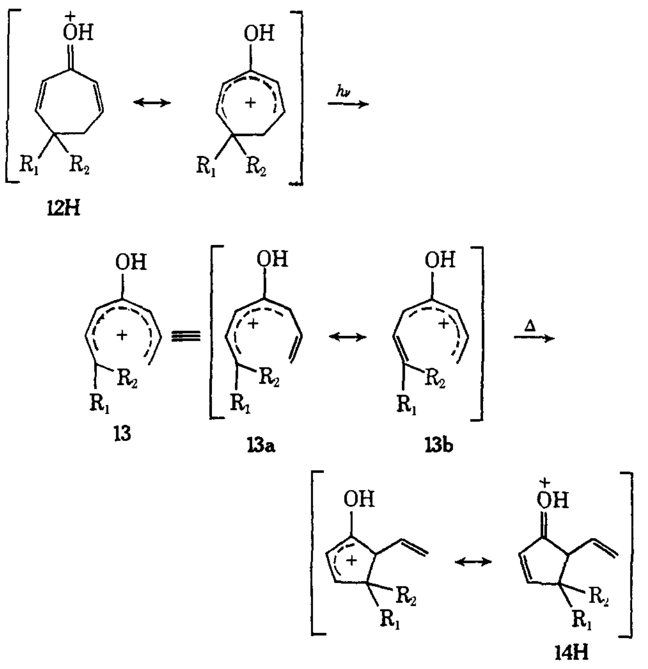
Scheme II



with the corresponding hydroxypentadienyl cation having a 4π-electron system.[8] The cationic species is thermally stable since the symmetry-allowed ring closure in a conrotatory fashion[8] is precluded by the existence of the $CR_1R_2CH_2$ bridge. Upon irradiation, it undergoes conrotatory ring opening to produce the reactive cation **13**, which, in turn as vinylpentadienyl cation, gives rise *via* thermal, conrotatory cyclization to the protonated five-membered ketone of type **14H**.[9] Regioselectivity of the rearrangement of unsymmetrical substrates would be controlled by the relative significance of resonance canonical forms of the cation **13**. Introduction of the methyl group at the terminal position should perturb the resonance hybrid **13a** ↔ **13b** ($R_1 = CH_3$ and $R_2 = H$, or $R_1 = H$ and $R_2 = CH_3$) so as to increase the contribution of **13a** leading to **14H**, as is consistent with the finding (**6H** → **7H**). Attempts to detect the cations of type **13** with spectroscopic aids at −78° have not yet met with success.[10]

The rearrangement of the protonated seven-membered dienones might *a priori* be interpreted as a concerted [1,3] sigmatropic reaction from an excited state having a conformation distorted considerably from the planar form. The direct process, however, could not account for the observed regioselectivity of the reaction.

Acknowledgment. We gratefully acknowledge support of this work by the Kurata Foundation.

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[8] R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 58.

[9] For the facile conversion of pentadienyl cation to cyclopentenyl cation, see P. H. Campbell, N. W. K. Chiu, K. Deugau, I. J. Miller, and T. S. Sorensen, *J. Amer. Chem. Soc.*, **91**, 6404 (1969). The related cyclization of heptatrienyl cation to vinylcyclopentenyl cation is known as well [T. S. Sorensen, *ibid.*, **87**, 5075 (1965)].

[10] Stability of hydroxy polyenylic cations is highly influenced by the position of the OH group, as might be rationalized in terms of *formal charge* calculated by the Pople method (M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, p 183). Protonated forms of conjugated ketones, which can be viewed as cations having OH function at the odd-numbered carbon atom (cationic center), are generally stable. In contrast, no confirmatory evidence for stable cations bearing an OH group at an even-numbered carbon atom of the conjugated system has been presented, though their intermediary existence has very frequently been postulated (for example, see ref 11). Only the nmr of cyclopropanone in FSO_3H–SO_2 at −80° was tentatively interpreted in terms of a mixture of protonated cyclopropanone and 2-hydroxyallyl cation.[12]

[11] B. Parrington and R. F. Childs, *Chem. Commun.*, 1581 (1970); N. Filipescu and J. W. Pavlik, *J. Amer. Chem. Soc.*, **92**, 6062 (1970); K. E. Hine and R. F. Childs, *ibid.*, **93**, 2323 (1971).

[12] G. A. Olah and M. Calin, *ibid.*, **90**, 938 (1968).

Organocopper Chemistry. Halo-, Cyano-, and Carbonyl-Substituted Ketones from the Corresponding Acyl Chlorides and Organocopper Reagents

Sir:

Organic chemists are continually seeking new reagents for specific and mild formation of carbon–carbon bonds. Organocopper reagents are now becoming widely used in conjugate addition reactions with α,β-unsaturated carbonyl substrates[1] and in coupling reactions with organic halides.[2] We have recently reported formation of methyl and *n*-alkyl ketones from carboxylic acid chlorides and lithium diorganocuprate(I) reagents,[3] and now we describe a significant extension of this ketone synthesis to acid chlorides substituted by iodo, cyano, acyl, and carbalkoxy groups (eq 1). The

$$R'COCl + R_2CuLi \xrightarrow[-78°]{Et_2O} R'COR \qquad (1)$$

relative and absolute reactivities of these functional groups toward organocopper reagents are established, thus defining conditions for other synthetic applications of these versatile reagents.

Summarized in Table I are the transformations which have been achieved using as representative *n*-alkylcopper reagents lithium dimethylcuprate(I) and lithium di-*n*-butylcuprate(I) in diethyl ether at −78° for 15 min. A typical procedure is illustrated by reaction of 6-oxodecanoyl chloride with lithium di-*n*-butylcuprate(I). Into a dry 50-ml two-necked round-bottomed flask equipped with a rubber septum was placed a magnetic stirring bar and cuprous iodide[4] (571 mg, 3.00

Table I. Reaction of Lithium Diorganocuprates(I), R_2CuLi, with Carboxylic Acid Chlorides in Diethyl Ether at −78° (Eq 1)

Acid chloride	Product	R, % yield[a]	
		CH_3	n-C_4H_9
$CN(CH_2)_{10}COCl$	$CN(CH_2)_{10}COR$	80	>95
n-$C_4H_9CO(CH_2)_4COCl$	n-$C_4H_9CO(CH_2)_4COR$	95	83
$CH_3O_2CCH_2CH_2COCl$	$CH_3O_2CCH_2CH_2COR$	<20	85
n-$C_4H_9O_2C(CH_2)_4COCl$,	n-$C_4H_9O_2C(CH_2)_4COR$	83[b]	93[b]
$ClCO(CH_2)_4COCl$	$RCO(CH_2)_4COR$	92	90
$I(CH_2)_{10}COCl$	$I(CH_2)_{10}COR$	91	93
p-IC_6H_4COCl	p-IC_6H_4COR	98	85
C_6H_5COF	C_6H_5COR	72	87

[a] Yield of isolated product. [b] Yield determined by quantitative vpc analysis.

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[1] G. H. Posner, *Org. React.*, **19**, 1 (1972).

[2] (a) G. H. Posner, manuscript in preparation; (b) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969), and references cited therein.

[3] G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 4647 (1970).

[4] "Cuprous iodide purified" was purchased from Fisher Chemical Co. and was used without further purification.

mmol). A three-way stopcock bearing a nitrogen-filled balloon was used to evacuate and then fill the flask with nitrogen. The purging procedure was repeated two more times, and the flask was gently flamed during the third evacuation. Anhydrous diethyl ether (8 ml) was added and the system was cooled to −40° (0° for lithium di*methyl*cuprate preparations). *n*-Butyllithium[5] (4.5 ml of a 1.32 *M* solution, 6.0 mmol) was injected. After about 5 min at −40°, the temperature was lowered to −78°. A precooled ethereal solution (1 ml) of 6-oxodecanoyl chloride[6] (bp 86–87.5° (0.23 mm), 213 mg, 1.04 mmol[7]) was injected. After 15 min at −78°, absolute methanol (352 mg, 11.0 mmol) was injected and the reaction mixture was allowed to reach room temperature. It was poured with stirring into an equal volume of saturated aqueous ammonium chloride; ether extraction followed by rotary evaporation gave 193 mg (83% yield) of 5,10-tetradecanedione, mp 59–62°, with consistent ir and nmr spectral properties. Recrystallization from *n*-pentane gave white needles (162 mg, 70%), mp 65–66° (lit.[8] mp 65°).

Side products are observed from only two substrates. Benzoyl fluoride is incompletely methylated by lithium dimethylcuprate(I); even when a fivefold excess of this reagent is used for 1 hr at −78°, methanol quenching produces methyl benzoate in 12% yield,[9] whereas butylation proceeds to completion under the standard conditions. β-Carbomethoxypropionyl chloride reacts with lithium dimethylcuprate(I) to give methyl levulinate in less than 20% yield, in contrast to butylation of this substrate which proceeds well; despite various changes in the work-up procedure (*e.g.*, nonaqueous and/or hydrogen sulfide work-up), the by-products of this reaction remain elusive.[10] Similar difficulties have been observed when β-carbonyl-substituted acid chlorides are treated with other organometallic reagents.[11] A control experiment shows that methyl levulinate itself is consumed by lithium dimethylcuprate(I) at −78° within 3 min.

Comparison with other organometallic reagents generally effective for coupling with acid chlorides shows that lithium diorganocuprates(I) are equally useful in most cases and occasionally more useful. Thus, organocopper reagents compare favorably with organozinc and organocadmium[11] reagents which react with carbalkoxy- and with acyl-substituted acid chlorides to form keto esters and diketones, respectively; reaction of iodo and cyano acid chlorides with organocadmium or organozinc reagents has not been reported.[12] Although organoaluminum reagents convert ester acid chlorides into keto esters, formation of diketones from acyl acid chlorides is a low-yield process.[11a] Finally, whereas organolithium reagents react with carboxylic acids to form ketones directly,[13] most of the transformations reported in this communication could not be achieved with organolithium reagents because, even at −78°, these reagents readily add across carbon–heteroatom multiple bonds.[14]

To study the relative and absolute reactivities of the various functional groups toward organocopper reagents, experiments were set up with lithium di-*n*-butylcuprate(I) or with lithium dimethylcuprate(I) and each type of substrate in diethyl ether at −90°. At every 10° interval as the temperature was allowed to rise at about 1°/min, aliquots were removed by precooled syringe and were quenched in cold methanol. Quantitative vpc analysis using an internal standard was used to follow the course of the reaction. Once the temperature was found at which the substrate began to react with organocopper reagent, a second experiment with the same substrate and organocopper reagent was started at low temperature and then was run for at least 15 min at 5–10° lower than this "critical" temperature. In all cases the substrates were recovered (≥85% yield) under these conditions (Table II). This temperature study suggests the use of organocopper reagents in new selective reactions [*e.g.*, $RCO(CH_2)_nCHO + LiR'_2Cu \rightarrow RCO(CH_2)_nCH(R')OH$].[15]

Table II. Highest Temperature at Which Substrate Can Be Recovered (≥85%) after Exposure to 3 Equiv of Lithium Diorganocuprate(I), LiR_2Cu, for ≥15 Min in Diethyl Ether[a]

Substrate	Temp, °C R = CH_3	R = n-C_4H_9
C_6H_5CHO	<−90	
n-$C_6H_{13}CHO$	<−90	
n-$(C_4H_9)_2CO$	−10	−35
n-$C_4H_9CO_2CH_3$	18	−10
n-C_3H_7CN	18	18

[a] The products formed when these reactions are run at high temperature are under study; unexpected results have been obtained in some cases (*e.g.*, ketone enolization as well as carbonyl addition).

Conversion of functionalized acid chlorides to functionalized ketones as described here has some limitations. First, aldehydes react with lithium diorganocuprates(I) even at −90° for 2 min. Second, 3 equiv of R_2CuLi (6 equiv of R) is needed for optimal yields, although substantial amounts of ketone are formed when

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(5) The organolithium reagents were purchased from Foote Mineral Co.; methyllithium in ether and *n*-butyllithium in pentane were used.

(6) This acid chloride was prepared from oxalyl chloride and 6-oxodecanoic acid, mp 43–44°; lit. mp 46–47°: D. G. M. Diaper, *Can. J. Chem.*, **33**, 1720 (1955).

(7) Successful conversion of this and other acid chlorides to ketones using organocopper reagents has been achieved also on a much larger scale (*e.g.*, 20 mmol of acid chloride).

(8) M. Renson and J. Bonhomme, *Bull. Soc. Chim. Belg.*, **68**, 667 (1959).

(9) Similar unexplained results have been observed by P. Crabbé and E. Velarde, *Chem. Commun.*, 241 (1972).

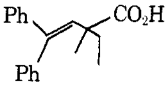
(10) Levulinyl chloride also reacts with lithium dimethyl- or di-*n*-butylcuprates(I) to give diketones in poor yields.

(11) (a) H. Reinheckel, K. Haage, and D. Jahnke, *Organometal. Chem. Rev., Sect. A*, **4**, 55 (1969); (b) H. Adkins and C. Scanley, *J. Amer. Chem. Soc.*, 73, 2854 (1951); (c) P. Fréon and F. Tatibouët, *C. R. Acad. Sci.*, **244**, 2399 (1957); (d) F. Tatibouët and F. Fréon, *ibid.*, **248**, 3447 (1959).

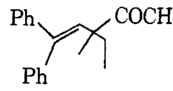
(12) D. A. Shirley, *Org. React.*, **8**, 28 (1958).

(13) M. J. Jorgenson, *ibid.*, **18**, 1 (1970).

(14) (a) For the low-temperature addition of *tert*-butyllithium to hexamethylacetone see P. D. Bartlett and E. B. Lefferts, *J. Amer. Chem. Soc.*, 77, 2804 (1955); (b) a control experiment with 1 equiv of methyllithium per equiv of pivaloyl chloride at −78° for 10 min shows formation of 2,3,3-trimethyl-2-butanol in substantial amounts; (c) attempts to convert acid i to methyl ketone ii using methyllithium or dimethylcadmium (with the corresponding acid chloride) routinely failed, whereas lithium dimethylcuprate(I) was highly successful (private communication from W. G. Dauben and J. Seeman).



i



ii

(15) We have found that aldehydes undergo carbonyl addition with organocopper reagents; thus, benzaldehyde and heptaldehyde react with lithium dimethylcuprate(I) at −90° for 10 min to give 1-phenylethanol and 2-octanol after work-up in 80–85% yields.

1.5 equiv of organocuprate(I) is used.[16] Third, organolithium reagents are generally less readily available than organomagnesium reagents.[17] Finally, secondary and tertiary alkylcopper reagents are generally more difficult to prepare than primary ones.[1,17] The functional group specificity (Table I) and the simplicity and mildness of experimental conditions, however, make synthesis of ketones from acid chlorides and organocopper reagents a useful new synthetic method.[18]

(16) Although cuprous ion "catalyzed" Grignard reaction with acid chlorides to form ketones has been reported, it appears that the ratio of copper to RMgX is 1.6:1.0; see J. E. Dubois and M. Boussu, *Tetrahedron Lett.*, 2523 (1970), and J. E. Dubois, M. Boussu, and C. Lion, *ibid.*, 829 (1971); see also J. A. MacPhee and J. E. Dubois, *ibid.*, 467 (1972).

(17) Organocopper reagents derived from Grignard reagents and cuprous iodide have recently been used to effect conversion of *cis*-4-*tert*-butylcyclohexanecarbonyl chloride to the corresponding aryl and *tert*-butyl ketones without epimerization at the α carbon; see N. T. Luong-Thi, H. Rivière, J. P. Bégné, and C. Forrestier, *Tetrahedron Lett.*, 2113 (1971).

(18) G. H. Posner and C. E. Whitten, *Org. Syn.*, submitted for publication (procedure currently being checked).

(19) NDEA Fellow, 1969–present.

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Dimethyl Sulfoxide–Water for Study of "Unobservable" General Base Catalysis and Anomalous Behavior of Hydroxide Ion[1]

Sir:

The data of this communication respond to two important questions which arise in studies of acid–base systems: (a) are there carbon acids which behave like normal oxygen and nitrogen acids in all respects, including their reaction with hydroxide ion, and (b) does the frequently observed anomalously slow reaction rate of hydroxide ion with carbon acids reflect a different degree of proton transfer in the transition state?

Eigen[2] has shown that reactions of major categories of acids and bases in aqueous solution exhibit a "normal" behavior in which the thermodynamically favored proton transfer occurs at a diffusion-controlled rate, *i.e.*, with a rate independent of the strength of the catalyst and hence with a Brønsted coefficient of 0. The reverse process then occurs with a Brønsted coefficient of unity. Deviation from this normal behavior usually occurs only in a transition region of a few pK units close to $\Delta pK = 0$, where ΔpK gives the pK difference for catalyst and substrate.

Carbon acids often depart widely from this behavior in that they exhibit intermediate Brønsted coefficients (0.4–0.8) for wide ranges and large values of ΔpK.[3,4] However, a recently studied group of cyanocarbon acids exhibits almost normal behavior in that their proton removal involves general base catalysis with a Brønsted β of virtually unity and a reverse reaction whose Brønsted α is almost zero and whose rate is within a factor of 10 of that of a diffusion-controlled process.[5-7] A strong implication of these results, which is confirmed by the observation of small primary hydrogen isotope effects (*ca.* 1.5) for the proton removal reaction, is that in the transition state the proton is virtually entirely transferred. For these cyanocarbon reactions proton removal by hydroxide ion is anomalously slow,[5,6] a behavior which is commonly observed with carbon acids but not with oxygen and nitrogen acids.[2,4]

The experiments which follow compare one of these cyanocarbon acids with chloroform, an acid which on the basis of its structure and also Hine's[8] earlier studies appears to be a good candidate for fully normal acid behavior. As a first experiment, we have compared the primary hydrogen isotope effects for reaction of these two with hydroxide ion, utilizing a new, accurate experimental procedure which involves measuring the rate of tritium uptake by the protio and deuterio compound from a tritiated aqueous solvent. For very small amounts of reaction, the appropriate equation for this procedure is

$$\left(\frac{\mathrm{d}\alpha}{\mathrm{d}t}\right)^{\mathrm{H}}_{t\to 0}\Bigg/\left(\frac{\mathrm{d}\alpha}{\mathrm{d}t}\right)^{\mathrm{D}}_{t\to 0} = (k_1^{\mathrm{OH^-}})^{\mathrm{H}}/(k_1^{\mathrm{OH^-}})^{\mathrm{D}}$$

where α is the atom per cent of tritium uptake in the compound. Isotope effects for reaction of such normal bases as morpholine and phenolate ion with the cyanocarbon acid give the small isotope effects of $k^{\mathrm{H}}/k^{\mathrm{D}}$ = 1.7 and 1.4, respectively, indicating a fully transferred proton in the transition state. Reaction of hydroxide ion with this same species shows a primary hydrogen isotope effect of 3.5. Similar experiments utilizing chloroform reacting with hydroxide ion gave a primary isotope effect of 1.42.

A second comparison is the entropy of activation for reaction of the two carbon acids with hydroxide ion. With rate coefficients in M^{-1} sec^{-1} units, ΔS^* for the reaction of hydroxide with the 1,4-dicyanobutene was -10 eu. In contrast, reaction of chloroform and hydroxide ion gives a ΔS^* of $+15$ eu. This latter is about the expected size for a reaction in which a proton is fully transferred from the carbon acid to hydroxide ion.

These results suggest the proton is fully transferred from chloroform to hydroxide ion, whereas with dicyanobutene the transfer is only partial.

Chloroform in aqueous solution revealed no observable catalysis by the general bases pyridine and morpholine. This observation, in conjunction with the results with hydroxide ion, can plausibly be interpreted by assuming that hydroxide ion is reacting in a fully normal way, with a Brønsted β of unity. With an acid as weak as chloroform this would lead to "unobservable general base catalysis," *i.e.*, the hydroxide ion process would effectively overwhelm catalysis by all weaker bases.

As a further comparison of chloroform and dicyanobutene, we have studied the reaction of the two carbon acids with hydroxide ion in the mixed solvent DMSO–H_2O. Bell and Cox[9] have previously utilized this mix-

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(1) Work supported by a grant from the Atomic Energy Commission.

(2) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).

(3) M. L. Bender, "Mechanisms of Homogenous Catalysis from Protons to Proteins," Part I, Wiley-Interscience, New York, N. Y., 1971.

(4) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(5) E. A. Walters and F. A. Long, *J. Amer. Chem. Soc.*, **91**, 3733 (1969).

(6) F. Hibbert, E. A. Walters, and F. A. Long, *ibid.*, **93**, 2829 (1971).

(7) F. Hibbert and F. A. Long, *ibid.*, **93**, 2836 (1971).

(8) J. Hine, N. W. Burske, M. Hine, and P. B. Longford, *ibid.*, **79**, 1406 (1957), and earlier papers.

(9) R. P. Bell and B. G. Cox, *J. Chem. Soc. B*, 194 (1970); (b) *ibid.*, 783 (1971).