This communication presents a preliminary survey of the scope of this new alkylation reaction.[7]

(1) For discussion and examples, see (a) J.-M. Conia, *Rec. Chem. Progr.*, **24**, 43 (1963); (b) H. O. House, *ibid.*, **28**, 99 (1967); (c) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 184–204.

(2) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615, 1620 (1962).

(3) (a) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968); (b) H. O. House, L. J. Czaba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(4) (a) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); (b) M. Larcheveque, *Ann. Chim. (Paris)*, **5**, 129 (1970).

(5) For similar double reductions of (a) β-alkoxy α,β-unsaturated esters, see R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2597, 2601 (1970); (b) β-alkoxy α,β-unsaturated acids, see J. E. Shaw and K. K. Knutson, *ibid.*, in press; and (c) β-ethoxy-2-cyclohexenone, see D. S. Watt, J. M. McKenna, and T. A. Spencer, *ibid.*, **32**, 2674 (1967).

(6) Ireland and Marshall[2] reported that sodium–ethanol–ammonia reduction of the *n*-butylthiomethylene derivative of 9-methyl-*cis,trans*-Δ^6-octalone-1 afforded the 2-methyl octalol in 31–37% yield. This conversion can be interpreted as involving initial double conjugate reduction followed by ketone reduction. It should be noted, however, that alkyl vinyl sulfides themselves undergo reductive cleavage in sodium–ammonia: L. Brandsma, *Recl. Trav. Chim. Pays-Bas.*, **89**, 593 (1970).

(7) This transformation could also be achieved by conversion to the α-alkylidene ketone through aldol condensation, followed by reduction–alkylation. Although this tandem operation has not to our knowledge

Table I. Reduction–Alkylation of α-*n*-Butylthiomethylene Ketones[a]

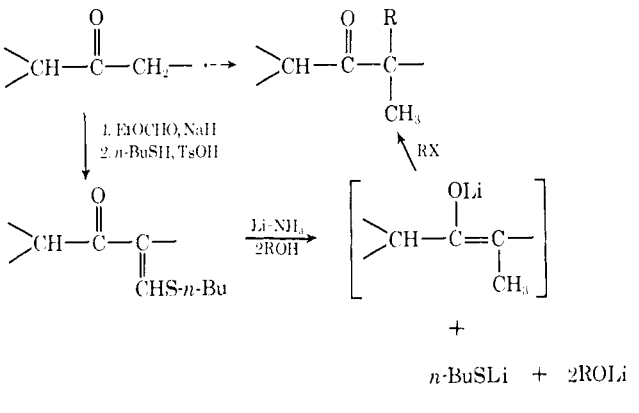
Entry	Substrate as *n*-butylthiomethylene derivative	Electrophile	Time: Addition	Time: Reaction	Yield,[b] %, reduction–alkylation	Other product(s)[b]
1	Cyclohexanone	CH_3CH_2I	30 min	30 min	75	2,6-Diethyl-2-methyl (10%)
2		$(CH_3)_2CHI$	30 min	50 hr[c]	15–20	2-Methyl (60%), 2-isopropyl-6-methyl (5–10%)
3		$CH_2{=}CHCH_2Br$	3 min	2 min	85	2,6-Dialkyl-2-methyl (5%)
4		$C_6H_5CH_2Br$	5 min	15 min	82	
5		CO_2	2.5 hr		56[e]	2-Methyl (25%)
6	2-Methylcyclohexanone	NH_4Cl			81	
7	1-Decalone	CH_3I	30 min	30 min	70[d]	
8	Cyclopentanone	$(CH_3)_2CHI$	30 min	45 hr[c]	40	2-Methyl (15%)
9		$CH_2{=}CHCH_2Br$	30 sec	30 sec	62	2,5-Dialkyl-2-methyl (15%)
10	3-Pentanone	$CH_2{=}CHCH_2Br$	30 sec	30 sec	82	

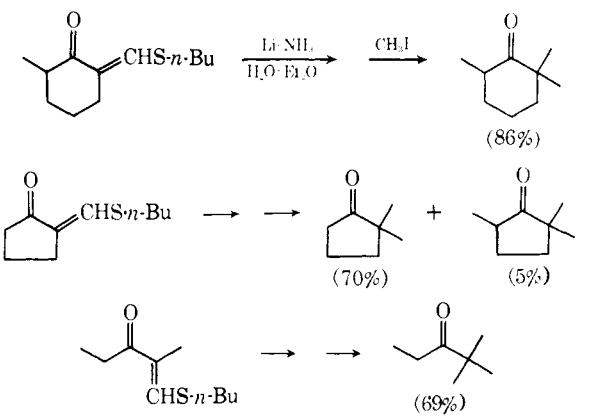
[a] Following example procedure in text with indicated changes. [b] Yield determined by glpc, except as noted. [c] At reflux in tetrahydrofuran. [d] After purification by column chromatography. [e] Isolated as methyl ester. No attempt has been made to optimize the reaction time.

Table II. Effect of Proton Donor and Alkylation Time on Reduction–Alkylation[a]

Entry	Substrate as *n*-butylthiomethylene derivative	Proton donor	Time: Addition	Time: Methylation	Yield,[b] %: α,α-Dimethyl	Yield,[b] %: α,α,α′-Trimethyl
11	Cyclohexanone	$(CH_3)_3COH$	30 min	30 min	73–75	15–17
12		Ph_3COH[c]	30 min	30 min	60–61	3–4
13		H_2O	30 min	30 min	83	2
14	Cyclopentanone	H_2O	5 min	10 min	51	22
15		H_2O	2 min	2 min	57	15
16		H_2O	30 sec	30 sec	70	5

[a] Following example procedure in text with indicated changes. [b] Yield determined by glpc, except as noted. [c] See L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith, *J. Org. Chem.*, **35**, 1881 (1970).





The procedure consists of adding the *n*-butylthiomethylene derivative[2] in ether containing 2 equiv of the proton donor to a solution of 6 equiv (50% excess) of lithium in liquid ammonia at −33°.[8] The alkylating agent is then introduced in large excess (12 equiv)[9] in order to consume the unreacted lithium and alkylate both the enolate and mercaptide anions. The alkyl *n*-butyl sulfide by-product is simply removed, if necessary, by stirring with aqueous mercuric chloride. Specific examples are illustrated in the reactions below and Tables I and II which follow.[10]

The most serious side reaction appears to be overalkylation, particularly with highly reactive ketones (*e.g.*, cyclopentanone) and alkylating agents (*e.g.*, allyl bromide). This complication can be minimized by the use of water as the proton donor[8] and brief reaction times for the alkylation step. In only one case (entry 2) have we detected any appreciable loss of site selectivity, indicating that enolate–ketone equilibration is slow compared to the rate of alkylation.[1] The alkylation proceeds efficiently with the primary reactants but poorly with the one secondary alkylating agent (isopropyl iodide) tested. The single examples of hydrolysis and carbonation afford the monomethyl and methylcarboxy product in good yield,[11] as expected.[12,13]

been reported, one example of reduction–alkylation of an alkylidene ketone (pulegone) has been mentioned.[4b]

(8) The procedure was based upon that used by H. A. Smith, B. J. L. Huff, W. J. Powers, and D. Caine, *J. Org. Chem.*, 32, 2851 (1967).

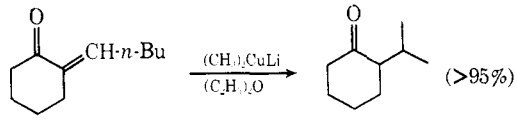
(9) No attempts have been made to determine the minimum quantity of alkylating agent required for good yields.

(10) All compounds gave nmr and ir spectra consistent with the structures. Satisfactory combustion analyses were obtained on all new compounds.

(11) No attempt has been made to optimize the reaction time in the carbonation example.

(12) T. A. Spencer, R. M. Villarica, D. L. Storm, T. D. Weaver, R. J. Friary, J. Posler, and P. R. Shafer, *J. Amer. Chem. Soc.*, **89**, 5497 (1967).

(13) Reduction–methylation of 2-methoxymethylenecyclopentanone with methanol as proton donor gave 2,2-dimethylcyclopentanone (42%) and 2,2,5-trimethylcyclopentanone (21%). The increase in overalkylation may be attributed to the greater basicity of lithium methoxide. Reduction–methylation of 2-*n*-butylthiomethylene-3-cholestanone gave



The mechanistic similarity between the reactions of α,β-unsaturated ketones with dissolving metals and dialkylcopper lithium reagents[14] suggested the possibility of effecting a double conjugate addition with the latter. Reaction of dimethylcopper lithium with 2-*n*-butylthiomethylenecyclohexanone in ether at 0° gave, after hydrolytic work-up, a virtually quantitative yield of 2-isopropylcyclohexanone. An attempt to alkylate the enolate intermediate was unsuccessful. This interesting reaction should prove useful for introducing symmetrically branched α substituents, a conversion which proceeds in poor yield by direct alkylation.

A typical procedure for the reduction–alkylation is as follows:[8] a solution of 2-*n*-butylthiomethylenecyclohexanone (1.57 g, 7.93 mmol) and 0.28 g (15.85 mmol) of water in 40 ml of ether is added to a refluxing solution of lithium (0.33 g, 47.6 mg-atoms) in 160 ml of liquid ammonia with stirring over a 30-min period. After an additional 30 min, 80 ml of ether and then a solution of 13.5 g (95.1 mmol) of methyl iodide in 40 ml of ether were added, the latter over a 30-min period. This mixture was allowed to stir for 30 min and the ammonia evaporated. After a standard extractive work-up and removal of the ether by distillation, a yellow liquid was obtained which consisted of methyl *n*-butyl sulfide, 2,2-dimethylcyclohexanone (83%), and 2,2,6-trimethylcyclohexanone (2%), according to glpc analysis using cyclohexanone as internal standard.

Acknowledgments. We are grateful for financial assistance from the National Institutes of Health and Eli Lilly and Company, through an unrestricted research grant.

2,2-dimethyl-3-cholestanone in poor yield, for reasons as yet unclear. Further experiments to improve these reactions are intended.

(14) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(15) University Fellow in Chemistry and Chemical Engineering, 1970–1971.

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The Dependence of Solvolytic α-Deuterium Rate Effects on the Nature of the Leaving Group[1]

Sir:

We wish to report experimental observations which confirm and extend earlier theoretical predictions[2] of how the characteristic *maximum* α-deuterium isotope effect on solvolysis rate varies as a function of leaving group. Earlier studies[3,4] on 1-phenylethyl bromide and chloride first indicated that the α-deuterium effect on solvolysis rates was dependent on the nature of the leaving group *even within the same reaction mechanism*. Calculations based on the methyl halides as models[2] indicated that this leaving group dependence was primarily caused by the dependence of *initial state* isotopic zero-point energy differences on the nature of the leaving group. The further conclusion was reached that the isotopic *transition-state* zero-point energy differences in the apparently limiting reactions studied were *not* (within the limits of accuracy involved) dependent on leaving group. The transition states could thus, to a good approximation, be represented as ion pairs R^+X^-, where the force constants of R^+ were independent of the nature of X^-. These calculations allowed the prediction that the maximum isotope effect for a limiting solvolysis of an iodide of ~1.09 would correspond to values of ~1.125 for the bromide and ~1.15 for the chloride if all reactions followed the same mechanism.

During a study of the mechanism of solvolysis of a series of propargyl derivatives it became apparent that 3-pentyne-2-toluenesulfonate, bromide, and iodide would solvolyze in aqueous trifluoroethanol at convenient rates by an apparently limiting mechanism. This series, therefore, provided a convenient way to test the earlier theoretical predictions and, of equal importance, a way to determine the maximum effect for a sulfonate leaving group, a value which could not be predicted accurately from theory.

The solvolysis rates and isotope effects are given in Table I. In the first two horizontal entries it appears from α-*d*, β-d_3, and δ-d_3 effects that the solvolysis of the toluenesulfonate in 60% ethanol may have a slight nucleophilic component. It seems reasonable to conclude, however, that the reaction in 70% trifluoroethanol is very predominantly, if not exclusively, limiting. The α-*d* effect (1.226) is one of the largest observed for the solvolysis of a sulfonate ester and is, within experimental error, the same as that observed for the trifluoroacetolysis of isopropyl-α-*d* toluenesulfonate (1.22 ± 0.02).[5,6] In the fourth entry of Table I it is seen that the bromide has, within very narrow limits, the same β-d_3 and δ-d_3 isotope effects in 70% trifluoroethanol as the toluenesulfonate. The α-*d* effect (1.123) is, however, considerably lower and, strikingly, almost the same as the α-*d* effect (1.122) in the apparently limiting solvolysis of α-phenylethyl bromide in 80% aqueous ethanol.[3] This reinforces the conclusion that the reactions of the three propargyl derivatives in 70% trifluoroethanol are near limiting.

The β-d_3 effect for the iodide in 70% trifluoroethanol (1.283) is very close to that for the bromide (1.280) and toluenesulfonate (1.281) in the same solvent indicating that all three derivatives follow the same mechanism. The α-*d* effect for the iodide in this solvent is 1.089. This compares favorably with the theoretical prediction

(1) (a) Taken in part from the Thesis of W. Dowd submitted to the Graduate School of Indiana University in partial fulfillment of the requirements for the Ph.D. degree, 1970. (b) Supported in part by a Petroleum Research Fund Fellowship for Graduate Education and Fundamental Research administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund. (c) Also supported in part by Grant No. AT(11-1)-1008 from the U.S. Atomic Energy Commission (Document No. COO-1008-13). (d) Electronic computations of rate constants were performed with the facilities of the Indiana University Research Computing Center.

(2) V. J. Shiner, Jr., M. W. Rapp, E. A. Halevi, and M. Wolfsberg, *J. Amer. Chem. Soc.*, **90**, 7171 (1968).

(3) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *ibid.*, 90, 418 (1968).

(4) V. J. Shiner, Jr., W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *ibid.*, 91, 4838 (1969).

(5) A. Streitwieser, Jr., and G. A. Dafforn, *Tetrahedron Lett.*, 1263 (1969).

(6) V. J. Shiner, Jr., and W. Dowd, *J. Amer. Chem. Soc.*, **91**, 6528 (1969).