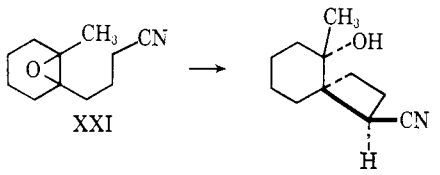
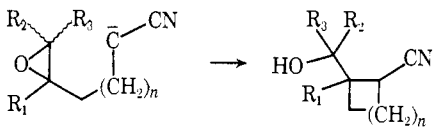
The high nucleophilicity of the nitrile anion permits ring formation even at a quaternary center. The epoxynitrile XXI undergoes cyclization after stirring overnight with potassium amide in liquid NH_3–glyme to give, in ~80% yield, the spirocyclononane XXII, bp 140° (bath,



XXI XXII

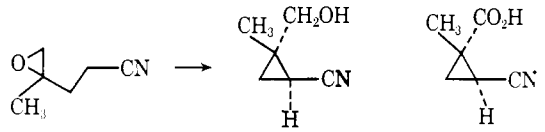
1 mm) (nmr $\delta(CCl_4)$ 1.05 (3 H, s), 2.9 (1 H, s), 3.4 (1 H, t)). The absorption of the hydrogen α to the nitrile is compatible with a cyanocyclobutane. The amide (mp 122.5–123.5°), also showed a 1 H triplet at δ 3.25 and so did the derived acid (nitric oxide on amide), mp 148.5–150°, obtained in 50% yield from the nitrile. The structure was further confirmed by dehydration of XXII with thionyl chloride–pyridine which gave the expected mixture of methylenecyclohexane and methylcyclohexene.[11]

The study of a number of other cases in this laboratory allows the conclusion that the epoxynitrile cyclization always yields the smaller ring, when both ends of the epoxide are equally substituted. This is true whether the smaller ring formed is three-, four-, five-, or six-membered.



$R_1, R_2 = H; R_3 = alkyl$ $n = 0, 1, 2, 3$
$R_1 = H; R_2, R_3 = alkyl$
$R_1, R_2, R_3 = alkyl$

In the special case of $n = 0$, the rate of cyclopropane formation is such that this ring is produced in preference to a cyclobutane, *regardless* of the relative degree of substitution of the oxirane ring. Thus, cyclization of the epoxynitrile XVII (potassium amide, liquid ammonia–glyme) gave the cyanocyclopropane XVIII, oxidized with Jones reagent to the acid XIX, mp 115–116°



XVII XVIII XIX

(nmr $\delta(CDCl_3)$ 1.54 (3 H, s), 1.26 (1 H, t, J ~5.3 Hz), 1.6–2.4 (2 H, m)).[5,12]

(10) We thank Zoëcon Corp., Palo Alto, Calif., for this gas chromatography comparison.

(11) Preliminary experiments on this cyclization were carried out at Columbia by D. R. Coulson, and a more thorough investigation was made by Lovji D. Cama. The cyclized nitrile XXII and the derived amide and acid gave satisfactory carbon and hydrogen analyses and spectral data.

(12) This work was supported by the National Science Foundation and the National Institutes of Health.

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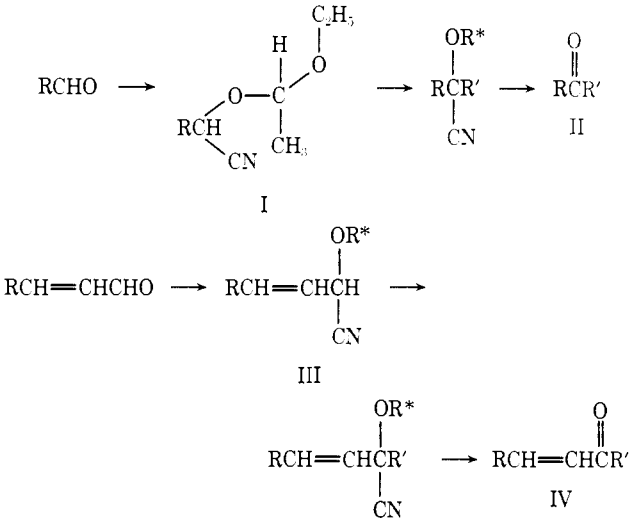
Conjugate Addition of Acyl Carbanion Equivalents *via* the Protected Cyanohydrin Method

Sir:

The conjugate addition of acyl carbanion equivalents is a potentially important reaction. We now report that some of the protected cyanohydrins which we have employed as masked acyl carbanions in the synthesis of ketones[1] (I → II; III → IV) often readily undergo con-



jugate addition to enone systems. This is especially important as the widely used dithiane anions[2] generally undergo only 1,2-addition.[3]

We have examined the reaction of protected cyanohydrin anions with cyclohexenone, cyclopentenone, and benzalacetophenone. In all cases the additions were performed by addition at −78° of 1 equiv of the enone in dry tetrahydrofuran to a solution of the lithium salt of the protected cyanohydrin, prepared exactly as described previously.[1] After 5–10 min the solution was warmed to 0°, quenched with water, and extracted with ether and the product was purified by chromatography or alumina or Florisil. Under these conditions, the cyanohydrins derived from saturated aldehydes, *e.g.*, I, R = CH_3, gave considerable quantities of 1,2-adduct, in addition to the desired 1,4-product (V:VI = 60:40).[4]

This initial result was very encouraging and raised the question why the anions derived from protected

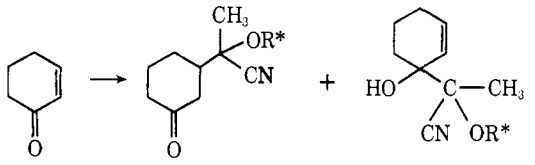
(1) G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971). In the formulas the symbol R* denotes the α-ethoxyethyl protecting group (*cf.* I).

(2) For an excellent review, see D. Seebach, *Synthesis*, 1, 17 (1969). Some more recent work has demonstrated the possibility of carrying out conjugate additions with copper reagents derived from phenyl thioacetals (T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Amer. Chem. Soc.*, **94**, 8641 (1972)), although additions to cyclic enones have not yet been reported with these reagents. Another very promising route to conjugate addition of acyl carbanion equivalents involves the anions of thioacetal monosulfoxides (J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 3271 (1973)).

(3) An intramolecular 1,4-addition of the protected cyanohydrin of an *aromatic* aldehyde has been reported in a case in which 1,2-addition could not compete (E. Aufderhaar, J. E. Baldwin, D. H. R. Barton, D. J. Faulkner, and M. Slaytor, *J. Chem. Soc.*, 2175 (1971)). See also G. Stork and R. Schultz, *J. Amer. Chem. Soc.*, **93**, 4074 (1971), for the 1,4-addition of the anion of a protected α-hydroxy ester to an unsaturated lactam. Stetter, *et al.* (H. Stetter and M. Schreckenberg, *Angew. Chem.* **85**, 89 (1973); *Tetrahedron Lett.*, 1461 (1973); *Chem. Ber.*, **107**, 210 (1974)), apparently unaware of previous work with anions derived from protected cyanohydrins (*vide supra* and ref 1), also report on the use of *aromatic* cyanohydrins in conjugate additions.

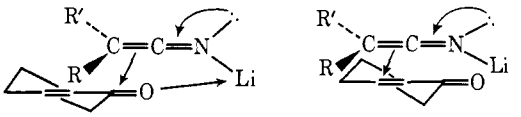
(4) Spectral data (ir, nmr) clearly established the proposed structure.

cyanohydrins should find it easier than those from dithianes to undergo 1,4-addition.

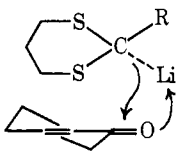


V VI

The necessity of transferring the lithium cation in the aprotic medium used suggests VII and VIII as probable transition states for the 1,2- and 1,4-addition of the alkoxy nitrile anions. The corresponding transition state for the dithiane anion is shown in IX for its 1,2-



VII VIII



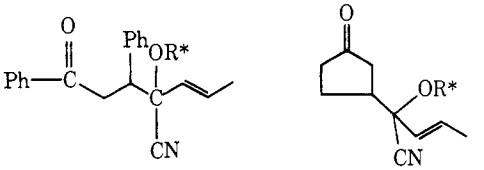
IX

addition. Two facts emerge. It is clear that the dithiane anion would not be expected to undergo kinetic 1,4-addition since the carbanion center cannot reach the γ-carbon atom. (The same phenomenon is encountered with acetylide anions and alkyl lithiums which also give 1,2-additions.)

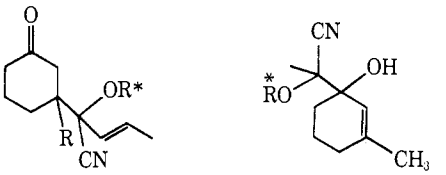
One other conclusion emerges from the models corresponding to VII and VIII. The larger the substituent on the α-carbon of the alkoxynitrile, the more one should observe 1,4-addition. This turns out to be the case; the protected cyanohydrin derived from *n*-hexanal (I, R = C_5H_{11}) gives, with cyclohexenone, a 1:4 to 1:2 ratio of 2.7:1. Hindering the carbonyl has the same favorable effect; 6-methyl cyclohexenone gives, with I, R = CH_3, a ratio of ~6:1 in favor of 1,4-addition.[5]

A more general method for achieving 1,4-addition would be to make the 1,2-addition reversible. *We have now found that 1,4-addition takes place in very high yield with the protected cyanohydrins derived from α,β-unsaturated aldehydes*, even in cases where addition has to take place at a fully substituted double bond (*cf.* 3-methylcyclohexenone → XII, R = CH_3).

Under the conditions described above, the protected cyanohydrin of crotonaldehyde (III, R = CH_3) gave the conjugate addition products X, XI, and XII, R = H and R = CH_3, from benzalacetophenone, cyclopentenone, cyclohexenone, and 3-methylcyclohexenone, respectively, in 70–85% yields.[4] The clean 1,4-addition observed between 3-methylcyclohexenone and *unsaturated* alkoxy nitriles (*e.g.*, III, R = CH_3) is in striking contrast with the result with saturated alkoxynitriles; the addition under the usual conditions of I, R = CH_3, gave (90% yield) almost entirely the 1,2-adduct XIII (nmr $\delta(CDCl_3)$ 1.75 (d, J = 1.5 Hz, CH_3C = CH–) 2.85 (b, O*H*), 5.63 (b, CH_3C=C*H*–)).

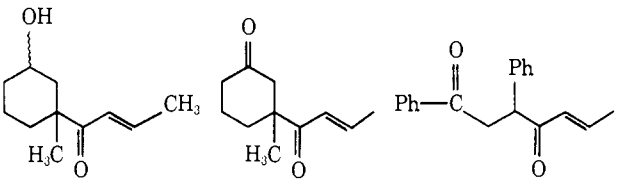


X XI

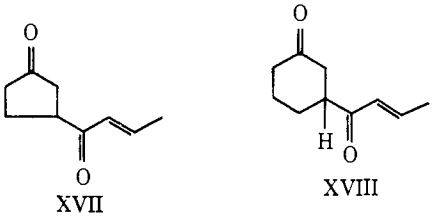


XII XIII

It is worth noting that the potential diketones are selectively protected (*cf.* XII) and permit reactions to be carried out at the carbonyls derived from the original enones. One can also reduce the carbonyl of the original adduct and deprotect at that point (XII → XIV), thus allowing selective operation, if desired, on the introduced group. We describe some of these operations with XII, R = CH_3. Reduction of the latter with sodium borohydride in isopropyl alcohol, followed by hydrolysis (with 1:1:2 acetic acid–water–tetrahydrofuran overnight at room temperature) and decomposition of the cyanohydrin by stirring for 2 hr at room temperature in acetone containing a few drops of triethylamine gave the hydroxyenone XIV (ir (film) 3400, 3025, 1695 (s-cis enone), 1640 (C=C) 970 (trans C=C) cm^{-1}). Oxidation of XIV with Jones reagent at 0–5° gave (70% overall from the original adduct XII) the enedione XV (ir (film) 3020, 1715, 1695, 1630, 970 cm^{-1}; nmr $\delta(CDCl_3)$ 1.23 (3 H, s), 1.90 (3 H, d of d, J_1 = 1.5, J_2 = 7 Hz), 6.47 (1 H, d of q, J_1 = 1.5, J_2 = 15 Hz), 7.07 (1 H, d of q, J_1 = 7, J_2 = 15 Hz)). The enediones XVI, XVII, and XVIII were prepared similarly.[6]



XIV XV XVI



XVII XVIII

We would finally like to point out that the vinyl ketone functionality resulting from the conjugate additions of III can serve as precursor (*via* hydrogenation,

(5) We thank Dr. A. Ozorio for carrying out these experiments.

(6) This route to enediones (*cf.* XV), involving initial reduction of the saturated carbonyl of the adduct, is desirable to avoid hydrogen cyanide transfer to the sometimes very stable (*e.g.*, with cyclohexanones) cyanohydrin derived from the saturated carbonyl of the enedione.

cuprate or Michael additions, *etc.*) of a variety of saturated and functionally substituted acyl groups.[7]

(7) We wish to thank Dr. Pierre Crabbé for his interest and Syntex S. A. for their generous gift of chemicals and the determination of a number of spectra. We also thank Research Corporation for a grant which allowed one of us (L. M.) to participate in this work.

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Stereospecific Aliphatic Hydroxylation by an Iron-Based Oxidant

Sir:

There has been much recent interest in the nature of iron species responsible for oxidation of organic substrates by mixed function oxidases as well as the relation of these intermediates to a number of nonenzymatic model systems.[1] While these studies have demonstrated the ability of nonenzymatic oxidants to effect aromatic hydroxylation and olefin epoxidation, there has been as yet no demonstration that a simple iron-derived reagent could mimic the stereospecific aliphatic hydroxylation observed in biological systems.[2] We report here an examination of the ferrous ion–hydrogen peroxide oxidation of cyclohexanol which has now revealed a pronounced regioselectivity and stereoselectivity for hydroxylation to cyclohexanediols. We interpret these results as evidence for the interception of a metal-bound oxidant, not free hydroxyl radical, which is subject to strong substituent-derived directive effects and may be a prototype of the reactive oxy–iron intermediates of the mixed function oxidases.

In a typical experiment, 30% hydrogen peroxide in acetonitrile was added to an acetonitrile solution of cyclohexanol containing perchloric acid and ferrous perchlorate.[1e] The entire reaction mixture was acetylated with acetic anhydride–pyridine for analysis of products by glpc. The only significant products were cyclohexanone and the diacetates of all six possible cyclohexanediols.[3]

Analysis of the diol products (Table I) reveals several startling features of this reaction. First, it is apparent that C-3 of cyclohexanol is intrinsically more reactive than either C-2 or C-4 when ferrous ion is used, accounting for more than 70% of the hydroxylation in the less aqueous medium. When cuprous ion is substituted for iron this specificity is lost and the most reactive position becomes C-4 with reactivity decreasing at positions closer to the electronegative substituent. This latter result is more in accord with predictions based on the operation of a polar effect,[4] even if the proportion of 1,2-diol is anomalously low. The specificity for C-3 attack is favored by removal of water from the system but temperature seems to have little effect between 25 and −18°.

Table I. Product Distribution for Cyclohexanol Hydroxylation

Isomer	%[a] a	b	c[b]	d
Cis-1,2	5.2	4.8	6.7	0.25
Trans-1,2	14.3	8.8	12.3	4.0
Cis-1,3	37.0	70.1	71.9	30.35
Trans-1,3	15.0	5.1	2.5	26.4
Cis-1,4	17.5	3.7	3.8	17.8
Trans-1,4	11.0	7.1	2.9	21.2
Diol yield (%)	36	25	66	29
Conversion (%)	17	12	6	7

[a] Results for adding 30% H_2O_2 (3.68 equiv) to a solution of cyclohexanol (0.19 *M*) and perchloric acid (0.1 *M*) in: (a) 50% CH_3CN–H_2O containing $Fe(ClO_4)_2$ (0.19 *M*) at 25°; (b) 90% CH_3CN–H_2O containing $Fe(ClO_4)_2$ (0.19 *M*) at 25°; (c) 90% CH_3CN–H_2O containing $Fe(ClO_4)_2$ (0.19 *M*) at −18°; (d) 50% CH_3CN–H_2O containing $Cu(ClO_4)_2$ (0.19 *M*) at 25°. [b] Relative rates of hydroxylation (per hydrogen): C-1, 150; C-2, 13; C-3, 106; C-4, 10; cyclohexane, 1.00.

The cis–trans ratios of the products are also revealing. In 50% aqueous acetonitrile the amounts of cis and trans products are comparable; however, in the less aqueous medium the ratio of cis- to trans-1,3-diol increases dramatically to 28.8:1. Thus, *the major diol product is formed with greater than 96% stereoselectivity* at −18°.

In competition experiments with toluene we find that k(cyclohexane)/k(toluene) = 0.27 on a per-hydrogen basis. This is not in accord with results obtained for chlorine atoms or *tert*-butoxy radicals for which k(cyclohexane)/k(toluene) is reported to be 2.35[5] and 1.50,[6] respectively. Another contrast is observed upon comparison of the relative rates of reaction of cyclohexane and cyclohexanol (Table I). First, the much greater reactivity of cyclohexanol is not in accord with the expected polar effect on an electrophilic free radical[4] (for example, k(cyclohexane)/k(cyclohexanol) = 1.63 for *tert*-butoxy radicals).[7] More interesting, however, is the comparison of the reactivity of C-3 in cyclohexanol to cyclohexane, *the former being 106 times more reactive.*

While these results appear inconsistent with a mechanism involving free hydroxyl radical,[1e,8] they are in accord with a scheme mediated instead by an iron species[9] (Scheme I). Chelation of this intermediate by cyclohexanol and hydrogen abstraction through a cyclic transition state reminiscent of the Barton reaction[10] would explain the high reactivity of the alcohol.

(1) (a) H. J. Fenton, *Proc. Chem. Soc., London*, **9**, 113 (1893); (b) W. A. Waters, "The Chemistry of Free Radical," Oxford University Press, New York, N. Y., 1948, p 247; (c) S. Undenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie, *J. Biol. Chem.*, **208**, 731 (1954); (d) G. A. Hamilton, J. W. Hanifin, and J. P. Friedman, *J. Amer. Chem. Soc.*, **88**, 5269 (1966); (e) C. Walling and S. Kato, *ibid.*, **93**, 4275 (1971); (f) K. B. Sharpless and T. C. Flood, *ibid.*, **93**, 2318 (1971); (g) K. B. Sharpless and R. C. Michaelson, *ibid.*, **95**, 6137 (1973); (h) H. S. Mason, *Annu. Rev. Biochem.*, **34**, 595 (1965).

(2) Stereospecific hydroxylation by chromium salts has been observed, K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1965, p 109 ff.

(3) These products accounted for all the cyclohexanol consumed. Appropriate controls were performed to establish the integrity of the products under the reaction conditions and the quantitative viability of the work-up and assay. Specifically absent were cyclohexenyl acetates, cyclohexane triacetates, and 4,4′-diacetoxydicyclohexyls.

(4) (a) C. Walling and B. Miller, *J. Amer. Chem. Soc.*, **79**, 4181 (1957); (b) G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958).

(5) G. A. Russell, *J. Amer. Chem. Soc.*, **80**, 4987 (1958).

(6) C. Walling and W. Thaler, *J. Amer. Chem. Soc.*, **83**, 3877 (1961).

(7) E. L. Patmore and R. J. Gritter, *J. Org. Chem.*, **27**, 4196 (1962).

(8) F. Haber and J. Weiss, *Proc. Roy. Soc., Ser. A*, **147**, 332 (1934).

(9) (a) W. C. Bray and M. H. Gorin, *J. Amer. Chem. Soc.*, **54**, 2124 (1932); (b) I. M. Kolthoff and A. I. Medalia, *ibid.*, **71**, 3777, 3784 (1949); (c) A. E. Cahill and H. Taube, *ibid.*, **74**, 2312 (1952); (d) D. L. Ingles, *Aust. J. Chem.*, **26**, 1621 (1973).

(10) (a) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechot, *J. Amer. Chem. Soc.*, **82**, 2640 (1960); (b) *ibid.*, **83**, 4076 (1961).