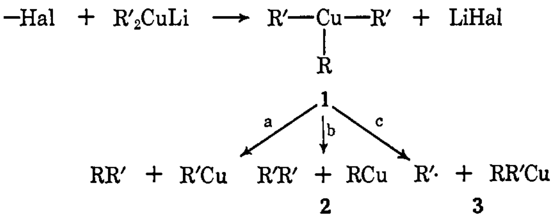
Communications to the Editor

Reaction of δ- and ε-Halo Ketones with Certain Anionic Transition Metal Complexes. A Useful New Cyclization Method

Sir:

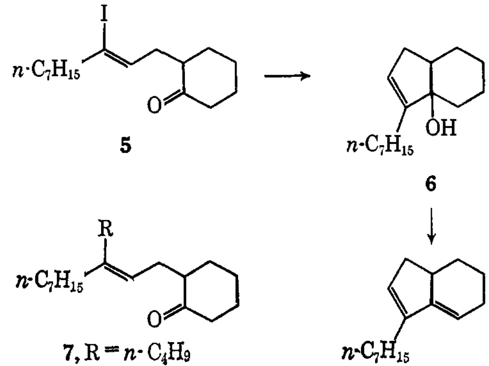
Although the intermolecular addition of an organometallic reagent to a carbonyl group is one of the most powerful and useful synthetic methods in organic chemistry, the intramolecular counterpart has never been developed to a useful level due to the lack of a satisfactory reagent for converting a halo carbonyl compound into a reactive organometallic derivative. This note describes a promising new method for effecting such cyclizations starting with δ- or ε-iodo (or bromo) ketones.

The reaction of di-*n*-butylcopperlithium with alkyl, vinyl, and aryl halides, described previously,[1,2] leads to selective cross coupling or to replacement of halogen by metal, depending upon reaction conditions, of which temperature and solvent are most critical.[1] A possible first step in the reaction is the formation of intermediate 1[3] which can lead to coupling or halogen replacement by metal.



Of crucial importance to the present studies was the observation that the reaction of dialkylcopperlithium reagents with iodides or bromides is fast relative to the reaction with (nonconjugated) ketonic carbonyl groups.[4] These considerations suggested the possibility that halo ketones might undergo cyclization involving the attachment of C_{Hal} to C_{CO} under the influence of anionic copper reagents given the proper circumstances. Verification of this hypothesis has been obtained as follows.

The iodo ketone **5** was synthesized for use as a substrate of the vinylic halide type in the cyclization studies. 3-Iodo-*trans*-2-decen-1-ol[2b] was converted to 1-bromo-3-iodo-*trans*-2-decene (PBr$_3$ in ether at 0°[5]) which when applied to the alkylation of the pyrrolidine enamine of cyclohexanone[6] gave the substrate **5**[7] in 67% yield. Treatment of **5** with 5 equiv of di-*n*-butylcopperlithium[1] in 5.7:1 pentane–ether under argon at 0° for 24 hr[8] led to the formation of the desired cyclization product **6**[7] as a colorless oil in excellent (>90%) yield; only trace amounts of two by-products (**7** and **8**) could be detected by gas chromatographic analysis. Exposure of **6** to acetic acid at 25° for 2 hr produced the diene **9**,[7] $\lambda_{\max}^{\mathrm{EtOH}}$ 242 nm (7000), which as expected underwent hydrogenation (over Pt in HOAc) to a saturated tetrahydro derivative.[7] The conditions cited above were quite critical for efficient cyclization. The use of pure ether, tetrahydrofuran, or dimethoxyethane as solvent in experiments otherwise comparable to that described above produced **6** in yields of only 51, 35, and 50%, respectively, together with substantial amounts of **7** (30–50%) and **8** (5–13%).[9] The use of pentane–ether (4:1) as solvent with reaction temperatures of 0, −25, and −50° afforded **6** in yields of 77, 40, and 30%, respectively, and **7** in yields of 10, 45, and 60%, respectively. The fact that cyclization of **5** to **6** is seen to be remarkably sensitive to solvent and temperature is not surprising in view of a similar dependence previously observed[1] for cross-coupling reactions of di-*n*-butylcopperlithium with halides. The copper reagents R$_2$CuLi with R = methyl, phenyl, or mesityl were ineffective in promoting cyclization of **5**. However, the reagent (5 equiv) prepared from 1,5-dilithiopentane and cuprous iodide (1:1) in tetrahydrofuran–ether (6:1) converted **5** to **6** in 80% yield (3 hr at −20°).



Cyclization reactions of 6-iodo-2-hexanone (**10**)[10] and 7-iodo-2-heptanone (**11**)[11] were also investigated, but it was ascertained that the desired cyclization was

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[1] E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **90**, 5615 (1968).

[2] See also (a) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967); (b) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *ibid.*, **89**, 4245 (1967); (c) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968); and (d) G. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Baske, and H. O. House, *ibid.*, **91**, 4871 (1969).

[3] Perhaps by frontside or backside attack by nucleophilic copper on carbon; see, for example, G. Schrauzer, *Accounts Chem. Res.*, **1**, 97 (1968).

[4] Unpublished results of G. Posner and I. Kuwajima in these laboratories. In addition, it has long been known that the reagent dimethylcopperlithium is unreactive toward Michler's ketone (Gilman test): H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17** 1630 (1952).

[5] J. M. Osbond, *J. Chem. Soc.*, 5270 (1961).

[6] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrel, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

[7] Satisfactory analytical and spectral data were obtained for this intermediate.

[8] A total of 6.70 ml of solvent was used per mmol of the reagent R$_2$CuLi. The black-blue colored reaction mixtures were stirred well. All reactions described herein were performed under a rigorously dry argon atmosphere.

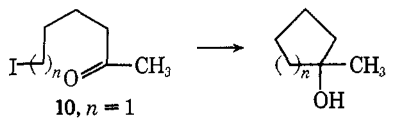
[9] The conversion of **5** to **6** in pure pentane as solvent is extremely slow.

[10] Prepared by the action of sodium iodide in acetone on the corresponding bromide; see E. P. Anderson, J. V. Crawford, and M. L. Sherill, *J. Amer. Chem. Soc.*, **68**, 1294 (1946).

[11] Prepared by reaction of sodium iodide in acetone on the corresponding chloride which was obtained by thermal decomposition of 1-methylcyclohexyl hypochlorite; see (a) J. W. Wilt and J. W. Hill, *J. Org. Chem.*, **26**, 3523 (1961); (b) F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *ibid.*, **28**, 55 (1963).

not promoted efficiently by a number of reagents of type R_2CuLi including R = n-C_4H_9, i-C_4H_9, and CH_3 under a variety of conditions. For example, the reaction of the butyl reagent with **10** in pentane–ether (5.5:1) at 0° for 9 hr produced the cyclic product **12** in only 18% yield. The reagent prepared from cuprous iodide and 1,5-dilithiopentane (1:1) converted **10** to the 1-methylcyclopentanol (**12**) in *ca.* 35% yield (tetrahydrofuran, −20°, 6 hr). In all these instances noncyclic products predominated.

In view of the inefficiency of cyclization of the iodo ketones **10** and **11** by reagents of type R_2CuLi and the occurrence of side reactions such as cross coupling, the behavior of certain anionic transition metal complexes having "fixed" ligands was studied, for example, the anion derived by two-electron transfer to copper phthallocyanine[12] and the ions similarly derived from copper and nickel tetraphenylporphine.[13] Of these reagents the anion prepared by reaction of nickel tetraphenylporphine[14] with 2 equiv of lithium naphthalene in tetrahydrofuran (at 0° under argon) was clearly the most effective; this anion is designated herein as $NiTPP^{2-}$. The reaction of 6-iodo-2-hexanone (**10**) with 3 mol equiv of $NiTPP^{2-}$ in tetrahydrofuran at −50° for 7 hr produced 1-methylcyclopentanol (**12**) in 61% yield.[15] Similarly, 7-iodo-2-heptanone was converted to 1-methylcyclohexanol by reaction with 3 mol equiv of $NiTPP^{2-}$ in tetrahydrofuran at 0° for 20 hr in 88% yield. Surprisingly, the vinylic iodo ketone **5** was unaffected by exposure to excess $NiTPP^{2-}$ at 0° for 20 hr, indicating the inertness of vinylic halides and carbonyl groups toward this reagent. In contrast to the good yields of cyclization products obtained from **10** and **11** using the reagent $NiTPP^{2-}$ are previous findings that the reaction of these halo ketones with lithium–liquid ammonia, sodium, naphthalene, or sodium phenanthrene affords cyclic alcohols in only low yields (7–33%).[16]



10, $n = 1$
11, $n = 2$

12, $n = 1$
13, $n = 2$

On the basis of the studies described above, it would seem that the reagents di-n-butylcopperlithium and $NiTPP^{2-}$ can effectively bring about the cyclization of iodo or bromo ketones to cyclopentanol or cyclohexanol derivatives, the former reagent being applicable to C_{sp^2} halides and the latter to C_{sp^3} halides. The investigation is currently being extended to ascertain in more detail the scope of these reactions relative to a range of halo carbonyl substrates and anionic organometallic reagents. There is at present no basis for mechanistic conclusions, especially with regard to the question of whether the primary process consists of nucleophilic replacement of halogen by metal or electron transfer from metal to halide. An application of the new cyclization process to the synthesis of tetracyclic compounds in the gibberellic acid series is presented in the following communication.[17,18]

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[12] R. Taube and H. Arfert, *Z. Naturforsch.*, **22b**, 219 (1967).

[13] F. H. Felton and H. Linschitz, *J. Amer. Chem. Soc.*, **88**, 1113 (1966), and references cited therein. See also L. D. Rollmann and R. T. Iwamoto, *ibid.*, **90**, 1455 (1968).

[14] A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, and L. Korsakoff, *J. Org. Chem.*, **32**, 476 (1967).

[15] Lower yields of **12** were obtained at lower or higher temperatures.

[16] H. O. House, J.-J. Riehl, and C. G. Pitt, *J. Org. Chem.*, **30**, 650 (1965).

[17] E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *J. Amer. Chem. Soc.*, **92**, 396 (1970).

[18] This study was aided by a grant from the National Science Foundation.

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Studies on the Total Synthesis of Gibberellic Acids. A Simple Route to the Tetracarbocyclic Network

Sir:

The preceding communication describes a method for the construction of carbon rings by intramolecular reductive addition of a δ- or ε-halo ketone.[1] We outline herein the application of this process as a key step in a synthesis of the carbon network and bridged-ring functionality which characterize the gibberellin family of plant hormones.[2]

The crystalline tricarbocyclic ketal **2** was synthesized from the corresponding ketone **1** which in turn was obtained by a Robinson annelation sequence. Reaction of 2-(N-pyrrolidyl)indene[3] with methyl vinyl ketone (1 equiv) in tetrahydrofuran at 0° for 47 hr[4] produced after isolation in the usual way an oily 1:1 Michael (keto–enamine) adduct which was subjected to cyclization in dioxane–glacial acetic acid–water–sodium acetate trihydrate (10:1:1:1) at 97° for 11 hr[4] to form tricyclic ketone **1**,[5] mp 94–95°, after distillation and recrystallization from ether. In practice crude semisolid **1** was treated without purification with ethylene glycol and p-toluenesulfonic acid in benzene at reflux to afford after distillation at 130–132° (0.1 mm) the ketal **2**,[5] mp 43–47° (mp 49–50° after recrystallization), in 58% overall yield from 2-(N-pyrrolidyl)indene.

Reaction of the ketal **2** with 3.8 equiv of t-butyl nitrite and 3 equiv of potassium t-butoxide in dry t-butyl alcohol at 35° for 15 hr[4] resulted in formation of the oxime **3**,[5] mp 182–183°, which could be obtained in 91% yield by acidification at 0° with 2 N hydrochloric acid, extraction, and recrystallization. However, treatment of the reaction mixture with 2 N sodium hydroxide prior to acidification with 2 N hydrochloric acid at 40° afforded the keto ketal **4**,[5] mp 91–92° (64% yield), in addition to the oxime **3** in 35% yield. The ketone **4** and oxime **3** were readily separated on silica gel, and the oxime could be converted to ketone by sequential treatment with t-butyl nitrite–t-butoxide solution,[4] aqueous base, and aqueous acid at 40°.[6] Hydrogenation of the enone **4** using palladium-on-carbon catalyst and ethyl

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[1] E. J. Corey and I. Kuwajima, *J. Amer. Chem. Soc.*, **92**, 395 (1970).

[2] See N. Ya. Grigor'eva and V. F. Kucherov, *Russ. Chem. Rev.*, **35**, 850 (1966).

[3] From 2-indanone and pyrrolidine according to the procedure of A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961).

[4] Under an atmosphere of argon.

[5] Satisfactory (a) analytical and (b) infrared and nmr data were obtained for this intermediate.

[6] Further discussion of this interesting method for converting oxime to ketone in the presence of a ketal grouping will be presented in due course.