Tetrahedron Vol. 35, pp. 1183 to 1189
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0040-4020/79/0501-1183/$02.00/0

ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS—VI[1,2]

A MECHANISTIC STUDY OF THE CONJUGATE ADDITION OF ORGANOCUPRATE REAGENTS TO α,β-UNSATURATED KETONES

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(*Received in UK 26 October 1978*)

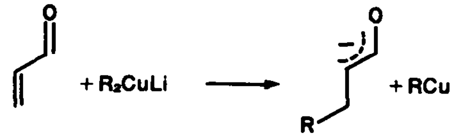
Abstract—Organocuprate conjugate addition reactions involve an electron transfer process without the production of any longlived paramagnetic intermediate species. The reduced organic substrate can be trapped by internal displacement, and from studies of the reaction stoichiometry, a mechanism involving an organocopper(III) intermediate is proposed.

The preference for conjugate addition in reactions of organocuprates (R$_2$CuLi)[3] with α,β-unsaturated ketones (Scheme 1) has been widely exploited in organic synthesis.[4] The mechanism of this reaction has received some attention[5] however, to date, a comprehensive mechanism has not evolved. We were interested in examining the stereochemistry of organocuprate conjugate additions, and during this study became involved in consideration of several mechanistic features of the reaction. Herein we report the results of this involvement.

The most notable features of the conjugate addition with R$_2$CuLi are that the reaction produces an enolate anion[6] as initial product and the stereochemistry of the migrating alkyl group (R in R$_2$CuLi) is retained.[7] Organocuprates are relatively unreactive towards saturated carbonyl compounds and consideration of these results lead to the proposal[5] of an electron transfer process occurring during conjugate addition. A relationship between the success of conjugate addition and the ability of the unsaturated ketone to accept electrons, as measured by reduction potentials (E_{red}), has evolved which is in accordance with the electron transfer mechanistic concept.

One-electron transfer from R$_2$CuLi to α,β-unsaturated ketones would lead to radical anions, which have established properties, and formally organocopper(II) species. The formation of radical anions in mixtures of R$_2$CuLi and α,β-unsaturated ketones has been demonstrated[8] using a stereochemical probe and we attempted to obtain direct evidence for paramagnetism in these mixtures.

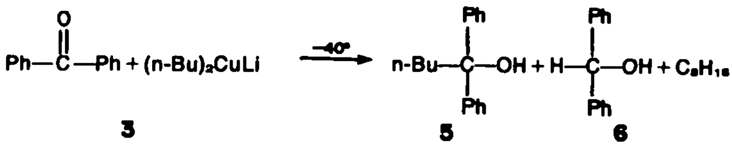
4-Cholesten-3-one **1** reacts with Me$_2$CuLi at 0° to give 5β-methylcholestan-3-one **2** in high yields.[9] Addition of an ethereal solution of **1** to ethereal Me$_2$CuLi at −130° gave a bright orange solution. Hydrolysis of an aliquot at −130° gave only unreacted **1**. On warming the orange solution to *ca.* −80° a rapid precipitation of yellow MeCu was observed and **2** was isolated in high yield. Repetition of this sequence in the probe of an ESR spectrometer gave no detectable signals for any paramagnetic species. It has been shown previously[10] that it is unlikely that R$_2$CuLi and the C=C double bond of the α,β-unsaturated CO system form a coordination complex, as the conjugate addition reaction is not retarded by phosphines nor pyridine which would be expected to compete with the unsaturated CO compound for coordination sites on copper. There is also no evidence for a Cu(I)-ketone complex, and hence the initial reaction of R$_2$CuLi and substrate would appear to involve a charge transfer complex.[11]



Scheme 1.

In an attempt to determine if an electron transfer process is involved in these reactions, **1** was reacted with Me$_2$CuLi in the presence of a series of nitro compounds which reportedly[12] inhibit electron transfer processes. When a mixture of **1** and 10 mole % of 1,5-dinitronaphthalene was added to Me$_2$CuLi a purple solution was formed rapidly. Work up gave only unreacted **1**. Repetition with nitrobenzene or 2-chloro-2-nitropropane gave similar results. This inhibition of Me$_2$CuLi conjugate addition to **1** is presumably caused by the organometallic reagent being preferentially oxidized by the nitro compounds.[13]

The concept of R$_2$CuLi reactions proceeding by electron transfer lead to the possibility of reaction with other easily reduced carbonyl compounds. Accordingly benzophenone **3** was found to react with Me$_2$CuLi at 0° and gave 1,1-diphenylethanol **4**. A similar reaction at −78° gave a red solution from which **3** was recovered unchanged. Reaction of (n-Bu)$_2$CuLi with **3** at −40° gave a mixture of 1,1-diphenyl-1-pentanol **5** and benzhydrol **6** in 32% and 68% yield respectively (based on amount of **3** consumed) and n-octane (Scheme 2). These results are consistent with an electron transfer process proceeding via a charge transfer complex. At the time this work was being pursued a report appeared of a comprehensive investigation of the reaction of Me$_2$CuLi with diaryl ketones[11] and our results and interpretations are in agreement with this report. In an effort to investigate the nature of the oxidized organocopper species resulting from electron transfer to **3**, the radical trap 2,4,6-tri-t-butylnitrosobenzene **7**[14] was added to a solution of



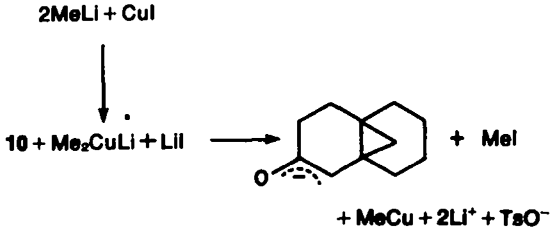
Scheme 2.

Me$_2$CuLi and 3. ESR examination of the resulting red solution showed a spectrum consistent with the formation of 8 which can be explained[15] as resulting from electron transfer to 7 (Scheme 3). Hence the electron transfer properties of R$_2$CuLi systems are well established.

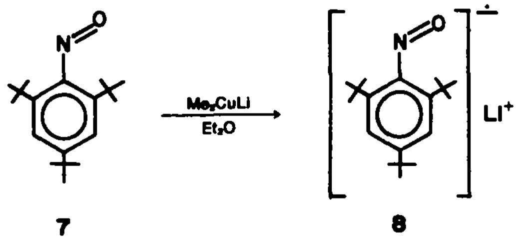
Another feature of R$_2$CuLi conjugate addition reactions is the necessity for a CO group to be in an accessible position. This is shown by the lack of reactivity of R$_2$CuLi with easily reducible non-CO substrates[11] e.g. anthracene, and we observed no reaction between Me$_2$CuLi and 5-cholesten-7-one 9, a compound expected to have a comparable E_{red} to 1[5] but considerably more steric hindrance at the CO oxygen.

The inability to directly detect intermediates resulting from electron transfer in the reactions of R$_2$CuLi promoted possibility of trapping a reduced form of the unsaturated substrate. Electron transfer to an α,β-unsaturated ketone must result in increased electron density on the unsaturated system and, in particular, the β-carbon now becomes a site for electrophilic attack irrespective of the nature of the intermediate formed. Systems were therefore examined which could efficiently trap any incipient β-carbanionic species. Keto tosylate 10 has been reported[16] to react intramolecularly under similar circumstances in metal/ammonia reduction studies, thus 10 was reacted with Me$_2$CuLi and was found to give 11 in 96% yield. The structure for 11 followed from spectroscopic analysis, literature data, and by reaction on acid treatment to give octalone 12. The enolate nature of the initially formed product was shown by the isolation of 13 from the reaction after treatment with acetic anhydride (Scheme 4). The rationale for these results is that during the reaction the β-carbon does indeed develop anionic character which is effectively trapped intramolecularly.

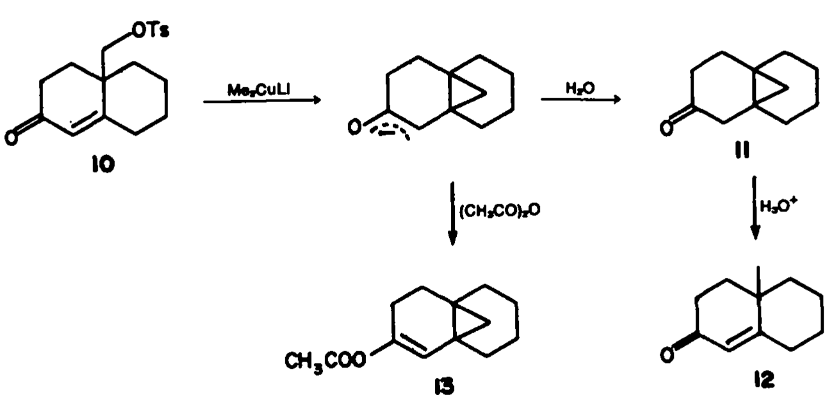
R$_2$CuLi conjugate addition reactions are routinely carried out with excess reagent in order to maximize the yield of the organic product. This procedure is generally adopted because of the thermal instability of many organocuprates. Using the relatively stable Me$_2$CuLi, prepared from carefully purified reagents, and a 1:1 copper-substrate stoichiometry we have been able to achieve high yields of conjugate addition products. Reaction of 10 with 1.1 equivalent of Me$_2$CuLi followed by acetic anhydride gave 13 in 78% yield. In Me$_2$CuLi conjugate addition reactions one of the Me groups is transferred to the (reduced) α,β-unsaturated ketone and the other Me group remains attached to copper, but in the internal trapping reaction transfer of Me group is not observed. Accordingly, an examination of the fate of the Me group was undertaken. Reaction of 10 with Me$_2$CuLi gave a solution which, after hydrolysis, was found to contain iodomethane in 86% yield. Standard experiments showed that solutions of Me$_2$CuLi and the reaction mixture from the conjugate addition of Me$_2$CuLi to 12 contained insignificant amounts of iodomethane. From these results the stoichiometry for the reaction is:



This implies that a nett transfer of two electrons per copper is occurring producing a formally organocopper(III) species which, being electrophilic, reacts with the nucleophilic iodide ion, present in the solution from



Scheme 3.



Scheme 4.

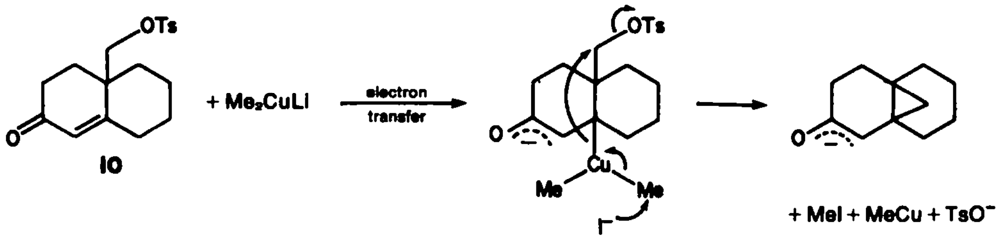
the preparation of Me_2CuLi, to give the observed iodomethane product.

These results do not provide evidence in favour of R_2Cu^+ over R_2CuR^1 nor any intermediate partially complexed organocopper(III) species and Scheme 5 presents an interpretation of the results which involves a polarized β-C–Cu bond. The production of an isolated Me_2Cu^+ species would appear unlikely as this would require the concurrent conversion of the α,β-unsaturated ketone into a dianion, a process expected to be energetically improbable.[5]

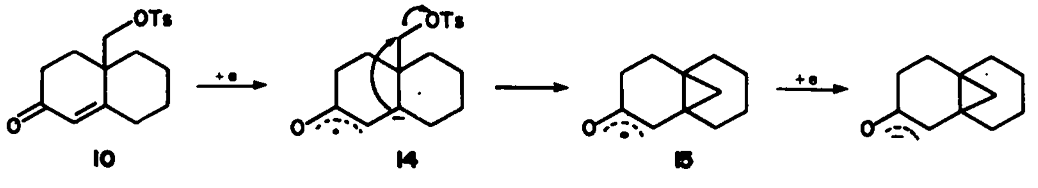
The overall two-electron transfer process can be envisaged as occurring by two one-electron transfer steps or by a single two-electron transfer. From our earlier results, a one-electron transfer process leading to a radical anion must be rapidly followed by a second step leading to an organocopper(III) intermediate. With **10** it is possible to have tosylate elimination from the radical anion **14** followed by reduction of the tricyclic radical **15** to enolate (Scheme 6). To examine this possibility, **10** was reacted with triphenylmethyllithium, reportedly[17] a good one-electron transfer agent, but **11** was not observed in the reaction products. This result indicates either the elimination does not occur at the radical anion stage or, alternatively, the triphenylmethyl anion is not a sufficiently powerful electron donor to induce electron transfer to **10**. Comparison of the measured[5] E_{red} value for triphenylmethyl anion (−1.3 V) and the calculated E_{red} for **10** (−2.2 V) would indicate that electron transfer is indeed energetically prohibitive but triphenylmethyllithium has been observed[18] to undergo conjugate addition to 2-cyclohexen-1-one (E_{red} = −2.1 V), presumably via an electron transfer mechanism, so conclusions based on relative E_{red} values in the case of triphenylmethyllithium would appear to be tenuous. Other observations[17] with triphenylmethyl anion have confirmed this view and the reactions appear to be also effected by steric hindrance at the β-carbon. Knowledge of whether the tosylate departs after the addition of one or two electrons to **10** has obvious important ramifications for the mechanism of R_2CuLi conjugate additions and an electrochemical study of this reaction is being undertaken at present.

It was also found that **16** reacted readily with Me_2CuLi to give tricyclic ketone **17**.† The structure of **17** followed routinely from spectroscopic analysis and by conversion on acid treatment to octalone **12**. Treatment[19] of **17** with D_2SO_4 in CH_3OD gave **12**-1,3,3,5,8,8-d_6 which, on back exchange, gave **12**-1,5-d_2 as shown by ^{13}C NMR. Reaction of Me_2CuLi or $(n\text{-}Bu)_2CuLi$ with the mesylate **18** also gave **17** in good yield, indicating that the displacement did not arise from initial electron acceptance by the aromatic tosyl group in **16**. These products can be accounted for by an intermediate **19** (Scheme 7) similar to that previously proposed for the formation of **11**. No reaction was observed with Me_2CuLi and **20**, excluding the possibility of prior formation of mixed cuprate **21** followed by intramolecular conjugate addition.

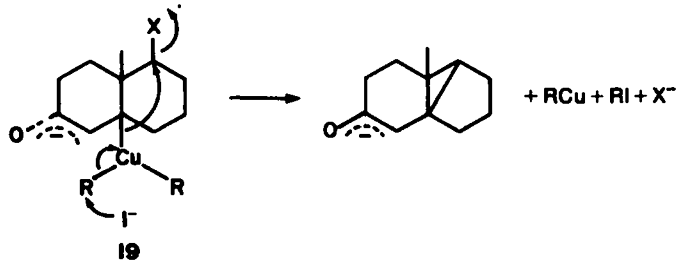
Reaction of the unstable monocyclic keto tosylate **22**, produced from thallium(III) nitrate dethioacetalisation of **23**, with Me_2CuLi gave a mixture of products containing mainly **24** and minor amounts of **25** and **26**. Presumably the conformational flexibility in the monocyclic system enables conjugate addition to compete effectively with the internal trapping alternative.



Scheme 5.



Scheme 6.



Scheme 7.

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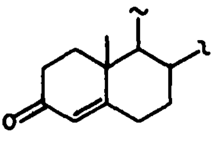
†Structure **17** represents one enantiomer (1R,5R,6R) of a racemic mixture.

Reaction of Wieland Miescher ketone 27 with lithium/ammonia has been reported[20] to give the cyclopropanol 28. Reaction of 27 with Me_2CuLi gave the conjugate addition product 29 in high yield with no evidence of 28. A possible explanation for this observation is that internal capture now requires a reversible aldol-type reaction whereas the previously successful internal trapping reactions involved essentially irreversible alkylations.

Ruden *et al.*[21] reported the reaction of Me_2CuLi with δ-substituted α,β-unsaturated ketones, including 10, gave internal displacement products. These results are consistent with the creation of a nucleophilic β-carbon in the α,β-unsaturated ketone system and, although the authors preferred a one-electron transfer sequence with displacement occurring at the radical anion stage because "a more comprehensive mechanism could be drawn", an overall two-electron transfer from copper was not excluded.

In summary, these results further demonstrate that organocuprates are efficient electron transfer reagents and conjugate addition reactions involve the acceptance of considerable electron density by the substrate which in turn reacts with the oxidized copper species to give the observed products. A possible mechanism which is consistent with the known facts is given (Scheme 8) involving a formally organocopper(III) species being created at the β-carbon following an electron transfer process. Reductive elimination of the organocopper(III) intermediate with retention of configuration at R and at the β-carbon gives the enolate product.

Organocopper(III) intermediates have been previously postulated in several other reactions.[22] Extensive experimental and theoretical studies of the reductive elimination of trialkylgold(III) compounds have been reported recently and the analogy of those results with the organocopper(III) situation has been noted.[23] The implication of Scheme 8 is that the stereochemistry of the product is determined by the stereochemistry of the organometallic intermediate and this feature has received some theoretical substantiation.[24]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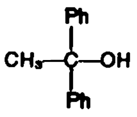

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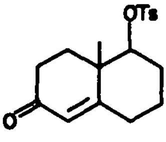

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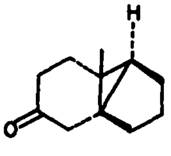

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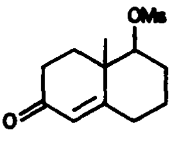

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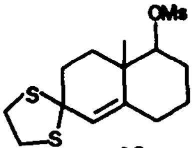

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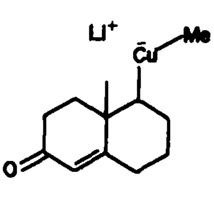

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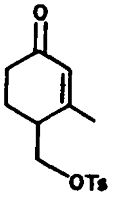

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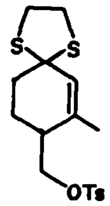

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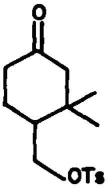

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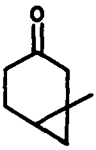

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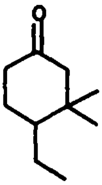

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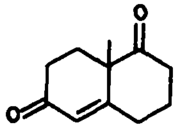

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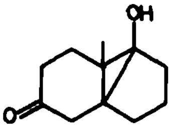

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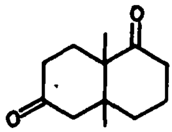

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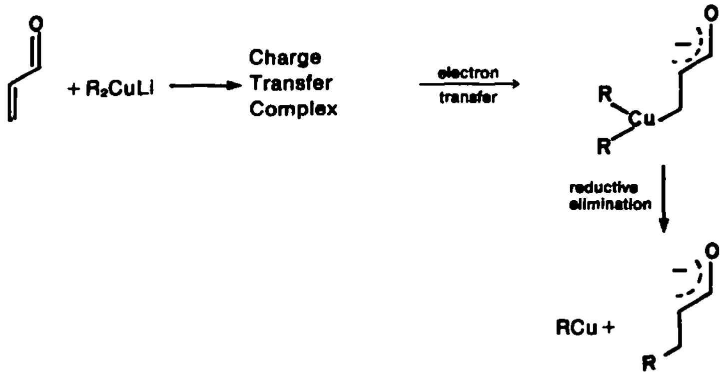
EXPERIMENTAL

For a general description of experimental procedures see Part V.[1] 10 - *Tosyloxymethyl* - 1(9) - *octal* - 2 - *one* (10),[16] cis - 10 - *methyl* - 5 - *tosyloxy* - 1(9) - *octal* - 2 - *one* (16)[25] and cis - 5 - *mesyloxy* - 10 - *methyl* - 1(9) - *octal* - 2 - *one* (18)[26] were prepared by literature methods.



Scheme 8.

Reaction of 4-cholesten-3-one 1 *with* Me$_2$CuLi

(i) A soln of 1 (0.5 g, 1.3 mmole) in ether (5 ml) was added to Me$_2$CuLi (2.6 mmole) in ether (20 ml) at 0°. After stirring the yellow mixture at 0° for 20 min 10% NH$_4$Cl aq (40 ml) was added and the mixture worked up in the usual manner to give *5β-methylcholestan-3-one* 2 (0.49 g, 94%); m.p. 86–88° (lit.[9] 90–90.5°). IR ν_{max} 1706 (C=O) cm^{-1}. ^{1}H NMR δ 0.69 (s, 3H, 18–CH$_3$), 0.87 (d, J = 7 Hz, 6H, 26 and 27–CH$_3$), 0.87 (s, 3H, 5–CH$_3$), 0.91 (s, 3H, 19–CH$_3$), 0.92 (d, J = 7 Hz, 3H, 21–CH$_3$).

(ii) A soln of 1 (0.5 g) in ether (10 ml) was slowly added to a soln of Me$_2$CuLi (2.6 mmole), preformed at 0°, in ether (20 ml) at −130° (liquid N$_2$-pentane). A bright orange soln formed and after 5 min an aliquot was hydrolysed with EtOH, poured into 10% NH$_4$Cl aq and worked up in the usual way to give unreacted starting material. The remainder of the soln was warmed slowly and at *ca.* −80° the orange colour was discharged and a thick yellow ppt formed. At −60° 10% NH$_4$Cl aq was added and the mixture worked up in the usual way to give a mixture containing mainly 2 (tlc, IR) together with a small amount of unreacted starting material.

(iii) An ether soln of 1 (0.2 ml, 0.1 M) was frozen with liquid N$_2$ at the bottom of an ESR tube fitted with a rubber septum cap. An ether soln of Me$_2$CuLi (0.2 ml, 0.1 M), preformed at 0°, was introduced to the ESR tube and frozen on top of the soln of 1. The tube was warmed to −100° in the probe of the ESR spectrometer and the layers mixed to give an orange soln. The tube and soln were slowly warmed at a rate of *ca.* 20° hr^{-1} and the ESR spectrum, centred at 3390 Gauss, was rapidly scanned with high gain over a 1000 Gauss range. At −80° to −75° a yellow ppt was formed but no ESR signal was observed. Hydrolysis of the mixture gave 2.

Reaction of 1 *with* Me$_2$CuLi *in the presence of nitro compounds*

(i) A mixture of 1 (0.5 g) and 1,5-dinitronaphthalene (0.038 g) in ether (5 ml) was added to Me$_2$CuLi (2.6 mmole) in ether (20 ml). A purple soln rapidly developed and after 10 min 10% NH$_4$Cl aq (40 ml) was added. The mixture was worked up in the usual way to give unreacted 1.

(ii) A mixture of 1 (0.5 g) and nitrobenzene (0.16 g) in ether (5 ml), was added to Me$_2$CuLi (2.6 mmole) in ether (2 ml). A brown colour developed which rapidly dispersed and a voluminous yellow ppt of MeCu formed. After 10 min 10% NH$_4$Cl aq (40 ml) was added and the ether layers separated. Glc analysis of the ether soln showed that nitrobenzene was recovered in 85% yield. Evaporation of the solvent gave unreacted 1.

(iii) Repetition of (ii) using 2-chloro-2-nitropropane instead of nitrobenzene gave a voluminous yellow ppt. After 10 min 10% NH$_4$Cl aq (40 ml) was added and the ether layer separated. Glc analysis of the ether soln showed 2-chloro-2-nitropropane (80%) and 2-methyl-2-nitropropane (7%). Evaporation of the solvent gave unreacted 1.

Reaction of benzophenone 1 *with* Me$_2$CuLi

(i) A soln of 3 (0.23 g, 1.3 mmole) in ether (5 ml) was added to Me$_2$CuLi (2.5 mmole) in ether (20 ml) at 0° to give a red brown soln. After 30 min a voluminous yellow ppt had developed and 10% NH$_4$Cl aq (50 ml) was added and the mixture was worked up in the usual way to give, after separation by plc (benzene), unreacted 3 (0.082 g) (IR, tlc) and *1,1-diphenylethanol* 4 (0.145 g); m/e 198 (M$^+$), 196, 178. IR ν_{max} 3410 (O–H), 1595 (aromatic), 1060 (C–O) cm^{-1}, identical with an authentic sample.

(ii) Repetition of (i) at −78° gave, after addition of 3, a red brown soln. After 1 hr at −78° 10% NH$_4$Cl aq was added and the mixture worked up in the usual way to give unreacted starting material.

Reaction of benzophenone 3 *with* Me$_2$CuLi

A soln of 3 (0.45 g, 2.5 mmole) in ether (5 ml) was added to a black soln of (n-Bu)$_2$CuLi (5 mmole) in ether (50 ml) at −40°. After 2 hr at −40° a metallic mirror had formed and 10% NH$_4$Cl aq (100 ml) was added. The ether layer was then separated in the usual way. Glc analysis of the organic layer showed octane (14% based on n-BuLi) and the mixture gave, after evaporation of the solvent and separation by plc (30% E/H), 3 (0.15 g); *1,1-diphenyl-1-pentanol* 5 (0.10 g); m/e 240 (M$^+$). IR ν_{max} 3390 (O–H), 1595 (aromatic), 1030 (C–O) cm^{-1}; and *benzhydrol* 6 (0.16 g), identical with authentic samples.

Reaction of 3 *with* Me$_2$CuLi *in the presence of 2,4,6-tri-t-butylnitrosobenzene* 7

An ether soln (0.2 ml) of 3 (0.1 M) and 7 (0.1 M) was frozen with liquid N$_2$ in the bottom of an ESR tube. An ether soln (0.2 ml) of Me$_2$CuLi (0.1 M) was added and frozen over the lower layer. The tube was placed in the probe of the ESR spectrometer held at −100°. The layers were mixed by agitation to give a brick red soln. The ESR spectrum of this soln at −60° (a(1N) = 12.0G, a(Li) = 1.0G, a(2H) = 1.2G) was assigned[15] to a *lithium 2,4,6-tri-t-butylnitrosobenzenide ion pair* 8. The spectrum remained unaltered from −80° to −35° but above −35° no signals were observed. Addition of EtOH at −40° and work up in the usual way gave a mixture of 3, 4 and 7.

Reaction of 5-cholesten-7-one 9 *with* Me$_2$CuLi

(i) A soln of 9[27] (0.17 g, 0.44 mmole) in ether (5 ml) was added to Me$_2$CuLi (0.9 mmole) in ether (10 ml) at 0°. After 30 min a yellow ppt had formed and the mixture was poured into 10% NH$_4$Cl aq and worked up in the usual way to give unreacted starting material.

(ii) Repetition of (i) using Me$_2$CuLi in toluene (10 ml) instead of ether gave, after work up in the usual way, unreacted starting material.

Reaction of 10-tosyloxymethyl-1(9)-octal-2-one 10 *with* Me$_2$CuLi

(i) A soln of 10 (0.1 g, 0.30 mmole) in ether (10 ml) was added to Me$_2$CuLi (1.5 mmole), preformed at 0°, in ether (10 ml) at −78°. A yellow ppt rapidly formed and, after stirring at −78° for 20 min, 10% NH$_4$Cl aq (30 ml) was added and the mixture worked up in the usual way to give *tricyclo* [4.4.1.0^{1,6}] *undecan-3-one* 11,[16] (0.047 g, 96%); m/e 164 (M$^+$). ν_{max} 1710 (C=O) cm^{-1}. ^{1}H NMR δ 0.42 and 0.53 (AB System, J$_{AB}$ = 6 Hz, 2H, cyclopropyl CH$_2$), 2.52 (s, 2H, C–2 CH$_2$).

(ii) Repetition of (i) except using 1 equiv of Me$_2$CuLi and adding Ac$_2$O (0.2 ml) before hydrolysis gave, after work up in the usual way, *3-acetoxytricyclo* [4.4.1.0^{1,6}] *undec-2-ene* 13 (0.048 g, 78%) as an oil b.p. 90°/0.04 mm; m/e 206 (M$^+$), 178, 164, 153.8 (M*, 206–178), 136, 112.7 (M*, 164–136) IR ν_{max} 1750 (CH$_3$COO), 1675 (C=C) cm^{-1}. ^{1}H NMR δ 0.49 (unresolved doublet, W$_{1/2}$ = 3.4 Hz, 2H, cyclopropyl CH$_2$), 2.06 (s, 3H, CH$_3$), 5.48 (d, J = 1.5 Hz, 1H, C=CH). (Found C, 75.2; H, 9.0; $C_{13}H_{18}O_2$ requires: C, 75.6; H, 8.8%).

(iii) A soln of 10 (0.12 g, 0.36 mmole) in ether (15 ml) was added to Me$_2$CuLi (0.40 mmole), preformed at 0°, in ether (15 ml) at −78°. After 10 min 10% NH$_4$Cl aq was added, the layers separated and made up to 50.0 ml in a standard volumetric flask. Analysis by a modified Zeisel procedure[28] gave iodomethane (0.044 g, 86%). The solvents were evaporated from the soln and the residue contained 11 (88%) and unreacted 10 (12%) determined by ^{1}H NMR.

Reaction of 11 *with acid*

A mixture of 11 (0.03 g) and conc. H$_2$SO$_4$, AcOH and water (4 ml, 1:2:2) was refluxed for 6 hr.[16] The mixture was poured into water, extracted with ether (3 × 10 ml) and the combined ether extracts washed with NaHCO$_3$ aq (sat), water and dried (Na$_2$SO$_4$). Evaporation of the solvents gave *10-methyl-1(9)-octal-2-one* 12 (0.012 g) identical with an authentic sample.

Reaction of cis-*10-methyl-5-tosyloxy-1(9)-octal-2-one* 16 *with* Me$_2$CuLi

A soln of 16 (0.28 g, 0.84 mmole) in CH$_2$Cl$_2$ (2.5 ml) was added to Me$_2$CuLi (3.7 mmole) in ether (30 ml) at 0°. An initial red colour was discharged within 20 sec and a voluminous yellow ppt was formed. After stirring for 15 min at 0° 10% NH$_4$Cl aq (50 ml) was added and the mixture worked up in the usual way to give, after purification by plc (70% E/H), (1RS, 5RS, 6RS) *6-methyltricyclo* [4.4.0.0^{1,5}] *decan-9-one* 17 (0.095 g, 70%); m/e 164 (M$^+$). IR ν_{max} 1700 cm^{-1}. ^{1}H NMR δ 1.07 (s, 3H, CH$_3$), 1.1–2.2 (m, 11H), 2.63 (s, 2H, C–10 CH$_2$). ^{13}C NMR δ 18.9 (q), 22.8 (s), 25.8

(t), 26.6 (t), 29.6 (d), 30.7 (t), 32.4 (t), 32.4 (s), 36.6 (t), 43.6 (t), 212.0 (s). (Found C, 80.5; H, 9.8. $C_{11}H_{16}O$ requires: C, 80.4: H, 9.8%).

Reaction of 17 with acid

A soln of 17 (0.05 g) and conc. H_2SO_4 (0.9 ml) in MeOH (2.5 ml) was prepared at 0°. After heating to 85° for 30 min, the mixture was poured into ice and worked up in the usual way to give 12 (0.038 g) identical with an authentic sample.

Repetition using anhyd MeOD and D_2SO_4 gave 12-1,3,3,5,8,8-d_6; *m/e* 170 (M^+). IR ν_{max} 2200 (C–D), 1670, 1610 (C=C–C=O) cm^{-1}.

A mixture of conc. H_2SO_4 and water (1 ml, 1:1) was added to 12-1,3,3,5,8,8-d_6 (0.03 g) in MeOH (2 ml) at 0°. After stirring overnight at room temp. the mixture was poured into water and worked up in the usual way to give 12-1,5-d_2 (0.02 g); *m/e* 166 (M^+). IR ν_{max} 2200 (C–D) cm^{-1}.

The ^{13}C NMR spectrum of 12-d_6 showed peaks at δ 32.8, 34.0, 41.6 and 123.9 with lower intensities compared with the ^{13}C NMR spectrum of 12. These peaks have been assigned[29] to positions 8,3,5 and 1 respectively. Similarly the ^{13}C NMR spectrum of 12-d_2 showed lower intensity peaks at δ 41.6 and 123.9 compared with 12 corresponding to deuteration at positions 5 and 1 respectively.

Reaction of cis-5-*mesyloxy*-10-*methyl*-1(9)-*octal*-2-*one* **18** *with organocuprates*

(i) A soln of **18** (0.26 g, 1.0 mmole) in CH_2Cl_2 (2 ml) was added to Me_2CuLi (3.0 mmole) in ether (30 ml) at 0° resulting in an immediate yellow ppt. After stirring for 15 min at 0° 10% NH_4Cl aq (50 ml) was added and the mixture worked up in the usual way to give 17 (0.162 g, 97%) identical with an authentic sample.

(ii) Repetition of (i) with $(n\text{-}Bu)_2CuLi$ at −40° gave a similar result.

Preparation of cis-5-*mesyloxy*-10-*methyl*-1(9)-*octal*-2-*one ethylene thioacetal* **20**

$NaBH_4$ (0.1 g) in EtOH (15 ml) was added to 9 - methyl - 5(10) - octalin - 1,6 - dione - 6 - ethylene thioacetal[30] (0.4 g) in THF (2 ml). After 10 min the mixture was poured into dil HCl and worked up in the usual way to give cis - 5 - *hydroxy* - 10 - *methyl* - 1(9) - *octal* - 2 - *one ethylene thioacetal* (0.4 g), m.p. 114–115° (pentane); *m/e* 256 (M^+). IR ν_{max} 3320 (O–H), 1040 (C–O) cm^{-1}. ^1H NMR δ 0.97 (s, 3H, CH_3), 3.25 (s, 4H, SCH_2CH_2S), 3.30 (m, 1H, 5–H), 5.54 (s, 1H, C=CH). ^{13}C NMR δ 16.5 (q, CH_3), 24.2 (t, C–7), 30.3 (t, C–6), 31.0 (t, C–8), 35.5 (t, C–4), 37.4 (t, C–3), 39.3 (t, SCH_2), 39.5 (s, C–10), 39.7 (t, SCH_2), 65.3 (s, C–2), 78.2 (d, C–5), 126.4 (d, C–1) 143.1 (s, C–9). (Found C, 60.6; H, 7.9; S, 24.5. $C_{13}H_{20}OS_2$ requires: C, 60.9, H, 7.9, S, 25.0%).

Mesyl chloride (0.17 g) was added to the ethylene thioacetal alcohol (0.34 g) in dry pyridine (4 ml) at 0°. After stirring overnight at room temp. the mixture was poured into dil HCl, extracted with CH_2Cl_2 and the solvent evaporated to give **20** (0.38 g, 85%) as a yellow solid, m.p. 99–100° (MeOH); *m/e* 334 (M^+). IR ν_{max} 1350, 1175, 980 cm^{-1}. ^1H NMR δ 1.11 (s, 3H, CH_3), 3.01 (s, 3H, SO_2CH_3), 3.34 (s, 4H, SCH_2CH_2S), 4.35 (m, $W_{1/2}$ = 16 Hz, 1H, 5–H), 5.67 (s, 1H, C=CH). ^{13}C NMR δ 17.7 (q, 10–CH_3), 23.9 (t, C–7), 28.7 (t, C–6), 30.6 (t, C–8), 35.4 (t, C–4), 37.1 (t, C–3), 38.8 (q, SO_2CH_3), 39.1 (s, C–10), 39.5 (t, SCH_2), 40.0 (t, SCH_2), 64.8 (s, C–2), 88.6 (d, C–5), 126.2 (d, C–1), 140.9 (s, C–9). (Found: C, 50.5; H, 6.9; S, 28.8. $C_{14}H_{22}O_3S_3$ requires: C, 50.3; H, 6.6; S, 28.8%).

Reaction of **20** *with* Me_2CuLi

A soln of **20** (0.33 g, 1 mmole) in CH_2Cl_2 (2 ml) was added to Me_2CuLi (3 mmole) in ether (30 ml) at 0°. After 15 min the mixture was poured into 10% NH_4Cl aq and worked up in the usual way to give **20** (0.32 g) identical with starting material.

Preparation of 3-methyl-4-tosyloxymethyl-2-cyclohexen-1-one 22

Tosyl chloride (1.4 g) in pyridine (6 ml) was added to 4 - hydroxymethyl - 3 - methyl - 2 - cyclohexen - 1 - one ethylene thioacetal[31] (1.0 g) in dry pyridine (20 ml) at 0°. After standing at room temp. overnight the mixture was poured into water (200 ml), ether extracted (4×20 ml), and the combined ether extracts were washed with dil HCl, water, then dried ($MgSO_4$).

Evaporation of the solvents gave 3 - *methyl* - 4 - *tosyloxymethyl* - 2 - *cyclohexen* - 1 - *one ethylene thioacetal* 23 (1.51 g, 89%), as a thick oil. ^1H NMR δ 1.65 (s, 3H, 3–CH_3), 2.46 (s, 3H, Ar–CH_3), 3.27 (s, 4H, SCH_2CH_2S), 3.94 (m, 2H, CH_2O), 5.61 (s, 1H, 2–H), 7.33 and 7.78 (AB system, J_{AB} = 8 Hz, 4H, aromatic H). ^{13}C NMR δ 21.4 (2q, Ar–CH_3 and 3–CH_3), 25.1 (t, C–5), 37.7 (t, C–6), 37.7 (d, C–4), 39.7 (2t, SCH_2), 64.7 (s, C–1), 70.4 (t, CH_2O), 127.7 (2d, aromatic C), 129.0 (s, C–3), 129.7 (2d, aromatic C), 130.7 (d, C–2), 132.5 (s, $\check{C}_{Ar}$–CH_3), 144.6 (s, SO_3C).

Thallium(III) nitrate (0.89 g) in MeOH (10 ml) was added to the ethylene thioacetal tosylate 23 (0.74 g) in MeOH–THF (15 ml : 5 ml).[32] After 15 min CH_2Cl_2 (20 ml) was added and the white thallium(I) nitrate ppt removed by filtration. The filtrate was washed with water, dried ($MgSO_4$), and evaporated to give 22 (0.56 g) as an unstable brown oil. IR ν_{max} 1660 (C=O), 1620 (C=C), 1595 (Ar) cm^{-1}. ^1H NMR δ 1.95 (s, 3H, 3–CH_3), 2.47 (s, 3H, Ar–CH_3), 4.16 (d, J = 5 Hz, 2H, CH_2O), 5.89 (s, 1H, 2–H), 7.33 and 7.78 (AB system, J_{AB} = 8 Hz, 4H, aromatic H). ^{13}C NMR δ 21.7 (q, $ArCH_3$), 22.6 (q, 3–CH_3), 24.9 (t, C–5), 34.0 (t, C–6), 39.2 (d, C–4), 69.3 (t, CH_2O), 127.8 (2d, aromatic C), 129.2 (d, C2), 129.9 (2d, aromatic C), 132.5 (s, C_{Ar}–CH_3), 145.1 (s, SO_3C), 158.6 (s, C–3), 197.9 (s, C–1).

Reaction of 22 with Me_2CuLi

A soln of 22 (0.53 g, 1.8 mmole) in CH_2Cl_2 (5 ml) was added to Me_2CuLi (7.9 mmole) in ether (65 ml) at 0° and a voluminous yellow ppt was formed. After 30 min the yellow mixture was poured into 10% NH_4Cl aq (150 ml) and, after work up in the usual way, gave a brown oil (0.22 g). Separation by plc (4% E/H) gave, in order of increasing R_F: 3,3 - *dimethyl* - 4 - *tosyloxymethylcyclohexanone* 24[31] (0.105 g); *m/e* 310 (M^+) 138 (M^+–TsOH), 61.4 (M^*, 310–138). IR ν_{max} 1712 (C=O) cm^{-1}. ^1H NMR δ 0.78 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.45 (s, 3H, Ar–CH_3), 4.05 (m, 2H, CH_2O), 7.36 and 7.81 (AB system, J_{AB} = 7 Hz, 4H, aromatic H). ^{13}C NMR δ 21.5 (2q), 25.5 (t), 29.6 (q), 31.7 (s), 39.8 (t), 44.4 (d), 55.7 (t), 70.7 (t), 127.8 (2d), 129.9 (2d), 132.9 (s), 144.8 (s), 209.9 (s); and a mixture (0.062 g) of 1 - *methylbicyclo* [4.1.0] *heptan* - 3 - *one* 25; *m/e* 124 (M^+). IR ν_{max} 1710 (C=O) cm^{-1}. ^1H NMR δ 0.41 and 0.48 (AB system, J_{AB} = 6 Hz, 2H, cyclopropyl CH_2), 1.13 (s, 3H, CH_3), 2.49 (d, J = 2 Hz, C–2 CH_2); and 4 - *ethyl* - 3,3 - *dimethylcyclohexanone* 26; *m/e* 154 (M^+). IR ν_{max} 1710 (C=O) cm^{-1}. ^1H NMR δ 0.79 (s, 3H, CH_3), 1.00 (t, J = 6 Hz, 3H, ethyl CH_3); 1.03 (s, 3H, CH_3). Comparison of the integrals of the peaks at δ 2.49 and δ 0.79 showed the ratio of 25 and 26 was 3:2.

Reaction of **10** *with triphenylmethyllithium*

Triphenylmethyllithium was prepared at 0° by the addition of n-BuLi (0.3 ml, 2.4 M) to triphenylmethane (0.165 g, 0.68 mmole) in THF (11 ml). After 30 min a solution of **10** (0.085 g, 0.25 mmole) in THF (5 ml) was added to the deep red triphenylmethyllithium soln. After 3 hr at 0° the red colour had been discharged and the mixture was worked up as usual to give a dark brown residue (0.238 g) which contained triphenylmethane and 10 - hydroxymethyl - 1(9) - octal - 2 - one, identical with authentic samples.

Reaction of 9-methyl-5(10)-octalin-1,6-dione 27 with Me_2CuLi

A soln of *27* (0.2 g, 1.1 mmole) in ether (5 ml) was added to Me_2CuLi (3.6 mmole) in ether (25 ml) at 0°. After stirring at 0° for 30 min, 10% NH_4Cl aq (50 ml) was added and the mixture worked up in the usual way to give 9,10-*dimethyldecalin*-1,6-*dione* 29 (0.18 g, 83%) which sublimed at 80°/0.2 mm; m.p. 147.5–148°; *m/e* 194 (M^+). IR ν_{max} 1685 (C=O) cm^{-1}. ^1H NMR δ 0.99 (s, 3H, CH_3), 1.23 (s, 3H, CH_3). ^{13}C NMR δ 20.9 (q), 21.6 (t), 23.1 (q), 31.3 (t), 34.3 (t), 36.9 (t), 38.6 (t), 44.6 (s), 50.5 (t), 51.5 (s), 209.3 (s), 214.4 (s). (Found: C, 74.0; H, 9.5. $C_{12}H_{18}O_2$ requires: C, 74.2; H, 9.3%).

Acknowledgements—This research has been assisted by grants from the Mellor Research Fund of the University of Otago and from the Research Committee of the University Grants Committee. We thank Miss Irene Teoh for assistance with some experiments and Professors R. Hoffmann and C. L. Liotta for helpful discussions.

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