Alkylation of Lithium Enolates of 2-Methylcyclohexanone

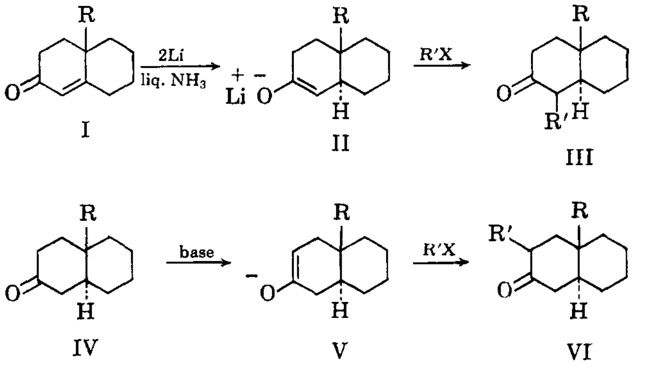
DRURY CAINE[1a,b]

Chandler Laboratories, Columbia University, New York 27, New York

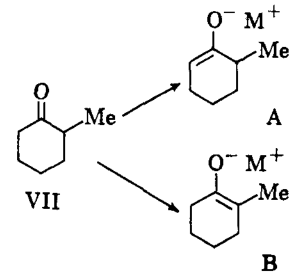
Received January 24, 1964

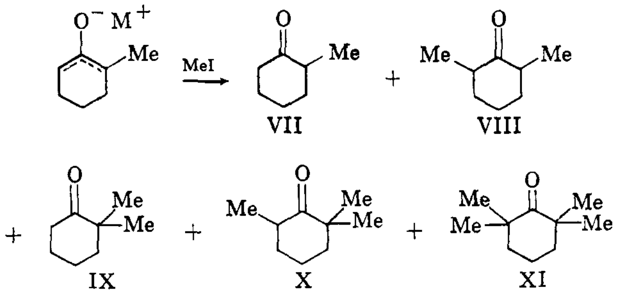
The products of methylation of lithium enolates of 2-methylcyclohexanone (VII) have been investigated. Reduction of 6-chloromercuri-2-methylcyclohexanone with lithium in liquid ammonia and methylation of the Δ^6-enolate product with methyl iodide in 1,2-dimethoxyethane gave 2,6-dimethylcyclohexanone (VIII) as by far the major monoalkylation product. VII, when treated with tritylithium in liquid ammonia–ether under kinetic conditions followed by methylation with methyl iodide in 1,2-dimethoxyethane and in tetrahydrofuran, gave mainly VIII *via* the less substituted lithium enolate. Under reaction conditions where equilibration of lithium enolates of VII was intentionally effected or unavoidable prior to the addition of the alkylating agent, 2,2-dimethylcyclohexanone (IX) derived from the more substituted enolate was found to be the major monomethylation product. The behavior of kinetic *vs.* equilibrium mixtures of lithium enolates of VII is compared, and the alkylations of metal enolates of VII with regard to the nature of the cation are considered.

It has recently been shown by Stork, Rosen, and Goldman[2] that the lithium–ammonia reduction of α,β-unsaturated ketones of the type I leads to the lithium enolate II which can be alkylated in liquid ammonia to produce *trans*-1-alkyl 2-decalones, *e.g.*, III. The enolate II is the less stable one of the *trans*-2-decalone system (IV) and direct alkylation of IV in the presence of strong base leads mainly to 3-alkyl substituted products (VI)[3] *via* the more stable enolate V. The success of the reductive alkylation of I to produce III depends on the fact that in liquid ammonia C-alkylation of the lithium enolate II is more rapid than its equilibration to the more stable enolate V by proton exchange with initially alkylated neutral ketone. From this result it seemed likely that alkylation could be directed to a specific α-carbon of an unsymmetrical ketone such as 2-methylcyclohexanone (VII) through the corresponding lithium enolate.[4] This objective has been achieved in part by (1) generation of the Δ^6-enolate of VII (A, M = Li) by reduction of 6-chloromercuri-2-methylcyclohexanone (XIII) with lithium in liquid ammonia, and (2) utilization of lithium enolates of VII formed kinetically with tritylithium in liquid ammonia–ether.



An unsymmetrical alicyclic ketone like VII can lose a proton to give either of two possible metal enolates, *i.e.*, A or B; it is well known[5] that, in the alkylation of such ketones with alkyl halides in the presence of strong base, mixtures of products are obtained and that the monoalkylation product derived from reaction at the more highly substituted carbon atom predominates. The ketone is usually converted to the enolate anion with strong base and alkylated in a suitable solvent with excess alkyl halide. The products of alkylation of VII with methyl iodide under these usual preparative conditions have been reinvestigated. A typical run which involved alkylation of the potassium enolate of VII with excess methyl iodide in 1,2-dimethoxyethane led as expected to a mixture of all possible products: unchanged VII, 2,6-dimethylcyclohexanone (VIII), 2,2-dimethylcyclohexanone (IX), 2,2,6-trimethylcyclohexanone (X), and 2,2,6,6-tetramethylcyclohexanone (XI). IX was the major product. The results of analysis of the recovered mixture of ketone by v.p.c. and n.m.r. as described in the Experimental are shown in Table I, item 1. Very similar results have recently been obtained by House and Kramer[6]; they have carried out a comprehensive study of the factors involved in the alkylation of unsymmetrical acyclic and alicyclic ketones, including VII, and conclude that the most important factor in product control is the equilibrium con-





---

[1] (a) National Institutes of Health Postdoctoral Fellow, 1961–1962; (b) Department of Chemistry, Georgia Institute of Technology, Atlanta, Ga. 30332.

[2] G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).

[3] Y. Mazur and F. Sondheimer, *ibid.*, **80**, 5220 (1958).

[4] This idea and some of the results reported herein have been discussed by G. Stork, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 23M.

[5] *Cf.*, *inter alia.*, H. M. E. Cardwell, *J. Chem. Soc.*, 2442 (1951).

[6] H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963). The author wishes to thank Professor House for making a copy of this manuscript available in advance of publication.

Table I

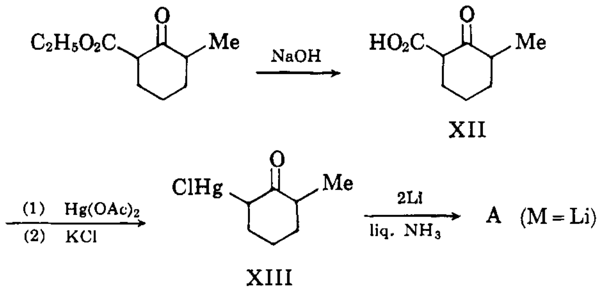
Alkylation of Metal Enolates of 2-Methylcyclohexanone (VII) with Methyl Iodide

Item	Method of generation of enolates	Solvent for alkylation[a]	% recovered ketones VII	VIII[b]	IX[b]	X	XI
1	KNH_2 in liq. ammonia	DME[c]	25	$\sim$10	41	24	1
2	Reduction of 6-chloromercuri-2-methylcyclohexanone (XIII) with Li in liq. ammonia	DME	16	72	<10	12	
3	$Ph_3C^-Li^+$ in liq. ammonia–ether (kinetic conditions)[d]	DME	11	55	27	7	
4	$Ph_3C^-Li^+$ in liq. ammonia–ether (kinetic conditions)	THF[e]	35	47	<10	13	
5	$Ph_3C^-Li^+$ in liq. ammonia–ether (equilibrium conditions)[f]	DME	14	13	73		

[a] After enolate formation was complete, the solvent system employed for that purpose was removed by distillation and replaced by the indicated solvent prior to methylation. [b] These values are considered to be accurate within 10% (see Experimental). [c] 1,2-Dimethoxyethane. [d] Excess trityllithium present at the end of the addition of VII. [e] Tetrahydrofuran. [f] Slight excess of VII to trityllithium added.

centration among the possible enolate anions.[7] Thus in the alkylation of potassium as well as sodium enolates[8] of VII, regardless of the kinetic concentrations of enolates A and B, equilibration among the anions by proton transfer reactions with initially produced alkylated ketone is faster than the alkylation reaction, and roughly the same product composition is always observed.

To demonstrate that alkylation of a specific lithium enolate of VII would occur faster than equilibration to the equilibrium mixture of A and B, the course of alkylation of the enolate A (M = Li) generated by indirect means has been investigated. The report by Nesmeyanov, *et al.*,[9] that chloromercuriacetaldehyde can be reduced to the lithium salt with lithium in liquid ammonia prompted investigation of a similar reaction of XIII for the purpose of generating A (M = Li). Using 6-carbethoxy-2-methylcyclohexanone as a starting material, XIII was prepared essentially according to the procedure of Nesmeyanov, *et al.*,[10] for the preparation of 2-chloromercuri-2-methylcyclohexanone. The β-keto ester was converted to 6-carboxy-2-methylcyclohexanone (XII)[11] on shaking with dilute sodium hydroxide at room temperature followed by acidification, and XIII was prepared by treating XII with aqueous mercuric acetate solution, heating to effect decarboxylation of the mercuric salt, and addition of potassium chloride solution. Compound XIII precipitated as a gummy white semisolid and resisted further purification by recrystallization.[12] Thus the crude compound was dissolved in 1,2-dimethoxyethane and added to 2 equiv. of lithium in liquid ammonia. After the ammonia had been removed and additional 1,2-dimethoxyethane added, reaction with methyl iodide led to a mixture of ketones having the compositions listed in Table I, item 2. The 2,6-dimethylcyclohexanone (VIII) which amounted to 72% of the product was obtained as an approximately 6:4 mixture of *cis* and *trans* isomers. However, for purposes of analysis, the entire reaction mixture was treated with 10% hydrochloric acid to convert the 2,6-dimethylcyclohexanones to the equilibrium mixture of which the *cis* isomer constitutes approximately 92%.[13] This result indicated that the less substituted lithium enolate of VII, *i.e.*, A (M = Li), was generated by the reduction of XIII and that indeed this enolate was alkylated in 1,2-dimethoxyethane with methyl iodide prior to significant equilibration among the enolates A and B. However, in view of the small amount of trimethyl ketone X and of recovered VII observed, the possibility that some proton exchange did occur before alkylation was complete cannot be excluded.



With the achievement of the objection of directing the alkylation of VII to the less substituted α-position *via* indirect formation of the enolate A (M = Li), the products of alkylation of lithium enolates of VII produced with strong base were investigated next. When methylations of VII were carried out using lithium amide in 1,2-dimethoxyethane and lithium *t*-butoxide in dimethyl sulfoxide, 2,2-dimethylcyclohexanone IX was found to account for 84% and 75%, respectively, of the monoalkylation products. These results compare closely with those obtained on methylation of potassium and sodium enolates of VII. In the former case, the covalent nature and low solubility of the lithium amide probably do not allow irreversible generation of the enolate, while in the latter case the result can be explained if enolate anion formation is reversible, or if in the solvent dimethyl sulfoxide proton transfer leading to equilibration is faster than C-alkylation.[2]

In search of a base that would allow for irreversible enolate formation, the products of methylation of the enolate of VII produced with trityllithium were next in-

---

[7] The work of House and Kramer (ref. 6) has proved incorrect the assumption by Cardwell (ref. 5) that the more highly substituted enolate of an unsymmetrical ketone is the more stable. They showed that in the case of acyclic ketones the less substituted enolate is definitely favored at equilibrium, and that in alicyclic ketones the more substituted enolate is only slightly favored. In 1,2-dimethoxyethane, the equilibrium concentrations of the potassium enolates of VII were found to be 48 ± 7% A and 52 ± 7% B.

[8] The composition of the mixture of ketones obtained by alkylation with methyl iodide of the sodium enolate of VII prepared from sodium hydride in 1,2-dimethoxyethane was very close to that obtained for the potassium enolate. Similar results have been reported for alkylations of the sodium enolate of VII in ether [see W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, **28**, 2184 (1963)].

[9] N. Nesmeyanov, I. F. Lutsenko, and R. M. Khomutov, *Dokl. Akad. Nauk SSSR*, **120**, 1049 (1958); *Chem. Abstr.*, **52**, 19,915 (1958).

[10] A. N. Nesmeyanov, I. F. Lutsenko, and S. N. Anachenko, *Uch. Zap. Mosk. Gos. Univ.*, **No. 132**, 136 (1950); *Chem. Abstr.*, **49**, 3836 (1955).

[11] E. J. Corey, T. H. Topie, and W. A. Woznick, *J. Am. Chem. Soc.*, **55**, 5415 (1955).

[12] On heating in organic solvents XIII underwent extensive decomposition with the formation of mercurous salts. Similar behavior has been observed for chloromercuricyclohexanone [see J. H. Robson and G. F. Wright, *Can. J. Chem.*, **38**, 1 (1960)].

[13] B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962).

vestigated. The method described by Hauser, *et al.*,[14] was employed for the preparation of this base. This involved addition of triphenylmethane in ether to lithium amide in liquid ammonia. Since reversion of the reaction to the hydrocarbon and lithium amide occurs when the liquid ammonia is removed, the enolates of VII were formed by addition of the ketone to the trityl lithium in the liquid ammonia–ether solvent. Reactions were carried out under kinetic and equilibrium conditions of enolate formation. Under kinetic conditions sufficient base was employed so that the red color of the trityllithium remained at the end of the dropwise addition of the ketone in ether. Under these conditions, if enolate formation is irreversible, the concentrations of the enolates A and B produced would depend on the relative rates of proton removal from C-6 and C-2, respectively. Under equilibrium conditions a slight excess of the ketone to trityllithium was added, as evidenced by the discharge of the red color of the base. Here the added excess neutral ketone should allow complete equilibration among the enolates A and B *via* proton transfer reactions. The results of methylations in 1,2-dimethoxyethane and tetrahydrofuran under kinetic conditions of enolate formation are shown in Table I, items 3 and 4, while item 5 shows the results obtained under equilibrium conditions. In both cases where the enolate was formed kinetically 2,6-dimethylcyclohexanone (VIII) was the major monoalkylation product, whereas under equilibrium conditions the 2,2-isomer IX predominated. As has been pointed out previously, alkylation of potassium and sodium enolates of VII yields mainly IX; but, by making use of the fact that under the proper conditions C-alkylation of a kinetic mixture of lithium enolates of this ketone occurs faster than proton exchange to the equilibrium mixture of enolates, it appears that this trend can be reversed in favor of VIII.

In both cases where methylations of kinetic mixtures of lithium enolates were carried out, recovered VII and the dialkylation product X were obtained along with the monoalkylation products. This result indicates that some proton transfer did occur during alkylation. Thus, attempts to relate the distribution of monoalkylation products (VIII and IX derived from VII) to the kinetic concentrations of the enolates A and B are of course questionable. However, if the structurally isomeric enolates react with methyl iodide at similar rates,[6] it appears likely that the less substituted enolate of VII (A, M = Li) is definitely preferred kinetically under the reaction conditions employed for enolate formation. Rosen[15] has shown that the sodium enolate of VII prepared kinetically with sodium amide in liquid ammonia yields 6-carbomethoxy-2-methylcyclohexanone on reaction with solid carbon dioxide in 1,2-dimethoxyethane followed by acidification and treatment with ethereal diazomethane. The carbonation reaction is rapid and unlike methylation presumably occurs without equilibration among the sodium enolates.[5] Since 6-carbomethoxy-2-methylcyclohexanone is derived from the enolate A (M = Na), it appears likely that the less substituted enolate of VII is preferred kinetically when sodium amide in liquid ammonia, as well as trityllithium in liquid ammonia–ether, is employed for enolate formation.

House and Kramer[6] have shown that the nature of the cation has considerable influence on the equilibrium concentrations of structurally isomeric enolates, and that in certain acylic ketones the less substituted lithium enolate is favored at equilibrium as compared with cases where sodium and potassium are used as the cations. In these cases methylation of the equilibrium mixture of lithium enolates was found to yield mainly monoalkylation products derived from the less substituted enolate anion. However, the data in Table I, item 5, do not indicate similar behavior for VII, since IX, derived from the more substituted enolate B, was obtained as the major monoalkylation product when equilibration of the lithium enolates was intentionally effected prior to methylation. The 2,2-isomer IX also was found to predominate when equilibration of enolates was unavoidable, as when lithium amide and lithium *t*-butoxide were used as the bases for enolate formation.

Studies are now in progress to determine the kinetic concentrations of enolates of unsymmetrical ketones produced under various conditions and to make further use of the reduction of α-chloromercuri ketones for generating specific metal enolates of unsymmetrical ketones.

Experimental[16]

Materials.—All ether solvents were purified by reflux over lithium aluminum hydride and distillation. The dimethyl sulfoxide (DMSO) was distilled from calcium hydride at reduced pressure. Anhydrous liquid ammonia was obtained by distillation from sodium directly into the reaction vessel.

The sample of 2-methylcyclohexanone (VII) employed for the work was prepared by oxidation of 2-methylcyclohexanol and after fractionation showed a boiling point of 165.0–165.2°. It was shown by v.p.c. to be of greater than 99% purity. The n.m.r. spectrum of VII showed broad absorption in the region of τ 7.5–8.8 (9H) and a doublet (J = 6 c.p.s.) centered at 9.07 (3H, CH_3–CH<).

Authentic samples[17] of the equilibrium mixture of *cis*- and *trans*-2,6-dimethylcyclohexanone (VIII) and of 2,2-dimethylcyclohexanone (IX) showed the following n.m.r. absorptions: VIII showed broad absorption at τ 7.5–8.8, an intense doublet (J = 6 c.p.s.) at 9.07 (CH_3–CH<, *cis* isomer), and very weak absorption at 8.92 corresponding to one peak of a doublet (J = 6 c.p.s.) centered at 8.97 (CH_3–CH<, *trans* isomer); the ratio of the total methyl to methylene and methinyl absorption was 6:8. The unsymmetrical isomer IX showed broad absorption at τ 7.5–7.9 (2H, CH_2–CO) and 8.0–8.5 (6H) and a singlet at 8.95 (6H).

Sufficient quantities of the trimethylated ketone X and the tetramethylated ketone XI for collection by v.p.c. were obtained by methylation of the sodium enolate of VII in DMSO. To a solution of sodium methyl sulfinyl carbanion[18] [prepared from 1.22 g. (0.055 mole) of sodium hydride and 80 ml. of DMSO] in DMSO was added dropwise 5.61 g. (0.05 mole) of VII in 20 ml. of DMSO over 30 min. at room temperature. The solution was stirred for 1 hr. and 8.5 g. (0.06 mole) of methyl iodide was added. After 2 hr. of stirring at room temperature, the reaction mixture was poured into ice–water, the mixture of methylated ketones was extracted with ether, and the ethereal solution was dried over anhydrous sodium sulfate. After removal of the solvent, v.p.c. analysis (see below) showed that the mixture was composed of

---

[14] C. R. Hauser, D. S. Hoffenberg, W. H. Puterbaugh, and F. C. Frostick, *J. Org. Chem.*, **20**, 1531 (1955).

[15] P. Rosen, Ph.D. dissertation, Columbia University, 1962.

[16] Melting points were determined by the open capillary method and are corrected. Boiling points are uncorrected. The v.p.c. separations were effected at 140° using a 10 ft. × 0.25 in. column containing 20% silicone SE-30 on Chromosorb-W. N.m.r. spectra were obtained in carbon tetrachloride solution with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard.

[17] Kindly supplied by Dr. S. Dowd and Dr. S. D. Darling.

[18] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

VII (14%), the dimethylcyclohexanones VIII and IX (40%), the trimethyl ketone X (33%), and the tetramethyl ketone XI (12%). Collected samples of X and XI showed the following n.m.r. absorptions: X gave broad absorption at τ 7.3–7.7 (1H) and at 8.0–8.5 (6H) and peaks at 8.90, 9.00, and 9.12 (9H) in the ratio 3:4.5:1.5; these three peaks correspond to the two methyl groups at C-2 (τ 8.90 and 9.00) and to one peak (9.12) of a doublet (J = 6 c.p.s.) centered at 9.07. The tetramethyl ketone XI showed broad absorption at τ 8.3–8.5 (6H) and a singlet at 8.97 (12H).

Analysis of Products.—After the usual work-up of the reaction mixture from the methylation of the metal enolates of VII, the percentage compositions of the products listed in Table I were determined by a combination of v.p.c. and n.m.r. spectroscopy. Using the silicone gas chromatography column, the methylated cyclohexanones were eluted as follows: first peak, unchanged 2-methylcyclohexanone (VII); second peak, the equilibrium mixture of dimethylcyclohexanones VIII and IX[19]; third peak, 2,2,6-trimethylcyclohexanone (X); and the fourth peak, 2,2,6,6-tetramethylcyclohexanone (XI). Thus by determining the relative areas (by multiplying the peak width at one-half height by the height) of the four peaks, the per cent of VII, the mixture of VIII and IX, X, and XI were obtained. The mixture of VIII and IX then was collected by v.p.c. and its composition was determined by integration of the methyl region of the n.m.r. spectrum at a 50-c.p.s. sweep width. Although slight overlap existed between the singlet at τ 8.95 and the low-field peak of the doublet at τ 9.07, a determination of the compositions of known mixtures of VIII and IX showed this method to be accurate within 10%.

Alkylation of the Potassium Enolate VII with Methyl Iodide in 1,2-Dimethoxyethane.—To 100 ml. of stirred anhydrous liquid ammonia containing a trace of anhydrous ferric chloride was added 0.98 g. (0.025 g.-atom) of freshly cut potassium metal. The blue color produced on addition of the metal soon disappeared, indicating the formation of potassium amide. After the solution had been stirred for 15 min., 2.24 g. (0.020 mole) of VII in 40 ml. of 1,2-dimethoxyethane was added dropwise over a period of 45 min. When the addition was complete, stirring was continued for 30 min. The liquid ammonia then was removed by warming the reaction vessel with warm water and 40 ml. of 1,2-dimethoxyethane was added to replace it. The 1,2-dimethoxyethane suspension of the enolate was heated to reflux, cooled to room temperature, and 28.4 g. (0.2 mole) of methyl iodide was added in one portion. After 2 hr. at reflux, the reaction mixture was cooled, and poured into water; the aqueous mixture was extracted with ether. After the organic layer had been washed with water and dried, and the solvent removed under pressure, analysis of the mixture as described previously showed VII (25%), VIII (~10%), IX (41%), X (24%), and XI (1%).

Methylation of Lithium Enolates of VII. A. From Reduction of 6-Chloromercuri-2-methylcyclohexanone with Lithium in Liquid Ammonia.—6-Carbethoxy-2-methylcyclohexanone,[20] 10.1 g. (0.055 mole), was shaken for 16 hr. at room temperature with 3.32 g. (0.083 mole) of sodium hydroxide in 30 ml. of water. The basic solution then was extracted with 50 ml. of ether, acidified to pH 3 with 5% hydrochloric acid, and again extracted with three 50-ml. portions of ether. The ethereal solution was dried over sodium sulfate and, on removal of the solvent at reduced pressure at room temperature, 6.40 g. (75%) of the acid XII, m.p. 88–91° dec. (lit.[11] m.p. 90–91° dec.), was obtained.

To 13.4 g. (0.042 mole) of mercuric acetate in 35 ml. of water was added 6.24 g. (0.040 mole) of XII in 10 ml. of 95% ethanol, and the mixture was warmed at 75° to effect decarboxylation of the mercuric salt of the acid. The hot solution then was filtered, cooled to room temperature, and treated with 2.98 g. of potassium chloride. A white precipitate of the chloromercuri compound XIII immediately formed and the mixture then was allowed to stand in an ice bath overnight. The product then was extracted with chloroform and the chloroform solution was dried over sodium sulfate. On removal of the chloroform under reduced pressure, 6.95 g. of XIII which could not be purified by recrystallization was obtained. Crude XIII, 5.63 g. (0.017 mole), then was dissolved in 40 ml. of 1,2-dimethoxyethane and added dropwise[21] to 0.25 g. (0.036 g.-atom) of lithium in 60 ml. of anhydrous liquid ammonia. As the last few drops were added, the blue color of the lithium in ammonia faded but was easily restored by the addition of a small piece of lithium metal. The mixture then was stirred for 30 min. and the ammonia was removed and replaced by 60 ml. of 1,2-dimethoxyethane. The reaction mixture then was brought to reflux, cooled to room temperature, and treated with 5.68 g. (0.04 mole) of methyl iodide and again brought to reflux for 1 hr. The precipitated lithium iodide and elemental mercury then were removed by filtration and the filtrate was poured into cold water. Work-up of the reaction mixture in the usual way with ether yielded 1.97 g. of a mixture of ketones. Preliminary v.p.c. of this mixture indicated that it consisted mainly of *cis*- and *trans*-2,6-dimethylcyclohexanone in a ratio of *ca.* 6:4. The mixture then was refluxed with 10% hydrochloric acid overnight and analyzed as previously described. The products were VII (16%), VIII (72%), and X (12%). Less than 10% of 2,2-dimethylcyclohexanone (IX) was present by n.m.r.

B. From Lithium Amide in 1,2-Dimethoxyethane.—To a slurry prepared from 0.58 g. (0.025 mole) of lithium amide in 50 ml. of 1,2-dimethoxyethane which had been brought to reflux under nitrogen was added 2.24 g. (0.020 mole) of VII, and the reaction mixture was refluxed overnight. The mixture then was cooled to room temperature, 5.68 g. (0.04 mole) of methyl iodide was added, and reflux resumed for 2 hr. After work-up of the mixture of products in the usual way with ether, removal of the solvent gave 1.5 g. of a mixture of methylated ketones which was found to contain VII (24%), VIII (10%), IX (55%), and X (11%). No tetramethylcyclohexanone XI was observed.

C. From Lithium *t*-Butoxide in DMSO.—A mixture composed of 0.184 g. (0.023 mole) of lithium hydride and 1.70 g. (0.023 mole) of *t*-butyl alcohol in 50 ml. of DMSO was warmed at 70° under nitrogen until homogeneous (14 hr.). The solution then was cooled to room temperature and 2.24 g. (0.020 mole) of VII in 10 ml. of DMSO was added dropwise with stirring over 30 min. When the addition was complete, the mixture was stirred for 2 hr. at room temperature, 3.6 g. (0.025 mole) of methyl iodide then was added, and the mixture was stirred for 1 hr. longer. The mixture was poured into ice–water and extracted with ether; the ethereal solution was dried over sodium sulfate. Removal of the solvent under reduced pressure yielded 2.0 g. of a mixture of methylated cyclohexanones which was found to contain VII (35%), VIII (14%), IX (42%), and X (9%). No XI was detected.

D. From Trityllithium in Liquid Ammonia–Ether. A. Kinetic Conditions with Methylation in 1,2-Dimethoxyethane.—The procedure by Hauser, *et al.*,[14] was employed for the preparation of trityllithium. To 75 ml. of anhydrous ammonia containing a trace of anhydrous ferric chloride was added 0.236 g. (0.034 g.-atom) of freshly cut lithium wire. The mixture then was stirred at liquid ammonia reflux temperature until the formation of lithium amide was complete as indicated by the disappearance of the blue color of lithium in liquid ammonia. Triphenylmethane, 8.30 g. (0.034 mole), in 100 ml. of anhydrous ether then was added at such a rate that the ammonia was condensed efficiently with the Dry Ice–acetone condenser. The red color of the trityllithium developed immediately on addition of the first few drops of the solution of triphenylmethane and at the end of the addition the lithium amide had dissolved and a deep red suspension of trityllithium remained. To this suspension was added dropwise with stirring 2.69 g. (0.024 mole) of VII in 25 ml. of ether over 40 min. The red color of the trityllithium persisted throughout the course of the addition and while stirring was continued for 30 min. thereafter. The liquid ammonia then was removed in the usual way (the red color of the excess trityllithium disappeared at this point), and the ether was distilled and replaced by 100 ml. of 1,2-dimethoxyethane. When the temperature of the distillate had reached 70°, the reaction mixture was cooled to room temperature, 16.0 g. (0.12 mole) of methyl iodide was added, and the reaction mixture refluxed for 2 hr. (An aliquot taken after 10

---

[19] In cases where significant quantities of *trans*-2,6-dimethylcyclohexanone were obtained in the alkylation reactions, a shoulder attributable to this material appeared on the second v.p.c. peak. However, since complete separation of this mixture of ketones could not be effected on the column employed, for purposes of analysis the entire mixture of ketones was refluxed with 10% hydrochloric acid to convert the 2,6-dimethylcyclohexanones to the equilibrium mixture.

[20] Prepared by Mr. C. Miller by the procedure of E. B. McCall and B. B. Willard, *J. Chem. Soc.*, 1911 (1959).

[21] Immediately on exposure of the 1,2-dimethoxyethane solution of XIII to ammonia vapor a copious precipitate, presumably a complex of XIII and ammonia, formed. However, the precipitate remained in suspension and the mixture could be added successfully to the lithium ammonia solution using a Hershberg dropping funnel.

min. showed the same composition by v.p.c. as did the product obtained after 2 hr.) Work-up of the reaction mixture in the usual way yielded VII (11%), VIII (55%), IX (27%), and X (7%). No XI was observed.

B. Kinetic Conditions with Methylation in Tetrahydrofuran (THF).—Trityllithium was prepared as described above by the addition of triphenylmethane, 8.30 g. (0.034 mole), in 100 ml. of anhydrous ether to lithium amide (from 0.236 g., 0.034 g.-atom, of lithium) in 75 ml. of liquid ammonia. To the red solution was added dropwise with stirring 2.69 g. (0.024 mole) of VII in 25 ml. of ether over 30 min. The liquid ammonia then was removed in the usual way (the red color of the excess trityllithium disappeared at this point) and was replaced by 100 ml. of THF. The ether was distilled from the reaction mixture until the temperature of the distillate reached 50°. The reaction mixture was cooled to room temperature, 16.0 g. (0.12 mole) of methyl iodide was added, and the mixture refluxed for 2 hr. After work-up of the reaction mixture and equilibration of the 2,6-dimethylcyclohexanones with 10% hydrochloric acid, analysis of the products gave VII (35%), VIII (47%), IX (<10%), and X (13%).

C. Equilibrium Conditions with Methylation in 1,2-Dimethoxyethane.—Trityllithium was made by addition of 8.30 g. (0.034 mole) of triphenylmethane in 100 ml. of ether to lithium amide (from 0.236 g., 0.034 g.-atom, of lithium) in 75 ml. of liquid ammonia and 3.36 g. (0.030 mole) of VII in 25 ml. of ether was added dropwise with stirring over 30 min. When the last few drops of ketone were added, the disappearance of the red color of the trityllithium indicated that a slight excess of ketone to this base was present. After the liquid ammonia had been removed and 100 ml. of 1,2-dimethoxyethane added to replace it, ether was distilled from the reaction mixture until the temperature of the distillate reached 70°. After cooling to room temperature and the addition of 16.0 g. (0.12 mole) methyl iodide, the reaction mixture was refluxed for 2 hr. Work-up in the usual way yielded a mixture of ketones which contained VII (14%), VIII (13%), and IX (73%). No other methylation products were observed.

Acknowledgment.—The author is sincerely grateful to Professor Gilbert Stork for his advice and assistance throughout the course of the work.

The Reaction of Lithium Acetylide·Ethylenediamine with Ketones

OSCAR F. BEUMEL, JR., AND ROBERT F. HARRIS

Research and Development Laboratories, Foote Mineral Company, Exton, Pennsylvania

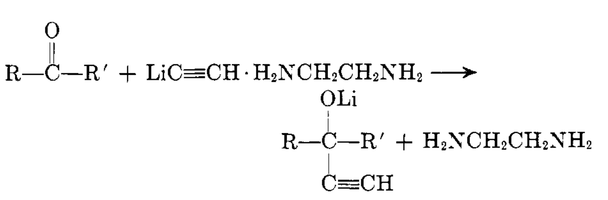
Received December 5, 1963

The reaction between lithium acetylide·ethylenediamine and a variety of ketones has been studied in several organic solvents under argon and acetylene atmospheres. High yields of ethynylcarbinols were obtained. A relationship between the yield of ethynylcarbinol and the dielectric constant of the solvent is discussed.

In a recent paper[1] we reported the preparation and some properties of lithium acetylide·ethylenediamine. This crystalline complex is stable up to about 45°, in contrast to uncomplexed lithium acetylide which is stable only in liquid ammonia at −33°.[2]

This new reagent with its higher stability has a potential of being used over a wide range of temperatures in a variety of organic solvents and in standard equipment. In this paper, this new versatility is discussed, and the effect of some of the variables on the reaction with ketones to form ethynylcarbinols is shown.

Lithium acetylide·ethylenediamine was found to add readily across a ketonic linkage to produce the lithium salt of the corresponding ethynylcarbinol.



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}R' + LiC{\equiv}CH\cdot H_2NCH_2CH_2NH_2 \longrightarrow R{-}\underset{C\equiv CH}{\underset{|}{\overset{OLi}{\overset{|}{C}}}}{-}R' + H_2NCH_2CH_2NH_2} \quad (1)$$

The yield obtained was found to vary widely, depending upon the reaction conditions and the solvent.

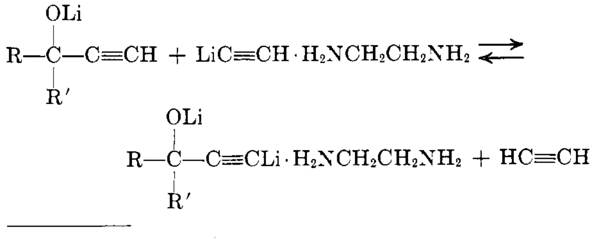
Table I summarizes the results obtained when stoichiometric quantities of lithium acetylide·ethylenediamine were allowed to react with the various ketones. Yields are based on starting materials added, and no correction is made for recovered ketone. Several runs were made with 10% excess acetylide where low yields were experienced with stoichiometric quantities. Yield was determined by analysis, not by isolation. Duplicate runs gave yields varying up to 2%.

If the yields given in Table I are plotted against the dielectric constant of the solvent, an interesting curve is obtained for each ketone. These curves can be grouped into several different types (see Fig. 1–4) and reflect two major side reactions.

In low dielectric solvents (such as benzene) there is usually a drop in yield. In most cases this loss is due mainly to base-catalyzed enolization. Evidence for this is the fact that after hydrolysis all of the starting ketone can be accounted for either as ethynylcarbinol or as unchanged ketone. Additional evidence is the relationship between the yields obtained in benzene and the base-catalyzed enolization constants determined by H. Shechter, *et al.*,[3] and listed in Table II.

The two marked exceptions to this simplification are the diaromatic ketones benzophenone and 9-fluorenone. Although it is impossible for them to enolize, they have the most dramatic drop in yield in low dielectric solvents. In fact, 1,1,4,4-tetraphenyl-2-butyne-1,4-diol is the major product obtained from benzophenone in benzene. This anomoly will be discussed in more detail under metalation.

At the high end of the dielectric scale (and to a lesser extent over the entire range), the reduction in yield appears to be due to metalation of the resulting ethynylcarbinol. This product may react further with an-



$$\mathrm{R{-}\underset{R'}{\underset{|}{\overset{OLi}{\overset{|}{C}}}}{-}C{\equiv}CH + LiC{\equiv}CH\cdot H_2NCH_2CH_2NH_2 \rightleftharpoons R{-}\underset{R'}{\underset{|}{\overset{OLi}{\overset{|}{C}}}}{-}C{\equiv}CLi\cdot H_2NCH_2CH_2NH_2 + HC{\equiv}CH} \quad (2)$$

---

[1] O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963).

[2] M. Corbellini and L. Turner, *Chim. Ind.* (Milan), **42**, 251 (1950); *Chem. Abstr.*, **54**, 19,250 (1960).

[3] H. Shechter, M. J. Collins, R. Dessy, Y. Okuzumi, and A. Chen *J. Am. Chem. Soc.*, **84**, 2095 (1962).