The Reduction–Methylation of Cyclohexenone Derivatives

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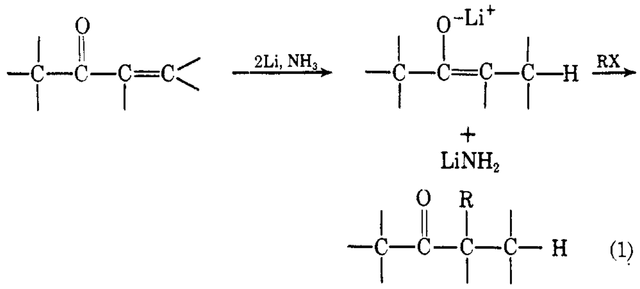
The lithium–liquid ammonia reduction and reduction–methylation of several α,β-unsaturated cyclohexenone derivatives having hydrogen or methyl substitution at the β position have been investigated. The β-unsubstituted enones gave more complete lithium enolate formation when 1 equiv of a proton donor, usually anhydrous *t*-butyl alcohol, was added along with the enone to lithium in liquid ammonia. For each compound subjected to reduction–methylation, the only monoalkylation product obtained was derived from alkylation of the specific lithium enolates produced in the reduction step.

The reduction–alkylation procedure developed by Stork and co-workers[2] often provides an excellent method for directing alkylation to relatively inaccessible α positions of unsymmetrical ketones and it has been applied successfully in a number of decalone,[2] hydrindanone,[2] and steroid systems.[3] In general terms, the procedure involves (1) generation of a specific lithium enolate of an unsymmetrical ketone by reduction of the corresponding α,β-unsaturated ketone with 2 equiv of lithium in liquid ammonia and (2) reaction of this enolate with an alkylating agent either in liquid ammonia or other solvent systems (eq 1). The success of the method depends upon the now well-established fact that alkylation of specific lithium enolates (as opposed to other alkali metal enolates) of unsymmetrical ketones with relatively reactive alkylating agents occurs faster in a variety of solvents than does equilibration among the structurally isomeric enolates *via* proton-transfer reactions.[2-5]



(1)

Our interest in directing alkylation to specific α positions of unsymmetrical ketones has led us to study the reduction–methylation of several cyclohexenone derivatives including 2-methylcyclohex-2-enone (**1a**), 6-methylcyclohex-2-enone (**2a**), 2,4,4-trimethylcyclohex-2-enone (**1b**), 4,4,6-trimethylcyclohex-2-enone (**2b**), and 3-methylcyclohex-2-enone (**3**).

In order to determine the optimum conditions for carrying out the first step in the reduction–alkylation procedure, that is, the generation of the lithium enolate, the simple lithium–liquid ammonia reduction of some of these enones as well as of carvone (**4**) was investigated. The results of these studies are recorded in Table I. Compounds **1a**, **1b**, **2b**, and **4** are cyclohexenone derivatives which are unsubstituted at the β position. When the reduction of these compounds was carried out in the usual way by dropwise addition of the enone in anhydrous ether to a solution of 2 equiv of lithium in anhydrous liquid ammonia followed by addition of excess ammonium chloride and work-up, vpc analysis showed that the volatile products consisted of the α,β-dihydro derivative contaminated with a considerable quantity of unchanged starting material (Scheme I). (Similar results were obtained in cases in which the reverse procedure of addition of lithium metal to a solution of the enone in liquid ammonia was employed.) However, in each case in which the reduction was conducted in exactly the same manner as above, except that an equivalent amount of a proton donor (usually anhydrous *t*-butyl alcohol) was added along with the enone to the solution of lithium in liquid ammonia,[6] the α,β-dihydro derivative was the only volatile material obtained after addition of ammonium chloride and work-up. Thus in these cases the addition of *t*-butyl alcohol along with the enone led to improved yields of reduced ketones and made it possible to obtain a pure product by simple distillation of the reaction mixture. As indicated in Table I, the enone **3** having a methyl substituent at the β position was reduced smoothly to 3-methylcylcohexanone (**12**) regardless of

TABLE I

LITHIUM–LIQUID AMMONIA REDUCTION OF CYCLOHEXENONE DERIVATIVES

Enone	Proton donor (1 equiv) added	Yield of recovered ketones, %: Starting enone	Yield of recovered ketones, %: Reduction product
1a	*t*-BuOH	0	50[a]
1a	None	15[b]	47[b]
1b	*t*-BuOH	0	46[a]
1b[c]	None	47[d]	53[d]
2b	*t*-BuOH	0	80[b]
3	*t*-BuOH	0	62[a]
3	None	0	66[b]
4	*t*-BuOH	0	61[b]; 50[a]
4	None	15[b]	50[b]

[a] Yield determined on the basis of the quantity of distilled product recovered. [b] Yield determined by vpc analysis using *m*-xylene as internal standard. [c] Run performed by adding the enone to liquid ammonia and then adding 2 equiv of lithium. [d] These values represent the ratio of the ketones in the recovered mixture by vpc analysis. The actual yield was not determined in this run.

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(1) (a) National Science Foundation Faculty Research Participant, summer 1965; (b) NASA Trainee; (c) to whom enquiries should be addressed.

(2) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).

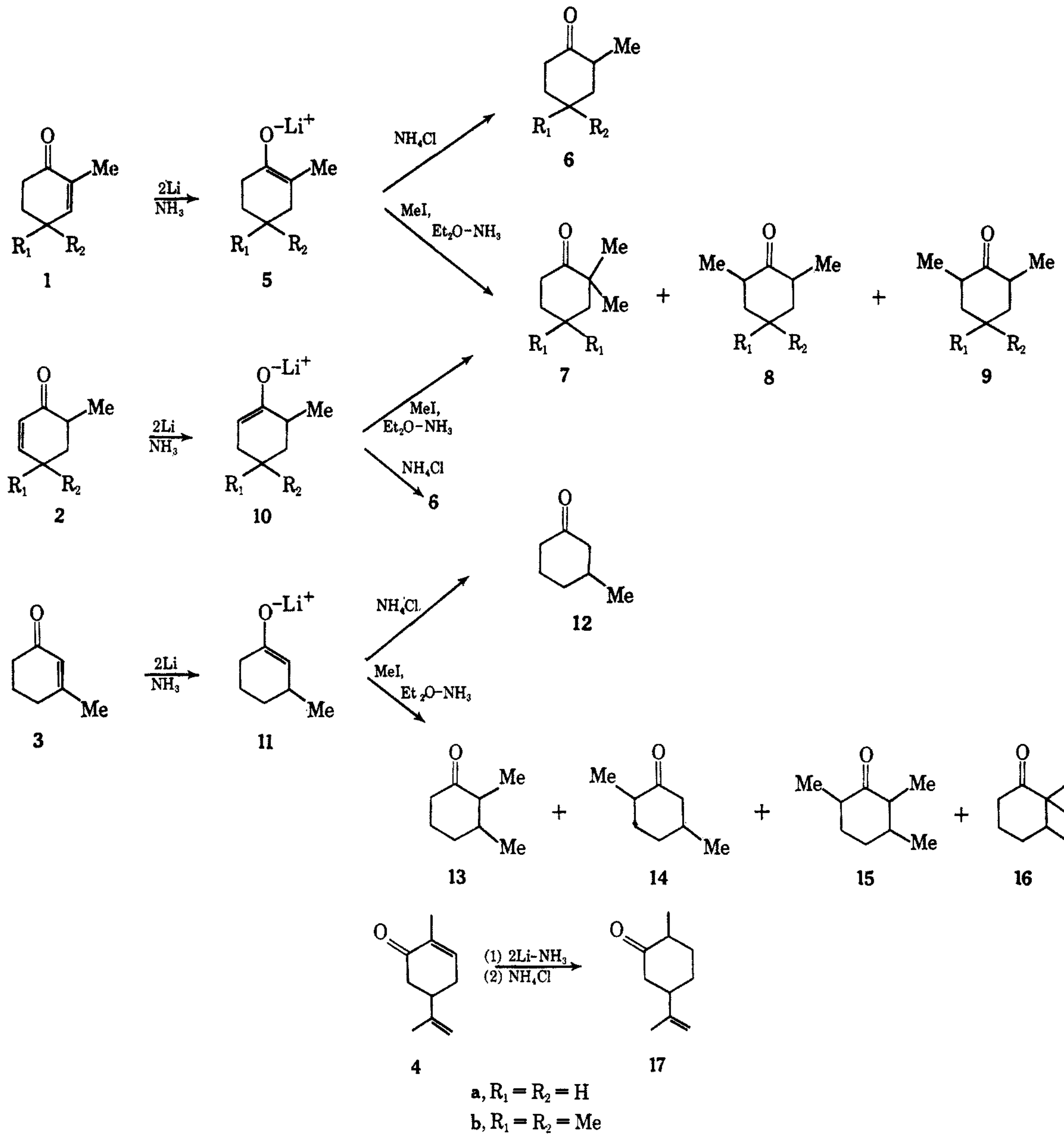
(3) (a) R. E. Schaub and M. J. Weiss, *Chem. Ind.* (London), 2003 (1961); (b) R. Deghenghi and R. Gaudry, *Tetrahedron Letters*, No. 11, 489 (1962); (c) M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr., and C. J. Coscia, *Chem. Ind.* (London), 118 (1963); (d) R. Dehgenghi, C. Revesz, and R. Gaudry, *J. Med. Chem.*, **6**, 301 (1963); (e) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(4) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

(5) (a) D. Caine, *ibid.*, **29**, 1868 (1964); (b) D. Caine and B. J. L. Huff, *Tetrahedron Letters*, 4695 (1966).

(6) These reaction conditions are essentially the same as those described by Stork and co-workers[2] for the reduction of $\Delta^{1,9}$-2-octalone to *trans*-2-decalone.

SCHEME I



the presence of the equivalent of alcohol in the reduction scheme.[7–9]

The role of the proton donor in bringing about more complete reduction of the β-unsubstituted enones has not been definitely established. One possibility is that in these cases it serves to prevent competing side reactions of the enone with lithium amide, formed as the reduction proceeds, which lead to its deactivation toward reduction. Conjugate enolate formation, or 1,2[10] or 1,4 addition, are possible reactions of the enone with lithium amide which would convert it into a species which resists reduction but from which it could be regenerated on work-up of the reaction mixture. The proton donor might prevent such reactions either by increasing the rate of reduction[11] or simply reacting with lithium amide as it is formed, or both. Conjugate enolate formation has been proposed in order to explain results in reduction–alkylations of the 3-ethylene ketal of 16-dehydroprogesterone.[3e] However, no unsaturated alkylation products were observed when reduction–methylations of **1a** and **1b** were performed in the absence of a proton donor (see Experimental Section). This suggests that conjugate enolate formation is not an important side reaction in the reduction of these compounds and that it is not likely to be very important for the other cyclohexenones studied. Thus we suggest that amide addition reactions are likely to be re-

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(7) The literature contains a number of other examples (*cf.* J. M. Conia and F. Rouessac, *Bull. Soc. Chim France*, 1925 (1963)) of lithium–liquid ammonia reductions of β-substituted cyclohexenones where recovery of unchanged starting material is not an apparent complication.

(8) The addition of alcohols has been employed in a number of instances in order to improve yields in metal–ammonia reductions of α,β-unsaturated ketones.[9] In cases where excess alcohol is used, the enone is reduced to the corresponding saturated alcohol and an oxidation step is required in order to obtain the corresponding saturated ketone. However, when 1 equiv of alcohol was employed under the reduction conditions described above, no more than trace quantities of alcohols were obtained from any of the enones studied.

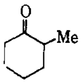
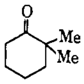
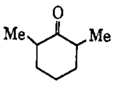
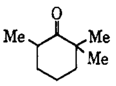
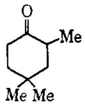
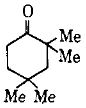
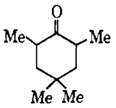
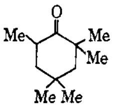
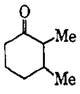
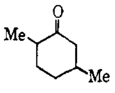
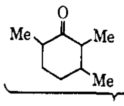
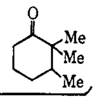
(9) (a) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964); (b) M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

(10) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3317 (1966).

(11) Because of the presence of the methyl substituent at the β position, the radical anion or dianion (it is not certain which of these species is actually protonated[9a]) derived from addition of one or two electrons to **3** should be more basic than similar species derived from **1**, **2**, or **4**. Thus, if β protonation is the rate-determining step in metal–ammonia enone reductions, **3** would be expected to undergo reduction faster than the β-unsubstituted enones. Perhaps it is for this reason that the proton donor is not required to prevent the recovery of unreacted starting material in reductions of **3**.

Table II

Reduction–Methylation of Cyclohexenone Derivatives

Enone	Proton donor (1 equiv) added	Composition of recovered mixture of ketones, %				Yield, %
						
1a	*t*-BuOH	2	80	0	18[a]	49[b]
1a	H_2O	2	96	0	2	63[c]
2a	*t*-BuOH	12	0	86	2	43[b]
						
1b	*t*-BuOH	7	93	0	0	46[b]
2b	*t*-BuOH	5	0	95	0	60[c]
						
3	*t*-BuOH	87	0	13[d]		54[b]

[a] Mixtures having identical compositions were obtained in duplicate reduction runs on **1a**. [b] The yield is based on the quantity of material distilled considering it to be only the monoalkylation product. [c] The yield of monoalkylation product calculated by vpc analysis using *m*-xylene as internal standard. [d] The structure of this component of the alkylation mixture was not definitely established, but it was assumed to be **15** or **16** or a mixture of the two.

sponsible for the recovery of unreacted enone in the reductions of **1**, **2**, and **4** when no proton donor is added.

Thus results of reduction–methylation of the enones **1**–**3** are shown in Table II.[12] The enones were converted to the corresponding lithium enolates under the same conditions as described in the reduction reactions using *t*-butyl alcohol. Then, the reaction mixture was diluted with an approximately equal volume of ether and an approximately fivefold excess of methyl iodide was added dropwise over *ca.* 30 min. Examination of the data in Tables I and II shows that the yields in the reduction–methylation runs were generally quite close to those obtained in the corresponding reduction reactions.[13] This suggests that the alkylation step in the sequence takes place in high yield. Only trace amounts (usually less than 10% of the recovered mixture of ketones) of simple reduction products were obtained in the reduction–methylation runs. These products could arise by reaction of the lithium enolates with the added proton donor, traces of protonic impurities in the solvents, or with methyl–ammonium iodide produced by reaction of the liquid ammonia with methyl iodide.

In each case the reduction–methylation procedure yielded only the monoalkylation product derived from alkylation of the specific lithium enolate produced in the reduction reaction. As mentioned earlier, the slow rate of equilibration of lithium enolates often allows trapping of these species and apparently no interconversion among the more (**5**) and less (**10**) substituted enolates derived from **6** or the $\Delta^{1,2}$- (**11**) or $\Delta^{1,6}$-enolates derived from **12** occurs under the conditions of the alkylation step. The procedure thus provides a convenient means of synthesizing selectively alkylated cyclohexanone derivatives in cases where the necessary starting enones are available.[14,15] It provides distinct advantages over direct base catalyzed alkylations of unsymmetrical cyclohexanones since such methods generally lead to mixtures of difficultly separable monoalkylation products as well as extensive di- and polyalkylation.[5a,16,17] The direct conversion of **3** into 2,3-dimethylcyclohexanone (**13**) offers an interesting example of the utility of the reduction–alkylation procedure. 2-Alkyl-5-methylcyclohexanones are the only monoalkylation products obtained either by direct base catalyzed alkylation of **12**[18] or by indirect methods such as the alkylation of the magnesium salt derived from the cyclohexylimine of **12**.[19]

Polyalkylation, as a result of base-catalyzed (either by lithium amide or lithium *t*-butoxide) conversion of monoalkylated materials into their enolate anions and subsequent alkylation, occurred to a signifi-

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[12] Several years ago (J. Schreiber, Ph.D. Dissertation, Zurich, 1953), it was found that 2-methyl-2-alkylcyclohexanones were produced on treatment of **1a** with lithium in liquid ammonia followed by addition of 1,3-dichloro-2-butene or methyl vinyl ketone. However, Stork and co-workers have pointed out (see ref 2, footnote 14) that this study alone did not allow the distinction to be made between direct enolate trapping and simple reduction followed by base-catalyzed alkylation at C-2 of **6a**. In view of the results obtained in the present study, it seems likely that enolate trapping was actually involved in the earlier work.

[13] Although the added proton donor likely reduces side reactions of lithium amide with the enone, other reactions such as aldol condensation and bimolecular reduction (J. Fried and N. A. Abraham, *Tetrahedron Letters*, No. 28, 1879 (1964)) can still compete with enolate formation. The bimolecular reduction product, 1,1′,3,3,3′,3′-hexamethyldicyclohexyl-5,5′-dione (J. W. Baker, *J. Chem. Soc.*, 663 (1926)) was isolated in low yields in a reduction run on isophorone. High-boiling products with spectroscopic properties consistent with similar dimeric structures were also obtained on reduction of some of the other enones listed in Table I.

[14] In many cases, suitably constituted cyclohexenones (particularly 2-alkylcyclohex-2-enones (*cf.* G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963); J. Pugach, Ph.D. Dissertation, Columbia University, 1964)) are more readily available than α-halomercuric,[5a] α-halo, and α-acetoxy ketones[3e] which also give specific lithium enolates on reduction with lithium in liquid ammonia.

[15] An interesting method of selective alkylation of unsymmetrical ketones involving generation of specific lithium enolates by treatment of enol acetates with 2 equiv of methyllithium in 1,2-dimethoxyethane has been developed recently.[4]

[16] H. O. House and V. Kramar, *J. Org. Chem.*, **26**, 3362 (1963).

[17] It is possible to obtain mainly **8a** or **7a** by methylation of lithium enolate mixtures prepared by treating **6a** with tritryllithium in 1,2-dimethoxyethane under conditions of kinetic or thermodynamic control, respectively. However, this method does not allow the production of either of the dimethylcyclohexanones completely free of the structural isomer.[5b]

[18] R. Cornubert and R. Humeau, *Bull. Soc. Chim. France*, **49**, 1238 (1931).

[19] G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

cant extent in the reduction–methylation of enone **1a** and probably also in the case of **3**. As shown in Table II, in reduction–methylations of **1a** it was found that the formation of the trimethyl ketone **9a** could almost be eliminated if an equivalent amount of water was substituted for *t*-butyl alcohol as the proton donor in the reaction. Substitution of water for *t*-butyl alcohol in the reduction would lead to the formation of lithium hydroxide and this relatively weak base would be expected to be less effective than lithium *t*-butoxide in promoting polyalkylation by converting **7a** to its lithium enolate.

It is particularly interesting that a significant quantity of **9a** was produced in the runs involving **1a** but not in those involving **2a** conducted under identical conditions. This suggests that the over-all process of lithium enolate formation and methylation is faster for **7a** than for **8a** under the reaction conditions. The results of other studies show that with potassium or sodium enolates of mixtures of **7a** and **8a** the symmetrical ketone **8a** undergoes polyalkylation faster than **7a** in ether and alcohol solvents.[16,20] Equilibration of potassium and sodium enolates is very rapid relative to subsequent reactions;[5a] thus a greater stability of the enolate anion derived from **8a** could account for this. Further work which hopefully will shed light on the differences in behavior of the potassium and sodium and the lithium enolates in these cases is in progress.

Experimental Section[21]

2-Methylcyclohex-2-enone (**1a**), bp 85–87° (35 mm) (lit.[22] 83–85.5 (35 mm)), was prepared in 41% yield by the procedure of Warnhoff, Martin, and Johnson.[22]

6-Methylcyclohex-2-enone (**2a**), bp 70–72° (25 mm) (lit.[23] 74–75° (24 mm)), was prepared in 29% yield by the procedure of Stork and White.[23]

3-Methylcyclohex-2-enone (**3**) was purchased from Aldrich Chemical Co.

Carvone (**4**) was purchased from the Matheson Coleman and Bell Chemical Co.

2,4,4-Trimethylcyclohex-2-enone (**1b**) was prepared according to the general procedure of Stork, *et al.*,[24] for the synthesis of substituted cyclohexenones. To 45 g (0.36 mole) of ice-cold pyrrolidine enamine of isobutyraldehyde[25] under nitrogen was added with stirring 30 g (0.36 mole) of ethyl vinyl ketone during 45 min. When the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 24 hr. It was then treated with 300 ml of 15% hydrochloric acid, stirred at room temperature for 44 hr, and warmed on a steam bath for 45 min. The organic layer was separated and the aqueous layer was saturated with sodium chloride and extracted with four 75-ml portions of ether. The ether extracts and the organic layer were combined and dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure and distillation of the residue gave 31 g (63%) of 2,4,4-trimethylcyclohex-2-enone (**1b**), bp 83–85°(18 mm) (lit.[26] bp 81–82° (20 mm)), and 2,4-dinitrophenylhydrazone, mp 168–169° (lit.[26] 164–165).

4,4,6-Trimethylcyclohex-2-enone (**2b**).—Using 119 g (0.95 mole) of pyrolidine enamine of isobutyraldehyde and 66.9 g (0.94 mole) of methyl vinyl ketone in a procedure similar to that described for the synthesis of **1b**, 87 g (75%) of 4,4-dimethylcyclohex-2-enone, bp 81–84° (21 mm) (lit.[27] bp 54–56° (4 mm)), was obtained. Alkylation[28] of the 6-hydroxymethylene derivative[29] of this ketone was employed for the synthesis of **2b**. To a stirred mixture of 12.3 g (0.23 mole) of sodium methoxide and 400 ml of anhydrous ether in a 1-l. three-necked flask purged with nitrogen and cooled in an ice bath a solution of 18.3 g (0.25 mole) of ethyl formate (refluxed for 1 hr over phosphorus pentoxide and freshly distilled) and 28.1 g (0.23 mole) of 4,4-dimethylcyclohex-2-enone was added dropwise with stirring over 1 hr. The ice bath was removed and the reaction mixture was stirred overnight at the ambient temperature. After the addition of 200 ml of anhydrous ether, the slurry was filtered using a Büchner funnel and the filter cake was washed with several portions of dry ether. The solid sodioformyl ketone was dissolved in 500 ml of water and the ethereal filtrate was extracted with three 150–ml portions of 3% aqueous sodium hydroxide. The caustic extracts and the aqueous solution were then combined, washed with two 100-ml portions of ether, and acidified with 15% hydrochloric acid. Crude 6-hydroxymethylene-4,4-dimethylcyclohex-2-enone was obtained after extraction of the acidic mixture with three 250-ml portions of ether, drying of the ether solution over anhydrous magnesium sulfate, and removal of the solvent under reduced pressure.

The crude product, 19.0 g, was then added to a mixture of 500 ml of anhydrous acetone, 17.3 g (0.13 mole) of potassium carbonate, and 42.6 g (0.30 mole) of methyl iodide, and the reaction mixture was refluxed with stirring for 24 hr (an additional 20-ml portion of methyl iodide was added to the reaction mixture at 2-, 6-, and 19-hr intervals). The reaction mixture was then cooled to room temperature and anhydrous ether was added until no precipitation occurred on further addition. The solid was removed by filtration and the volume of the filtrate reduced to *ca*. 100 ml under reduced pressure. After the addition of 600 ml of ether, the solution was extracted with two 150-ml portions of ice-cold 10% sodium hydroxide and washed with 2% hydrochloric acid, aqueous sodium bicarbonate, aqueous sodium chloride, and dried over magnesium sulfate. After removal of the solvent under reduced pressure, distillation of the residue yielded 5.8 g (34%) of **2b**:[30] bp 55–57° (2.0 mm); $\lambda_{\max}^{\mathrm{CCl_4}}$ 5.97 and 6.21 μ; $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 0.96 (d, 6.0 cps, 3 H, C-6 Me), 1.05 (s, 3 H, C-4 Me), 1.11 (s, 3 H, C-4 Me), 1.21–2.50 (br absorption, 3 H), 5.21 (d, 1 H), and 5.99 ppm (d, 1 H) (J_{AB} = 9.5 cps, -CH═CH).[31]

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.00; H, 9.99.

Further distillation yielded 9.5 g (46%) of a material boiling at 94–100° (2 mm) which was not completely identified but showed infrared and nmr spectral properties consistent with those expected for the O-alkylation product, 6-methoxymethylene-4,4-dimethylcyclohex-2-enone.

General Procedure for Lithium–Liquid Ammonia Reduction of Cyclohexenones.—The reduction of the various α,β-unsaturated ketones was carried out in the following manner. A three-necked flask fitted with a mechanical stirrer, dropping funnel, and Dry Ice condenser was flame dried under a positive nitrogen flow and the system was maintained under nitrogen throughout the remainder of the experiment. Anhydrous liquid ammonia (100–200 ml/0.1 g of lithium used) was introduced into the reaction vessel by distillation from sodium. The liquid ammonia was

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[20] H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).

[21] Melting points were determined on a Fisher-Johns apparatus and are uncorrected and boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 137 infrared spectrophotometer. Nmr spectra were determined at 60 Mc with a Varian A-60 spectrometer. Vapor phase chromatography was performed using an Aerograph A-90-P3 with helium as the carrier gas. Ether solvents were dried by reflux over lithium aluminum hydride and distillation prior to use. *t*-Butyl alcohol was dried by reflux over sodium and distillation prior to use. Methyl iodide was dried over magnesium sulfate and distilled prior to use. Microanalyses were prepared by Galbraith Laboratories Inc., Knoxville, Tenn.

[22] E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 162.

[23] G. Stork and W. N. White, *J. Am. Chem. Soc.*, **78**, 4604 (1956).

[24] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

[25] G. Opitz, H. Hellman, H. Mildenberger, and H. Suhr, *Ann.*, **649**, 36 (1961).

[26] M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1725 (1954).

[27] F. G. Bordwell and K. M. Wellman, *ibid.*, **28**, 1347 (1963).

[28] W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).

[29] The general procedure of Mariella (R. P. Mariella, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 210) was used for the synthesis of sodio-6-formyl-4,4-dimethylcyclohex-2-enone.

[30] Deformylation of the intermediate 6-formyl-4,4,6-trimethylcyclohex-2-enone is apparently a quite facile process since it occurred under the relatively mild conditions of the work-up step.

[31] We assign the low-field doublet of the AB quartet to the C-3 proton of **2b**. The peaks of this doublet showed splitting (*ca.* 1.5 cps). Long-range coupling of the C-3 proton with the C-5 proton in an "M" arrangement with it presumably accounts for this (*cf.* J. Wiemann, S. Risse, and P.-F. Casals, *Bull. Soc. Chim. France*, 381 (1966)).

deemed dry if, after addition of *ca.* 0.001 g of lithium wire, the blue color persisted for 5 min. Sufficient freshly cut lithium wire was added to bring the total quantity of lithium to 2.2 g-atoms/mole of ketone employed and the solution was stirred for 15 min. While stirring was continued, a solution of equimolar quantities of the enone and *t*-butyl alcohol (in the runs conducted in the absence of a proton donor, the *t*-butyl alcohol was omitted) in ether was added dropwise over 30 min. (Generally the reaction mixture remained blue throughout the addition period.) The reaction mixture was stirred for 30 min and excess of ammonium chloride was added in small portions with continued stirring. After 30 min, the Dry Ice condenser was replaced by a water condenser and the ammonia was allowed to evaporate. Ether and water were added and the ether layer was separated. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined ethereal solutions were washed with 5% hydrochloric acid, saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure and the residue was either distilled and analyzed by vpc or analyzed directly by vpc using an internal standard.

Reductions of 2-Methylcyclohex-2-enone (1a).—Using 0.50 g (0.072 g-atom) of lithium in 500 ml of liquid ammonia, 3.63 g (0.033 mole) of **1a** and 2.44 g (0.033 mole) of *t*-butyl alcohol in 50 ml of ether, and 5.25 g (0.099 mole) of ammonium chloride, 1.82 g (50%) of material, bp 78–81° (30 mm), was obtained. The product was shown to be pure by vpc analysis[32] and it showed vpc behavior and spectral properties identical with those of authentic 2-methylcyclohexanone (**6a**). In a run using 0.175 g (0.025 g-atom) of lithium in 200 ml of liquid ammonia, 1.10 g (0.020 mole) of **1a** in 50 ml of ether, and 1.65 g (0.030 mole) of ammonium chloride, the recovered mixture of ketones showed calculated yields[32,33] of 47% **6a** and 15% **1a**.

Reductions of 2,4,4-Trimethylcyclohex-2-enone (1b).—Using 0.178 g (0.026 g-atom) of lithium in 200 ml of liquid ammonia, 1.77 g (0.013 mole) of **1b** and 0.954 g (0.013 mole) of *t*-butyl alcohol in *ca.* 50 ml of ether (the blue color of lithium in liquid ammonia disappeared after *ca.* 80% of solution had been added and the addition was stopped), and 5.0 g of ammonium chloride, 0.80 g (46%) of 2,4,4-trimethylcyclohexanone (**6b**), bp 83–87° (23 mm) (lit.[26] bp 87–89° (30 mm)), 2,4-dinitrophenylhydrazone mp 149–150° (lit.[34] mp 150–151°), was obtained. The sample was shown to be pure by vpc analysis.[32]

In another run **1b**, 1.88 g (0.014 mole), was dissolved in *ca.* 200 ml of liquid ammonia, and freshly cut lithium wire, 0.208 g (0.030 g-atom), was added to the solution in small pieces with stirring. After 30 min excess ammonium chloride was added and the reaction mixture was worked up in the usual manner. On analysis by vpc,[32] the recovered mixture was shown to contain the reduced ketone **6b** and the starting enone **1b** in a 53:47 ratio. The product yields were not determined in this run.

Reduction of 4,4,6-Trimethylcyclohex-2-enone (2b).—Using 0.137 g (0.020 g-atom) of lithium in 250 ml of liquid ammonia, 1.08 g (0.008 mole) of **2b** and 0.579 g (0.008 mole) of *t*-butyl alcohol in 50 ml ether, and 1.66 g (0.031 mole) of ammonium chloride, 2,4,4-trimethylcyclohexanone (**6b**) was obtained. The calculated yield by vpc analysis[32,33] was 80%.

Reductions of 3-Methylcyclohex-2-enone (3).—Using 0.320 g (0.046 g-atom) of lithium in 500 ml of liquid ammonia, 2.00 g (0.018 mole) of **3** and 1.36 g (0.018 mole) of *t*-butyl alcohol in 50 ml ether, and 4.00 g (0.028 mole) of ammonium chloride, 1.24 g (62%) of material, bp 85–95° (40 mm), was obtained. This product was shown to be pure by vpc analysis[35] and it showed vpc behavior and spectral properties identical with those of an authentic sample of 3-methylcyclohexanone (**12**).

Using 0.0470 g (0.0068 mole) of lithium in 100 ml of liquid ammonia, 0.297 g (0.0027 mole) of **3** in 50 ml of ether, and 0.570 g (0.0108 mole) of ammonium chloride, a product showing only one component by vpc analysis[35] and having a retention time identical with that of **12** was obtained. The calculated yield by vpc analysis[33,35] was 66%.

Reductions of Carvone (4).—Using 0.50 g (0.072 g-atom) of lithium in 500 ml of liquid ammonia, 5.00 g (0.033 mole) of **4** and 2.44 g (0.033 mole) of *t*-butyl alcohol, and 5.25 g (0.099 mole) of ammonium chloride, 2.54 g (50%) of dihydrocarvone (**17**), bp 107–108 (23 mm), was obtained. The product was shown to be pure by vpc analysis,[32,33] and it showed vpc behavior and spectral properties identical with those of authentic dihydrocarvone. Vpc analysis[32] of the crude reaction mixture before distillation showed that no unreacted **4** was present. The calculated yield[32,33] of **17** was 61%. In a run conducted in a manner identical with that described above but in which the *t*-butyl alcohol was omitted, vpc analysis[32] showed that a mixture of **17** and **4** was recovered. The calculated yields by vpc analysis[32,33] were 50% **17** and 15% **4**.

General Procedure for the Reduction–Methylation of Cyclohexenone Derivatives.—The enones listed in Table II were converted into the corresponding lithium enolates by a procedure identical with that described for the reduction runs. A solution of lithium in liquid ammonia was prepared by addition of freshly cut lithium wire (2.2 g-atoms/mole of enone used) to anhydrous liquid ammonia and stirred for 15 min. The enone, dissolved in anhydrous ether, was then added dropwise with stirring over 30 min to this solution. (Unless otherwise specified, 1 equiv of anhydrous *t*-butyl alcohol was dissolved in the ether solution of the enone. In one run in which water was used as the proton donor, 1,2-dimethoxyethane was employed as the solvent at this stage.) The reaction mixture was stirred for 30 min and diluted with an equal volume of anhydrous ether. For the alkylation step, an excess of methyl iodide dissolved in ether was added dropwise over 30–40 min. After the mixture had been stirred for an additional 30-min period, the liquid ammonia was allowed to evaporate and the reaction mixture was worked up in a manner similar to that described for the reduction runs.

Reduction–Methylation of 2-Methylcyclohex-2-enone (1a). *t*-Butyl Alcohol as Proton Donor.—Employing 0.958 g (0.138 g-atom) of lithium in 500 ml of liquid ammonia, 6.60 g (0.060 mole) of **1a** and 4.44 g (0.060 mole) of *t*-butyl alcohol in 50 ml ether, and 400 ml of ether followed by 42.6 g (0.300 mole) of methyl iodide in 50 ml of ether, 3.70 g (49%) of a mixture of ketones, bp 80–85° (35 mm), was obtained. Analysis of this mixture by a combination of vpc[33] and nmr spectroscopy as described previously[5a] showed that it contained 80% 2,2-dimethylcyclohexanone (**7a**), 18% 2,2,6-trimethylcyclohexanone (**9a**), and 2% 2-methylcyclohexanone (**6a**). No 2,6-dimethylcyclohexanone (**8a**) was detected. A mixture of ketones of identical composition was obtained from a duplicate run on **1a**.

Water as Proton Donor.—Employing 0.525 g (0.075 g-atom) of lithium in 500 ml of liquid ammonia, 3.30 g (0.030 mole) of **1a** and 0.540 g (0.030 mole) of water in 50 ml of 1,2-dimethoxyethane, and 400 ml of ether followed by 26.5 g (0.180 mole) of methyl iodide in 50 ml of ether, a mixture of ketones containing 96% **7a**, 2% **9a**, and 2% **6a** was obtained. The calculated yield [32,33] of **7a** was 63% in this run.

No Proton Donor Added.—Employing 0.525 g (0.075 g-atom) of lithium in 500 ml of liquid ammonia, 3.12 g (0.028 mole) of **1a** in 50 ml of ether, and 400 ml of ether followed by 23.7 g (0.167 mole) of methyl iodide in 50 ml of ether, 2.80 g of a mixture of ketones was obtained. Vpc analysis[32] of the mixture revealed the presence of two peaks in a 95:5 ratio. The minor component of the mixture had a retention time identical with that of the trimethylcyclohexanone **9a**. The major peak was collected by preparative vpc and integration of the nmr spectrum of this material revealed that it contained 60% **7a** and 40% unreacted enone **1a**. No unsaturated methylation products were observed. The product yields were not determined in this run.

Reduction–Methylation of 6-Methylcyclohex-2-enone (2a).—Employing 0.483 g (0.069 g-atom) of lithium in 500 ml of liquid ammonia, 3.30 g (0.030 mole) of **2a** and 2.22 g (0.030 mole) of *t*-butyl alcohol in 50 ml of ether, and 400 ml of ether followed by 21.3 g (0.150 mole) of methyl iodide in 50 ml of ether, 1.60 g (42%) of a mixture of ketones, bp 75–78° (20 mm), was obtained. Analysis of the mixture as described above showed that it contained 86% of the equilibrium mixture of *cis*- and *trans*-2,6-dimethylcyclohexanone (**8a**), 2% 2,2,6-trimethylcyclohexanone (**9a**), and 12% 2-methylcyclohexanone (**6a**). No 2,2-dimethylcyclohexanone was detected.

Reduction–Methylation of 2,4,4-Trimethylcyclohex-2-enone (1b). *t*-Butyl Alcohol as Proton Donor.—Employing 0.360 g (0.051 g-atom) of lithium in 500 ml of liquid ammonia, 2.76 g (0.020 mole) of **1b** and 1.48 g (0.020 mole) of *t*-butyl alcohol in 50 ml of ether, and 300 ml of ether followed by 17.04 g (0.12 mole) of methyl iodide in 50 ml of ether, 1.46 g (46%) of a mixture

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(32) A 10 ft × 0.25 in. column containing 10% silicone SE-30 on Chromosorb W was employed for the analysis.

(33) Yield calculated by vpc using *m*-xylene as an internal standard.

(34) M. Brenner and H. Schinz, *Helv. Chim. Acta*, **35**, 1615 (1952).

(35) A 5 ft × 0.25 in. column containing 15% silicone SF-96 on Chromosorb W was employed for the analysis.

of ketones, bp 81–83° (17 mm), was obtained. Vpc analysis[32,36] showed that the mixture contained 93% 2,2,4,4-tetramethylcyclohexanone (**7b**) and 7% 2,4,4-trimethylcyclohexanone (**6b**). No 2,4,4,6-tetramethylcyclohexanone (**8b**) or 2,2,4,4,6-pentamethylcyclohexanone (**9b**) was observed. A sample of **7b** was collected by vpc and showed $\lambda_{\max}^{\mathrm{CCl_4}}$ 5.85 μ and absorption at $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 1.07 (s, 6 H) and 1.08 ppm (s, 6 H) for the four methyl groups and at 1.5–1.85 (br absorption, 4 H) and 2.2–2.5 ppm (br absorption, 2 H) for the remaining six protons.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.75. Found: C, 77.62; H, 11.59.

No Proton Donor Added.—Employing 0.18 g (0.25 g-atom) of lithium in 250 ml of liquid ammonia, 1.38 g (0.010 mole) of **1b** in 25 ml of ether, and 150 ml of ether followed by 8.52 g (0.06 mole) of methyl iodide in 25 ml of ether, 1.21 g of a mixture of ketones was obtained. Vpc analysis[32,36] showed that this mixture contained 23% **1b**, 28% **6b**, and 49% **7b**. No unsaturated methylation products were detected in this run.

Reduction–Methylation of 4,4,6-Trimethylcyclohex-2-enone (2b).—Employing 0.268 g (0.0375 g-atom) of lithium in 250 ml of liquid ammonia, 2.07 g (0.0150 mole) of **2b** and 1.10 g (0.0150 mole) of *t*-butyl alcohol, and 150 ml of ether followed by 10.7 g (0.0750 mole) of methyl iodide in 50 ml of ether, 1.40 g (60%) of a mixture of ketones, bp 57–59° (3.5 mm), was obtained. Vpc analysis[32] showed that it contained 95% 2,4,4,6-tetramethylcyclohexanone (**8b**) and 5% 2,4,4-trimethylcyclohexanone (**6b**). No 2,2,4,4-tetramethylcyclohexanone (**7b**)[36] or pentamethylcyclohexanone was detected. A sample of **8b** was collected by preparative vpc[32] and refluxed for 10 hr with 15% hydrochloric acid to ensure formation of the thermodynamic mixture of *cis* and *trans* isomers.[37] It showed $\lambda_{\max}^{\mathrm{CCl_4}}$ 5.85 μ and absorption at $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 0.91 ppm (d, J = 7 cps, 6 H) for the C-2 and C-6 methyl groups,[38] 0.97 (s, 3 H) and 1.27 (s, 3 H) for the methyl groups at C-4, and 1.42–2.25 (br absorption, 6 H) for the remaining six protons.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.75. Found: C, 77.87, H, 11.96.

Reduction–Methylation of 3-Methylcyclohex-2-enone (3).—Using 0.928 g (0.132 g-atom) of lithium in 500 ml of liquid ammonia, 5.83 g (0.053 mole) of **3** and 3.92 g (0.053 mole) of *t*-butyl alcohol, and 400 ml of ether followed by 32.3 g (0.227 mole) of methyl iodide in 50 ml of ether, 3.60 g (54%) of a mixture of ketones, bp 85–95° (40 mm), was obtained. Vpc analysis[32] showed that this mixture contained two components in a 87:13 ratio. The major component of the mixture was collected by vpc.[32] Its nmr spectrum showed absorptions expected for 2,3-dimethylcyclohexanone (**13**), that is, three peaks at $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 0.91, 1.03, and 1.10 ppm totalling six protons and resulting from overlapping doublets for the C-2 and C-3 methyl groups and at $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 1.25–2.5 ppm for the remaining eight protons. The minor component of the mixture was not positively identified, but, since its vpc retention time did not correspond with that of either **3** or **12** and since the infrared spectrum of the crude reaction mixture showed no hydroxylic absorption, it was assumed to be either the trimethylcyclohexanone **15** or **16** or a mixture of these.

In order to definitely establish that **13** was the only monoalkylation product produced in the reaction, the crude ketone mixture from above was converted to the semicarbazone, mp 185–195° (lit.[39] mp 205° for the semicarbazone of **13**), and this derivative was subjected to Wolff–Kishner reduction according to the method of Claudon, *et al.*[39] Vpc analysis[40] of the mixture of hydrocarbons obtained showed that it contained two components in a 85:15 ratio. The major component showed a retention time identical with that of *trans*-1,2-dimethylcyclohexane.[41] In addition, a sample of the major component was collected by vpc[41] and it showed an nmr spectrum identical with that reported by Muller and Tosch[42] for *trans*-1,2-dimethylcyclohexane. The minor component of the mixture had a retention time longer than that of any of the isomeric dimethylcyclohexanes.[41]

Registry No.—**1a**, 1121-18-2; **1b**, 13395-71-6; **2a**, 6610-21-5; **2b**, 13395-73-8; **3**, 1193-18-6; **4**, 99-49-0; **7b**, 13440-76-1; *cis* **8b**, 13395-74-9; *trans* **8b**, 13395-75-0; **13**, 13395-76-1; **17**, 7073-27-0.

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(36) The silicone column employed in the analysis did not separate mixtures of the tetramethyl ketones **7b** and **8b**. However, a 10 ft × 0.25 in. column packed with 4-methyl-4-nitropimelonitrile on firebrick did separate these ketones and was also used in the analysis.

(37) The equilibrium mixture would be expected to be composed almost completely of the *cis* product in this case.

(38) The low-field peak of the doublet at 0.91 ppm overlapped with the singlet at 0.97 ppm. This assignment was confirmed when it was found that reflux of **8b** with deuterium oxide and potassium carbonate resulted in a lowering of the intensity of the peaks at 0.87 and 0.97 ppm and the appearance of a triplet (J = 0.6 cps) at 0.91 ppm characteristic of methyl groups split by deuterium.

(39) M.-M. Claudon, R. Cornubert, H. Lemoine, and R. Malzieu, *Bull. Soc. Chim. France*, 837 (1958).

(40) A 10 ft × 0.25 in. column containing 20% Dow 550 silicone oil on Chromosorb W was employed for the analysis.

(41) Authentic samples of both *cis*- and *trans*-1,2-dimethylcyclohexane and *cis*- and *trans*-1,4-dimethylcyclohexane were separated on our gas chromatography column.[40] We are grateful to Professor James A. Stanfield for providing us with authentic samples of these hydrocarbons.

(42) N. Muller and W. C. Tosch, *J. Chem. Phys.*, **37**, 1167 (1962).