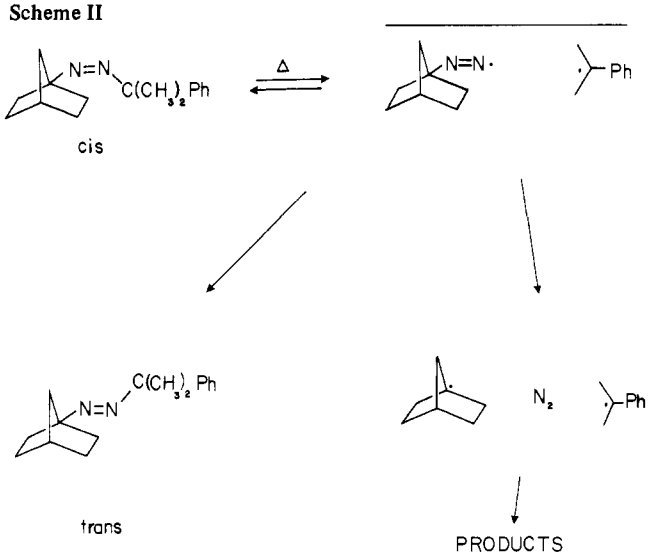
Scheme II



to decompose via intermediate diazenyl radicals,[2,3] this experiment provides strong support for alkyldiazenyl radicals during azo decomposition.

The proton CIDNP spectrum also supports the mechanism proposed in Scheme II. The vinyl and allylic protons of α-methylstyrene are polarized in the cumyl-1-norbornyldiazenyl radical pair. The AMS emission that results is predicted by the CKO rules[13,15] and is analogous to the results of ^{1}H CIDNP studies on the cumyl-phenyldiazenyl radical pair.[2,3]

Previously, evidence was presented that established the intermediacy of only two diazenyl radicals—the phenyl- and methyl-substituted species.[18] This work suggests that 1-norbornyl diazenyl radical also has a finite lifetime and emphasizes the effectiveness of ^{15}N CIDNP in studies of azo decomposition.

Acknowledgment. We gratefully acknowledge financial support from the National Science Foundation.

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(12) The enhancement factor for the cis signal was small but real (~1.5), and the trans enhancement factor was approximately 15.
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(14) We assume that $g_{diazenyl} < g_{cumyl}$ and that a (^{15}N) for both diazenyl nitrogens is negative. Gerhart and Seifert have calculated positive ^{14}N a values for the phenyldiazenyl radical (K. G. Seifert and F. Gerhart, *Tetrahedron Lett.*, 829 (1974)). However, because of the negative gyromagnetic ratio, the sign of the ^{15}N hyperfine should be the negative of the ^{14}N value (A. R. Forrester, J. M. Hay, and R. H. Thompson, "Organic Chemistry of Stable Free Radicals", Academic Press, New York, N.Y., 1968, p 27).
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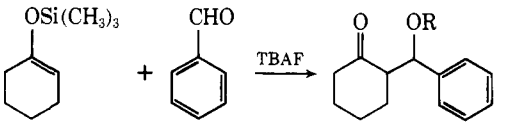
Fluoride Ion Catalyzed Aldol Reaction between Enol Silyl Ethers and Carbonyl Compounds

Sir:

The title reaction[1] exhibits various characteristic features which have not been observed in ordinary aldol reaction[2] involving Lewis acid-complexed enolates[3] or species in hydroxylic solvents.

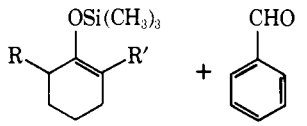
Under the influence of *a catalytic amount* (5-10 mol %) of tetrabutylammonium fluoride (TBAF), the enol trimethylsilyl ether **1** reacted with an equimolar amount of benzaldehyde in THF smoothly at low temperatures, giving the aldol silyl ether **2** in > 80% yield.[4] Workup with aqueous CH_3COOH, dilute HCl, or KF-CH_3OH afforded quantitatively the corresponding aldol **3**. This reaction gives no or very little products arising from undesired dehydration, self-condensation, or polyaldol condensation which frequently takes place under conventional aldol reaction conditions.[2]



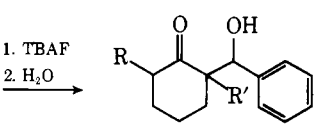
1

2, R = $Si(CH_3)_3$
3, R = H

This cross aldol reaction finds considerable generality. In place of **1**, enol trimethylsilyl ethers of cyclopentanone, cycloheptanone, diethyl ketone, pinacolone, etc., could be used as well. Enol silyl ethers derived from sterically hindered ketones such as diisobutyl ketone may be equally employable. Both aromatic aldehydes, ArCHO (Ar = C_6H_5, *p*-$CH_3OC_6H_4$, *p*-$NO_2C_6H_4$, α-furyl, etc.), and aliphatic aldehydes (heptanal, isobutyraldehyde, 3-phenylpropanal, etc.) are usable, but, in usual, aromatic aldehydes serve as a better receptor (usually 70-95% yield) than aliphatic ones (35-50%). When α,β-unsaturated aldehydes such as cinnamaldehyde or 2-hexenal were used, only 1,2-addition products were formed (50-60%). The catalyzed reaction proceeds regiospecifically. Thus each of the enol silyl ethers **4** and **6** reacted with benz-



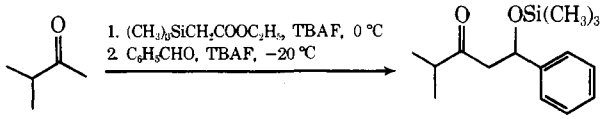
4, R = CH_3; R′ = H
6, R = H; R′ = CH_3



5, R = CH_3; R′ = H; 68%
7, R = H; R′ = CH_3; 62%

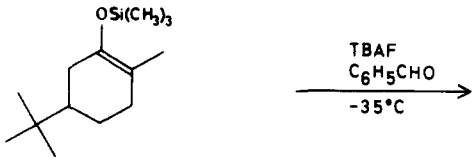
aldehyde to afford, without any crossover, the expected regioisomer of the aldol products, **5** or **7**.[5]

Nucleophilic attack of fluoride ion occurs specifically to silicon atom rather than electronegative sp^3- or sp^2-hybridized carbon.[1,7] Further, the reaction system is only moderately basic.[8] In view of such mildness of the conditions, the present aldol reaction, complementary to the previously discovered $TiCl_4$-promoted reaction,[6] provides a new tool in organic synthesis. Combination of this aldol reaction with the recently developed silyl-transfer method[9] has realized a cross-aldol reaction under extremely mild conditions. For example, reaction of isopropyl methyl ketone and benzaldehyde, giving **8**, was performed in a single pot without isolating the enol silyl ether.



8, 52%

Close examination of the reaction has disclosed several characteristics that distinguish the reactivities of the intermediates from those of the ordinary metal complexed enolates. The first point is a remarkably high specificity in the stereochemical course of the reaction. The TBAF-catalyzed reaction of the enol silyl ether **9** and benzaldehyde at −35 °C for 2 h yielded only the stereoisomers **10a** and **10b** that bear the newly introduced siloxybenzyl group in the axial position (64:36 ratio, 68% yield). This evidently indicates that the attack of the aldehyde onto the six-membered ring occurs exclusively through the axial approach via a kinetically favored chair-like transition state. This result is to be compared with the reaction of the zinc enolate that gives not only the axial aldols but also ca. 40% of the equatorial isomers.[3] Such a rigorous steroelectronic control has not been reported for the introduction of an α-substituent to simple cyclohexanone derivatives.



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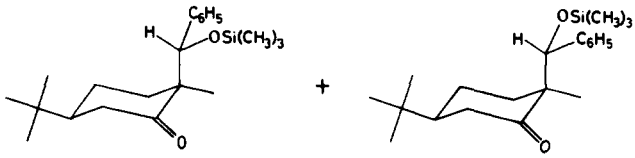
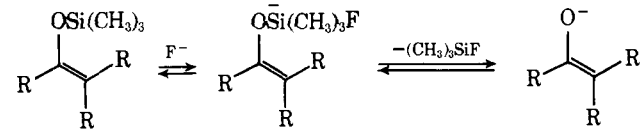


10a **10b**

The proportion of the aldol diastereomers depends on reaction period. For instance, ratio of *threo*-**7** to *erythro*-**7**, obtained by the TBAF-aided reaction of **6** and benzaldehyde at −78 °C followed by brief treatment with dilute HCl in CH_3OH,[10] changed gradually from 33:67 (5 min, 21% yield) until a 26:74 equilibrium was reached (10.5 h, 64% yield). When the reaction of **1** and benzaldehyde was monitored, ratio of *threo*-**3** to *erythro*-**3** was found to vary from 65:35 (5 min, 45%) to 54:46 (8 h, 86%). The latter ratio may be close to 1:1 observed in the reaction of cyclohexanone and benzaldehyde in aqueous NaOH at 25 °C (equilibrium conditions).[3] It lies, however, in marked contrast to the ratio observed for the case of zinc enolate (*threo*-**3**:*erythro*-**3** = 5:1)[3] or that of the $TiCl_4$-mediated reaction of **1** and benzaldehyde, 3:1,[6] where relative stabilities of the intermediary aldol chelates are the controlling factor.

Notably, the present aldol reaction displays unprecedented high chemoselectivity. Aldehydes undergo the aldol reaction quite readily, while ordinary aliphatic or aromatic ketones including benzophenone do not form the aldol adducts at all. In addition, epoxy rings are not displaced either, marking another point of difference in this reaction and those of lithium-[11] or other Lewis acid-complexed enolates.[12]

This reaction appears to proceed through a catalytic cycle involving reversible steps.[13] All the findings can be reasonably understood by considering the naked enolates of type **12** that are neither hydrogen-bonded nor interacted with any counter metal ions.[1] However, direct evidence for the intermediacy of **12** has not been obtained yet, and the anionic pentavalent silicon species **11** may also account for the characteristics of the present aldol reaction.



11 ·**12**

Acknowledgment. The author (R.N.) thanks Professor H. O. House for a generous supply of authentic aldol products derived from 5-*tert*-butyl-2-methylcyclohexanone and benzaldehyde.

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(6) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).
(7) Even in the presence of diethyl ethylidenemalonate, an extremely good electrophile, fluoride ion attacks specifically an enol silyl ether to effect Michael addition of the enolate molety.
(8) TBAF does not cause aldol reaction of cyclohexanone and benzaldehyde in THF. Moreover, it proved to be a mildly basic reagent; I. Kuwajima, T. Murofushi, and E. Nakamura, *Synthesis*, 602 (1976). See also note 4 in ref 9.
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(13) The reversibility of the reaction is attested to by several observations: (1) ratio of the diastereomeric products is time dependent; (2) treatment of trimethylsilyl ether of cyclohexanone–dibutyl ketone aldol product with a catalytic amount of TBAF caused complete decomposition, giving the two parent ketones in ca. 90% yields after aqueous workup; and (3) in

certain reactions, the product yield was increased by the addition of fluorotrimethylsilane (but not chlorotrimethylsilane). Cf. C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed, Cornell University Press, Ithaca and London, 1969, Chapter 13.

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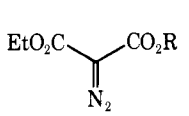
A New Class of Potential Photoaffinity Labels. α-Diazophosphonic Acids: Synthesis and Stability

Sir:

The technique of photoaffinity labeling has rapidly become a popular method for the covalent attachment of substrate analogues to protein binding sites.[1] Much of this popularity stems from an increasing demand for a versatile, specific labeling technique which is applicable to the study of heterogeneous systems, such as ribosomal and membrane-bound proteins.[2] Various problems are associated with the most commonly used photoactivated functional groups, the diazomalonyl esters (**1**)[3] and the aryl azides (**2**).[4] One of these problems arises from their "irrelevance" to most biological systems of interest, and requires that they be appended to a noninterfering region of a larger molecule which binds to the protein in question. This stricture precludes their use for small or highly selective binding sites, and no doubt in some cases forces them to project away from the protein, into solution. Recently, other functional groups, such as aryldiazirines,[5] aryl ketones,[6] phosphoryl azides,[7] 2-diazo-3,3,3-trifluoropropionates,[8] and α-diazobenzylphosphonate dianion,[9] have been suggested for photoaffinity labeling, but for the most part they do not address this problem.



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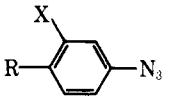
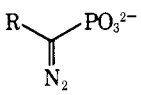


2

We are interested in α-diazophosphonic acids (**3**) as possible photoaffinity labeling reagents which may surmount these limitations. Our intention is that they may mimic the analogous phosphates (**4**) and make available a wide range of potential labeling reagents. In this communication we describe the synthesis and characterization of three diazophosphonic acids: the diethylsulfamoyl, diisopropylphosphono, and dimethylcarbamoyl derivatives of diazomethylphosphonic acid, **3a–3c**.



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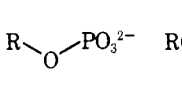

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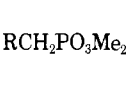

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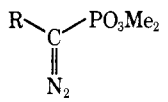

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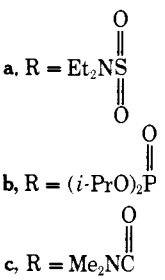
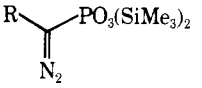


Except for a recent report[9] on the synthesis, in undisclosed yield, of the relatively unstable α-diazobenzylphosphonic dianion (**3**, R = Ph), no other α-diazophosphonic acid has been described, although the synthesis of their dialkyl esters is well-established.[10] In the present instance, condensation of dimethyl phosphorochloridate with the anions derived from *N,N*-diethylmethanesulfonamide and diisopropyl methylphosphonate afforded the methylene derivatives **5a**[11] and **5b**[11] in yields of 66 and 71%, respectively. The corresponding diazo compounds (**6**)[12] were prepared in more than 80% yield by treatment of these materials, and the dimethylcarbamoyl derivative (**5c**),[11,13] with potassium hydride and *p*-toluenesulfonyl azide in THF at 0–25 °C.[10] Transesterification of the methyl esters with bromotrimethylsilane[14] was rapid at 0–25 °C, cleanly furnishing the extremely moisture-sensitive bis(trimethylsilyl)esters (**7**), which were hydrolyzed under very mild



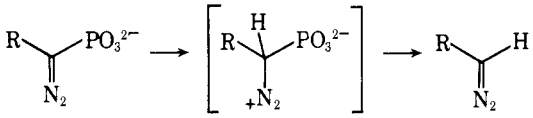
7

(pH 8–9) aqueous conditions without further purification. This two-step hydrolysis sequence is essentially quantitative and allows one to take advantage of the stability and convenience of phosphonate methyl esters.

Our major concern at the outset was the lifetime of the diazophosphonic acids at biochemically useful pH, when the stabilization of the diazo moiety by the phosphono group is reduced by ionization. For instance, while ethyl diazoacetate and diethyl diazomalonate are reasonably stable at neutral pH, diazoacetate ion and diazomalonate dianion have half-lives on the order of only 2 min and 3 h, respectively, under these conditions.[15] The half-life for decomposition of α-diazobenzylphosphonate dianion is also very short in aqueous solution (e.g., <1 min at pH 8.0 in 0.1 M Tris/KCl at 25 °C), although it can be prolonged by judicious choice of buffer.[9] However, the ^{13}C NMR spectra (Table I) of the materials produced on hydrolysis of **7a–7c** at pH > 9 clearly indicate that the desired functionality survives the ester hydrolysis procedure and that the diazophosphonic acids **3a–3c** can in fact be obtained by this route.

The most striking change in the ^{13}C NMR spectrum on going from the diesters to the dianions is the approximately 60-Hz decrease in the coupling constant of the diazo carbon to the phosphorus in question.[16] This reduction in coupling constant most likely reflects the expected decrease in interaction between the electron-rich α-carbon and the phosphorus as the electronegativity of the phosphorus moiety declines on ionization.

The stability and mode of decomposition of the phosphonates **3a–3c** were followed by ultraviolet spectroscopy at lower pH in 0.2 M potassium phosphate at 21–22 °C. In each case, the behavior was consistent with the two-step process of eq. 1,



3 **9** **10**

$$+ P_i \longrightarrow \text{loss of chromophore} \qquad (1)$$

with initial loss of phosphate followed in a slower step by decomposition of the neutral diazo compound (**10**). After completion, or near completion, of the first step in the decomposition of **3**, extraction of the aqueous solution with CH_2Cl_2 affords a neutral material, with the UV spectrum of the intermediate (Table II). In the case of the carbamoyl derivative, this substance was identical with an authentic sample of **10c**[17]