as room-temperature stable sources of singlet oxygen are likely to go unrewarded.

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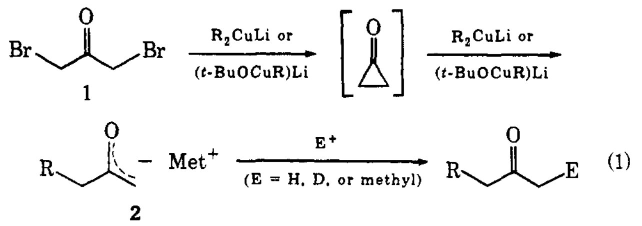
Reaction of α,α'-Dibromo Ketones with Organocopper Reagents. A New Method for α Alkylation of Ketones[1]

Sir:

We recently observed that 2-bromocyclododecanone reacts with lithium dimethylcuprate(I) in diethyl ether giving cyclododecanone in 95% yield after acidic work-up, giving 2-deuteriocyclododecanone in 88% yield after D_2O work-up, and giving 2-methylcyclododecanone in 67% yield after exposure to excess methyl iodide.[2] These results suggested the intermediacy of a metal (lithium or copper) enolate.[3] We were intrigued by the possibility that α,α'-dibromo ketones might also react with organocopper reagents leading initially to enolates in which internal displacement of bromide would produce cyclopropanones (or allene oxide or oxyallyl carbonium ion structures)[4] as in the Favorskii rearrangement. Further reaction with the organocopper reagent might produce a new enolate **2**,[5] and exposure of this species to various electrophiles would yield α-substituted and/or α,α'-disubstituted ketones (eq 1). We report herein the successful execution of this synthetic scheme and its application to α-secondary and α-tertiary alkylation of ketones.



Seven symmetrical cyclic (**1a–c**) and acyclic (**1d–f**) α,α'-dibromo ketones have been treated separately with 5 mol equiv of lithium dimethylcuprate(I) (concentration *ca.* 0.25 *M*) at −78° in diethyl ether during 0.5 hr[6] to give the corresponding α-methyl ketones consistently in good to excellent yields after −78° methanol quench and then aqueous work-up; no dimethylation is observed[7–9] (see Table I).

Table I. α-Methyl Ketones from α,α'-Dibromo Ketones and Lithium Dimethylcuprate(I) in Diethyl Ether at −78° (See Equation 1)

Substrate	Product	% yield[a]
cis-2,6-Dibromocyclohexanone (*cis*-**1a**)	2-Methylcyclohexanone	70[b] (95[c])
trans-2,6-Dibromocyclohexanone (*trans*-**1a**)	2-Methylcyclohexanone	98[b]
2,8-Dibromocyclooctanone (**1b**)	2-Methylcyclooctanone	80[c]
cis-2,12-Dibromocyclododecanone (*cis*-**1c**)	2-Methylcyclododecanone	97
4,6-Dibromo-5-nonanone (**1d**)	4-Methyl-5-nonanone	70
1,3-Dibromo-1,3-diphenyl-2-propanone (**1e**)	1,3-Diphenyl-2-butanone	72[d]
2,4-Dibromo-2,4-dimethyl-3-pentanone (**1f**)	2,2,4-Trimethyl-3-pentanone	54[e]

[a] The yield was determined by analytical vpc using an internal standard. [b] The variation in yield as a function of substrate stereochemistry is not yet understood. [c] Reaction temperature −78° for 5 min, then 25° for 1 hr before methanol quench. [d] 18% dimer: 1,3,4,6-tetraphenyl-2,5-hexanedione. [e] Reaction was performed in pentane at −50°.

Evidence pointing to a cyclopropanone (or allene oxide or oxyallyl carbonium ion)[4] intermediate in the reaction of α,α'-dibromo ketone **1e**, for example, with

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[1] Part of this work was presented at the 8th Middle Atlantic Regional Meeting of the American Chemical Society, Washington, D. C., Jan 14–17, 1973, Abstract H3.

[2] (a) Alkylation of α-bromo ketones and of α,α'-dibromo ketones in low yields using lithium dialkylcuprates(I) has recently been reported: J. E. Dubois, C. Lion, and C. Moulineau, *Tetrahedron Lett.*, 177 (1971); J. E. Dubois and C. Lion, *C. R. Acad. Sci. Paris, Ser. C*, **272**, 1377 (1971). (b) Zinc reduction of 2-bromocyclododecanone followed by addition of methyl iodide has been reported to form 2-methylcyclododecanone: T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967).

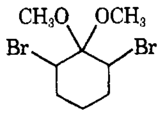
[3] The low reactivity of this enolate toward methyl iodide and other normally reactive electrophiles suggests that it is a copper rather than a lithium enolate; for some comments on copper enolate chemistry, see H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969).

[4] Much attention has been devoted recently to the intermediates formed in reductive elimination of bromine from α,α'-dibromo ketones using (a) electrochemistry: A. J. Fry and R. Scoggins, *Tetrahedron Lett.*, 4079 (1972); J. P. Dirlam, L. Eberson, and J. Casanova, *J. Amer. Chem. Soc.*, **94**, 240 (1972); (b) zinc–copper couple: H. M. R. Hoffmann, K. E. Clemens, E. A. Schmidt, and R. H. Smithers, *J. Amer. Chem. Soc.*, **94**, 3201 (1972); H. M. R. Hoffmann, T. A. Nour, and R. H. Smithers, *J. Chem. Soc., Chem. Commun.*, 963 (1972); and (c) iron carbonyls: R. Noyori, K. Yokoyama, S. Makino, and Y. Hayakawa, *J. Amer. Chem. Soc.*, **94**, 1772 (1972); R. Noyori, *et al.*, *ibid.*, **94**, 7202 (1972).

[5] For a discussion of nucleophilic attack on cyclopropanones, see N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).

[6] All reactions were performed routinely on a 1–2 mmol scale and in several cases on a 10–15 mmol scale with the usual precautions for rigorous exclusion of air and moisture. Cuprous iodide was purchased from Fischer Chemical Co. and was continuously extracted with THF in a Soxhlet extractor for about 12 hr and then dried under vacuum at 25°; the cuprous iodide thus purified remained pure on standing for several months, and aliquots were used for reaction with organolithium reagents to generate organocuprates(I).

[7] It should be noted that 1,3-dibromoalkanes are much less reactive than α,α'-dibromo ketones toward organocuprates(I); dibromide i, for example, is inert to lithium dimethylcuprate(I).



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[8] For an excellent discussion with leading references of the importance of ketones in organic chemistry and the difficulties in controlling α alkylation of ketones, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, Chapter 9.

[9] It should be noted that, in contrast to nucleophilic attack of an enolate ion or an enamine on an electrophilic methyl group, lithium dimethylcuprate(I) reaction with α,α'-dibromo ketones involves an electrophilic substrate and a nucleophilic methyl group; this difference may allow methylation of certain complex ketones not easily methylated by the enolate or enamine approach.

lithium dimethylcuprate(I) rests on isolation of a furan Diels–Alder adduct in approximately 20% yield when the reaction is carried out at $-78°$ in furan as solvent.[10] Evidence for methylated enolate **2** rests on quenching the reaction mixture at $-78°$ with excess D_2O or with excess methyl iodide, allowing the reaction mixture to reach 25°,[11] and isolating α-deuterio-α'-methyl ketone or α,α'-dimethyl ketone. For example, *cis*-2,12-dibromocyclododecanone is converted to 2-deuterio-12-methylcyclododecanone (95% d_1 and 5% d_0 by mass spectrometry) in 91% yield, or is regiospecifically dimethylated to 2,12-dimethylcyclododecanone in 94% yield. Similarly, dibromo ketone **1d** reacts with lithium dimethylcuprate(I) regiospecifically to give 4,6-dimethyl-5-nonanone in 62% yield after addition of methyl iodide.[12] These conversions allow direct and efficient functionalization of two carbon atoms (α and α' to the ketone carbonyl group) in one step.[13] Attempts to form enol acetates[8] or enol silyl ethers[14] in high yields from enolate **2** consistently failed.

Normal, secondary, and tertiary alkylation of symmetrical dibromo ketones **1a** and **1d**, for example, can be achieved using 5 mol equiv of the new lithium *tert*-butoxy(alkyl)cuprate(I) reagents[15] in tetrahydrofuran at $-78°$ for 0.5 hr; 2-*n*-butyl-, 2-*sec*-butyl-, and 2-*tert*-butylcyclohexanone were formed in 77, 73, and 66% yields, and 4-*n*-butyl-, 4-*sec*-butyl-, and 4-*tert*-butyl-5-nonanone were formed in 75, 65, and 60% yields, respectively; no dialkylation was observed.[16] This method for attachment of a nucleophilic tertiary alkyl group α to a ketone carbonyl is especially noteworthy because tertiary alkyl electrophiles undergo elimination rather than substitution reactions with enolate ions or enamines. Furthermore, the low reactivity of *tert*-butoxy-*tert*-alkylcuprates at $-78°$ toward isolated carbonyl and bromine groups[15] suggests that these reagents probably would react selectively with the α,α'-dibromo ketone functionality even in molecules having remote ketone or bromine units.

Unsymmetrical α,α'-dibromo ketones react with diorgano- and alkoxy(alkyl)cuprate(I) reagents to give mixtures of α- and α'-monoalkylated products. In the two unsymmetrical dibromo ketones studied thus far, alkylation of the less substituted α-carbon atom predominates, and the degree of regioselectivity increases from methylation (roughly 1:1 α:α') to normal butylation (3:1) to secondary butylation (7:1) to tertiary butylation (9:1). Reaction of 1,3-dibromo-2-heptanone, for example, with lithium *tert*-butoxy-*tert*-butylcuprate(I) gave 2,2-dimethyl-4-nonanone in 53% yield along with 6% of 3-*tert*-butyl-2-heptanone, and 2,6-dibromo-2-methylcyclohexanone reacted with lithium *tert*-butoxy-*sec*-butylcuprate(I) giving 2-*sec*-butyl-6-methylcyclohexanone in 60% yield along with 8% of 2-*sec*-butyl-2-methylcyclohexanone. Although indirect methods are available for methylation and normal alkylation of the less substituted α-carbon atom of an unsymmetrical ketone,[8,17] regioselective α-secondary and α-tertiary alkylation of unsymmetrical ketones has not been reported previously.

2-*tert*-Butylcyclohexanone. To a suspension of cuprous iodide[6] (4.75 g, 25 mmol) in 61 ml of dry tetrahydrofuran was added *via* syringe 26 ml of a 0.97 *M* *tert*-butoxylithium[18] (25 mmol) solution in tetrahydrofuran, and the mixture was stirred at 0° under a nitrogen atmosphere until formation of cuprous *tert*-butoxide was complete (as evidenced by the disappearance of gray, insoluble cuprous iodide, $\sim$5 min). Into the cooled ($-78°$) solution was then injected 11.8 ml of 2.12 *M* *tert*-butyllithium (25 mmol) in pentane, and the resulting cloudy, brown mixture was stirred for 5 min at $-78°$. Into the alkoxy(alkyl)cuprate thus formed was injected 4 ml of a THF solution of 1.28 g (5 mmol) 2,6-dibromocyclohexanone.[19] After stirring for 30 min at $-78°$, 2.0 ml of absolute methanol was injected. The product was isolated by pouring the reaction mixture into 100 ml of saturated aqueous ammonium chloride, extracting with ether, and drying with magnesium sulfate. The crude product (840 mg, $>100\%$), an orange oil (66% yield of 2-*tert*-butylcyclohexanone by vpc using a 7-ft SE-30 column at 100°), was column chromatographed on silica. Elution with pentane gave a small amount of cyclohexanone and 385 mg (50%) of pure, colorless 2-*tert*-butylcyclohexanone, n^{20}D 1.4591 (lit. n^{20}D 1.4579[20]), having appropriate infrared and nuclear magnetic resonance spectra.

This new method for α alkylation of ketones complements our recently reported procedure for preparing unsymmetrical ketones from acid chlorides and organocuprate(I) reagents.[15,21] The ready availability of α,α'-dibromo ketones and the convenience and mildness of the organocuprate(I) reactions[21] are important positive aspects of the novel synthetic method reported herein.

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(10) The Diels–Alder adduct had spectral properties and melting point fully consistent with those reported for this compound previously prepared by zinc–copper couple treatment of dibromo ketone **1e** in furan: R. C. Cookson and M. J. Nye, *J. Chem. Soc. C*, 2009 (1965).

(11) Stirring at 25° was continued for 12 hr in the methyl iodide quenching procedure to ensure complete dimethylation.

(12) Only those electrophiles which are highly reactive in S$_N$2 reactions (*e.g.*, methyl iodide and benzyl bromide) react successfully with enolate **2**.

(13) α,α'-Dimethyl ketones can be formed from ketones *via* 2-*n*-butylthiomethylene ketone intermediates: R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615, 1620 (1962); see also R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, **93**, 1027 (1971).

(14) G. Stork and P. Hudrlick, *J. Amer. Chem. Soc.*, **90**, 4462 (1968).

(15) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, in press.

(16) A small amount of parent ketone was also observed; addition of excess methyl iodide to cyclohexanone enolate **2** (R = Bu) unexpectedly produced very little methylated cyclohexanone.

(17) I. J. Borowitz, E. W. R. Casper, R. K. Crouch, and K. C. Yee, *J. Org. Chem.*, **37**, 3873 (1972).

(18) *tert*-Butoxylithium was prepared under nitrogen by the dropwise addition of 1.00 equiv of *n*-butyllithium in pentane to dry *tert*-butyl alcohol in tetrahydrofuran. Solutions of *tert*-butoxylithium ($\sim$1.0 *M*) could be stored under nitrogen at 0° for up to 5 days without significant discoloration or loss of reactivity. *tert*-Butoxypotassium could not be used in place of *tert*-butoxylithium for preparation of alkoxy(alkyl)cuprates(I).

(19) This was a 90:10 mixture of *cis*- and *trans*-2,6-dibromocyclohexanones which had been prepared according to the procedure of D. Q. Quan, *C. R. Acad. Sci.*, 267, 1074 (1968).

(20) L. Schmerling, *J. Amer. Chem. Soc.*, **69**, 1121 (1947).

(21) See, for example, G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Amer. Chem. Soc.*, **94**, 5106 (1972).

(22) Sonneborn Foundation Fellow, 1972–present.