This investigation is currently being extended to ascertain in more detail the scope and mechanism of these reactions.

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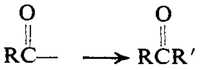
Anions of Protected Cyanohydrins as Acyl Carbanion Equivalents and Their Use in a New Synthesis of Ketones

Sir:

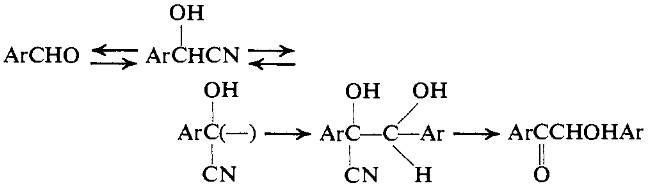
The obvious utility of acyl carbanion equivalents (*cf.* **1**) in the formation of a variety of carbonyl-containing systems by reaction with electrophilic reagents (*e.g.*, **1** → **2**) has prompted considerable synthetic work, of much ingenuity, toward the synthesis of species equivalent to **1**.[1] We now wish to report a new and generally useful type of acyl carbanion equivalent and its use in the synthesis of ketones.



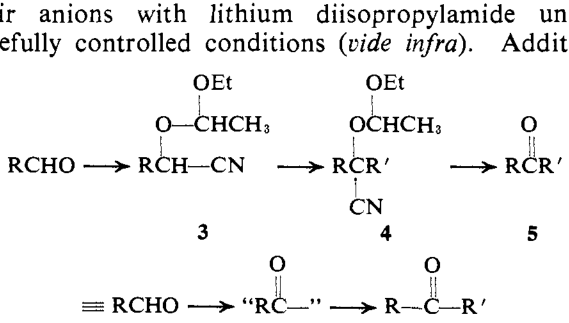
$$R\overset{O}{\overset{\|}{C}}— \longrightarrow R\overset{O}{\overset{\|}{C}}R'$$

1 **2**

It occurred to us that a simple solution to the problem would be at hand if one could generate and alkylate the carbanions derived from suitably protected aldehyde cyanohydrins. Indeed, a special case of such a process is implicated in the long-known benzoin condensation of *aromatic* aldehydes.[2] It is obvious from the occurrence of this reaction, *without protection of the cyanohydrin hydroxyl*, that the aryl ring provides considerable additional stabilization for the α-cyano carbanion. A general synthesis would require finding conditions which would allow the alkylation of cyanohydrin in derivatives of *aliphatic* aldehydes as well as aromatic ones.



We have found that aldehyde cyanohydrins, suitably protected as their easily prepared reaction products, **3**, with ethyl vinyl ether,[3] can indeed be transformed into their anions with lithium diisopropylamide under carefully controlled conditions (*vide infra*). Addition of an alkyl halide then produces a high yield of the protected cyanohydrin (**4**) of a ketone (**5**) which is then easily liberated, quantitatively and in a few minutes, by successive treatment with dilute sulfuric acid and dilute aqueous base.



The general procedure is described below.

A. Alkylation (3 → 4). To a solution of 0.022 mol of lithium diisopropylamide (from butyllithium and diisopropylamine) in 5–10 ml of dry tetrahydrofuran, under nitrogen and cooled to −78° in Dry Ice–acetone, a solution of 0.021 mol of freshly distilled **3** in 4.2–4.5 g of dry hexamethylphosphoramide is added dropwise, with vigorous stirring. After stirring for an additional 5 min, the halide R′X (0.025–0.030 mol) is added dropwise (5–10 min) followed by rinsing with an additional 10 ml of tetrahydrofuran. Stirring is continued for another 1–2 hr in the cold and 1 hr at room temperature. Addition of water, removal of solvent, and extraction (methylene chloride or ether) are followed by drying (Na_2SO_4), removal of solvents on the water pump, and percolation of the residue dissolved in 1:1 hexane–benzene through 25 g of silica gel. The product **4** can either be purified by distillation or used directly in the next step.

B. Regeneration of Ketone (4 → 5). To a mixture of 0.003–0.005 mol of **4** in 2–3 ml of methanol and 1 ml of 5% aqueous sulfuric acid enough methanol (2–5 ml) is added to make the mixture almost homogeneous. Disappearance of starting material (tlc) occurs after 5–10 min of stirring a room temperature. Removal of volatile components *in vacuo*, extraction with ether, and washing (saturated brine) leads to the crude cyanohydrin which can be isolated, if needed. Normally, the ketone is produced from the cyanohydrin by vigorous shaking of its ether solution with 20 ml of 0.5 *N* sodium hydroxide solution for 5–10 min. The ketone is then recovered from the ether solution in the usual way.

We wish to point out a number of features which make this new synthetic method of considerable interest. (a) Primary bromides (and iodides) give excellent yields in the alkylation of **3** to **4**. For instance, from the readily available **3** ($R = CH_3$), *n*-butyl, *n*-hexyl, and *n*-decyl bromides give the corresponding **4** in 80–85% yield.[4a] (b) Secondary bromides often give excellent yields with little dehydrohalogenation: **3** ($R = CH_3$) gave with isopropyl and cyclopentyl bromides the corresponding **4** in 80% yield. The easily dehydrohalogenated cyclohexyl bromide still gave an acceptable 41% yield.[4b] (c) Halides of the homoallylic type, which are often easily dehydrohalogenated, give good yields: **3** ($R = CH_3$) gave with 2-phenylethyl bromide and *cis*-3-hexenyl iodide the corresponding **4** in 84 and 61% yields,[4c] respectively. (d) Especially reactive halides such as allyl bromides and chloromethyl ether, as well as notably unreactive ones such as diethyl bromoacetal, give the respective **4** in 76, 71, and 59% yields.[4d] (e) Although most of our work has been with acetaldehyde cyanohydrin (thus leading to methyl ketones) the homologs can, of course,

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[1] For a good review, see D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969).

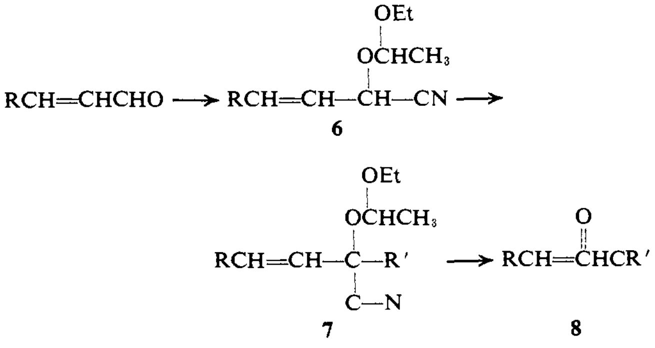
[2] *Cf.* K. Wiberg, *J. Amer. Chem. Soc.*, **76**, 5371 (1954).

[3] H. J. Sims, H. B. Parseghian, and P. L. DeBenneville, *J. Org. Chem.*, **23**, 724 (1958).

[4] (a) ($R = CH_3$) R′ = *n*-butyl, bp 97–99° (9 mm); R′ = *n*-hexyl, bp 75–80° (0.05 mm); R′ = *n*-decyl, bp 120–130° (0.09–0.11 mm); (b) R′ = *i*-Pr, bp 85–86° (9 mm); R′ = cyclopentyl, bp 69–70° (0.05 mm); R′ = cyclohexyl, bp 93–95° (0.1 mm); (c) R′ = *cis*-3-hexenyl, bp 75–76° (0.05 mm); (d) R′ = allyl, bp 59–62° (0.15 mm); R′ = CH_3OCH_2–, bp 92–94° (7 mm); R′ = $(C_2H_5O)_2CHCH_2$–, bp 90–91° (0.08 mm).

also be used. The protected cyanohydrin[5] from hexanal (3, R = *n*-pentyl) thus gave, with butyl bromide, 70% of **4** (R = *n*-pentyl; R′ = butyl, bp 87–90° (0.05 mm)) hydrolyzed essentially quantitatively, as usual, to 5-decanone (**5**, R = *n*-pentyl; R′ = butyl).[6]

A particularly interesting case is that of the synthesis starting with α,β-unsaturated aldehydes. The sequence then leads to α,β-unsaturated ketones.



$$RCH{=}CHCHO \longrightarrow RCH{=}CH{-}\underset{\mathbf{6}}{CH(OCH(CH_3)OEt){-}CN} \longrightarrow$$

$$RCH{=}CH{-}C(OCH(CH_3)OEt)(R'){-}C{-}N \; (\mathbf{7}) \longrightarrow RCH{=}CHC(=O)R' \; (\mathbf{8})$$

Terminal vinyl ketones can thus be made from the readily available acrolein cyanohydrin.[7] Alkylation of the ethyl vinyl ether adduct[8] **6** (R = H) with *n*-hexyl bromide gave an ~75% yield of **7** (R = H; R′ = *n*-hexyl; bp 87–88° (0.07 mm)), easily hydrolyzed, as usual, to 1-nonen-3-one (**8**, R = H; R′ = −*n*-hexyl), identical with an authentic sample.

Obviously, since the cyanohydrins derived from aromatic aldehydes are considerably more acidic than those from their aliphatic counterparts, alkylation by this method also gives excellent yields with these substances. The protected cyanohydrin of benzaldehyde thus gave overall conversions to valerophenone, isobutyrophenone, and 1,3-diphenyl-1-propanone ranging from 71% for the latter after crystallization (mp 69–71°; lit.[9] 72°) to 94% for the other two.[10] Furfural similarly gave 1-furyl-1-pentanone in ~90% yield.

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(5) Aldehyde cyanohydrins can be made easily by a variety of methods; *cf.*, *inter alia*, E. Pierson, M. Giella, and M. Tishler, *J. Amer. Chem. Soc.*, 70, 1450 (1948).

(6) This and other ketones were produced essentially quantitatively (4 → 5) as shown by vpc. The identity of the ketones was established by ir and nmr spectra and/or comparison with authentic samples.

(7) R. Rambaud, *Bull Soc. Chim. Fr.*, 1317 (1934).

(8) The procedure of ref 3 was used but without heating initially or at the end of the reaction. The low boiling material was removed at the water pump and the residue was distilled under vacuum, bp 42–45° (0.1 mm) (60% overall from acrolein). Redistillation through a short Vigreux column gave bp 58–59° (0.3 mm). This is a mixture of two diastereoisomers (54% A, 46% B; A, 8.9 min retention time, and B, 9.9 min on SE-30 at 130°). The mixture is used as such in the alkylation sequence.

(9) N. H. Cromwell and R. H. Johnson, *J. Amer. Chem. Soc.*, **65**, 316 (1943).

(10) The higher acidity of the protected cyanohydrins from aromatic aldehydes allows, in some cases, the use of sodium hydride in dimethoxyethane as base; the α-ethoxyethyl ether of benzaldehyde cyanohydrin thus gave 88% yield on alkylation with *n*-amyl bromide.

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Theoretical ^{13}C Nuclear Magnetic Resonance Chemical Shifts in CH_5^+ and $C_2H_5^+$

Sir:

At the present time there is considerable experimental and theoretical interest in the structure of small carbonium ions.[1] One of the main experimental techniques used to determine such molecular structures is nmr spectroscopy (^1H and ^{13}C).[2] Theoretically, both semiempirical[3,4] and *ab initio*[5–9] methods have been used to predict the equilibrium structures of carbonium ions. Recently we developed a theory of ^{13}C nmr chemical shifts, and applications to neutral molecules have led to results which are in good agreement with experimental values.[10,11] The theory is particularly successful in describing ^{13}C chemical shifts in molecules of comparable size and in which the carbon nucleus has a similar position relative to the origin of the vector potential describing the magnetic field. This suggests that the theory may give a good description of the relative ^{13}C chemical shift between a neutral molecule and the associated carbonium ion with the same number of electrons, *e.g.*, CH_4 and CH_5^+, C_2H_4 and $C_2H_5^+$. If successful, this would provide a useful link between theoretical studies of equilibrium geometries and the experimental nmr data. The aim of this note is to present calculated ^{13}C magnetic shielding constants for the equilibrium structures of CH_5^+ and $C_2H_5^+$ determined by Lathan, Hehre, and Pople.[7–9] While these systems have never been obtained experimentally, the calculated results can be compared with simulated experimental data derived from similar systems.[2]

The method used is Hartree–Fock perturbation theory formulated within the molecular orbital framework, each molecular orbital being written as a linear combination of a small extended basis set (4-31G)[12] of atomic functions φ_μ (LCAO)

$$\psi_i = \sum_\mu c_{\mu i}\varphi_\mu$$

The equilibrium geometries for CH_5^+ and $C_2H_5^+$ are taken from the work of Lathan, Hehre, and Pople.[9]

The calculated results are shown in Table I together with the energies reported in ref 9. Since there are no experimental values available for the ethyl cation (it has never been observed experimentally), we have attempted to estimate chemical shift values for the

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(1) For recent reviews, see C. C. Lee, *Progr. Phys. Org. Chem.*, 7, 129 (1970); J. L. Fry and G. J. Karabatsos in "Carbonium Ions," Vol. 2, G. A. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N. Y., 1970, Chapter 14.

(2) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, 91, 3954 (1969); 91, 5801 (1969).

(3) G. A. Olah, G. Klopman, and R. H. Schlosberg, *ibid.*, 91, 3261 (1969).

(4) R. Sustman, J. E. Williams, M. J. S. Dewar, L. C. Allen, and P. v. R. Schleyer, *ibid.*, 91, 5350 (1969).

(5) W. Th. A. M. Van der Lugt and P. Ros, *Chem. Phys. Lett.*, **4**, 389 (1969).

(6) H. Kollmar and H. O. Smith, *ibid.*, **5**, 7 (1970).

(7) W. A. Lathan, W. J. Hehre and J. A. Pople, *Tetrahedron Lett.*, 2699 (1970).

(8) J. E. Williams, V. Buss, L. C. Allen, P. v. R. Schleyer, W. A. Lathan, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, **92**, 2141 (1970).

(9) W. A. Lathan, W. J. Hehre, and J. A. Pople, *ibid.*, **93**, 808 (1971).

(10) R. Ditchfield, D. P. Miller, and J. A. Pople, *Chem. Phys. Lett.*, 6, 573 (1970).

(11) R. Ditchfield, D. P. Miller, and J. A. Pople, *J. Chem. Phys.*, **54**, 4186 (1971).

(12) R. Ditchfield, W. J. Hehre, and J. A. Pople, *ibid.*, **54**, 724 (1971).