**Table I.** $^{17}O$ Spectral Data for Polyoxomolybdates

| | Compound[a] | Solvent, Temp, °C | [Mo],[b] M | No. of pulses | Chemical shifts (line widths)[c] |
|---|---|---|---|---|---|
| **1** | $Na_6TeMo_6O_{24}\cdot 2H_2O$ | $H_2O$ (pH 5.8), 82 | 8.6 | 4 465 | −807 (15), −383 (15), −180 (40) |
| **2** | $Na_6Mo_7O_{24}\cdot 4H_2O$ | $H_2O$ (pH 5.5), 25 | 5.8 | 9 061 | −821 (60), −758 (18), −400 (25), −338 (20), −123 (15) |
| | | $H_2O$ (pH 5.5), 25 | 2.8 | 12 844 | −814 (40), −757 (14), −395 (18), −335 (15), −123 (11) |
| **3** | $Na_5IMo_6O_{24}\cdot 3H_2O$ | $H_2O$ (pH 5), 95 | 4.7 | 11 021 | −825 (6), −385 (8), −256 (50) |
| **4** | $Na_3H_6AlMo_6O_{24}\cdot 4H_2O$ | $H_2O$ (pH 4.1), 25 | 1.9 | 16 384 | −831 (20), −376 (20) |
| **5** | $Na_3H_6CoMo_6O_{24}\cdot 8H_2O$ | $H_2O$ (pH 2.6), 93 | 1.2 | 10 320 | −838 (6), −382 (8) |
| **6** | $[(n\text{-}C_4H_9)_4N]_2Mo_6O_{19}$ | $(CH_3)_2NCHO$, 25 | 1.4 | 5 729 | −927 (10), −559 (4), +32 (<2) |
| **7** | $\alpha\text{-}[(n\text{-}C_4H_9)_4N]_4SiMo_{12}O_{40}$ | $CH_3CN$, 75 | 0.2 | 131 072 | −928 (8), −579 (6), −553 (12), −42 (10) |
| **8** | $\alpha\text{-}[(n\text{-}C_4H_9)_4N]_3PMo_{12}O_{40}$ | $CH_3CN$, 79 | 0.3 | 18 701 | −939 (4), −586 (5), −554 (7) |
| | | $CH_3CN$, 25 | 0.1 | 131 072 | −939 (6), −584 (8), −553 (15) |

[a] All oxygen nuclei were $^{17}O$ enriched to about 2 atom % except for the four oxygens bonded to phosphorus in **8**. [b] Total molybdenum concentration in moles per liter. [c] Positive chemical shift is in parts per million upfield from pure $H_2O$ at 25 °C, externally referenced. Approximate line width is in parts per million at 13.5 MHz.

for nonequivalent doubly bridging oxygens in **7** and **8** to be resolved. The quadruply bridging oxygen resonance for **8** was not observed due to lack of enrichment at this site.

Examination of Figure 2 in its entirety confirms the correlation between upfield shift and increasing degree of bridging noted earlier. Moreover, the clustering of chemical shifts within the O-Mo and O-$Mo_2$ regions allow more detailed interpretation of $^{17}O$ chemical shifts to be made: (1) resonances from about −900 to −1000 ppm are all assigned to terminal oxygens bonded to molybdenums which have only one terminal oxygen, i.e., monoxo terminal oxygens; (2) resonances from about −800 to −900 ppm are all assigned to terminal oxygens bonded to molybdenums having two terminal oxygens, i.e., dioxo terminal oxygens; (3) the resonance at −757 ppm is assigned to oxygens bridging a molybdenum which has no terminal oxygen and a molybdenum which has two terminal oxygens; (4) resonances between about −500 and −650 ppm are all assigned to oxygens which bridge two molybdenums, each of which has only one terminal oxygen; (5) resonances between about −350 and −500 ppm are all assigned to oxygens which bridge two molybdenums, each of which has two terminal oxygens. We choose at this point to base this relationship between oxygen environment and chemical shift purely on empirical data. It should be mentioned, however, that this interpretation is entirely consistent with the postulate that lower electron density on an oxygen atom leads to a greater downfield shift.

The value of a chemical shift scale depends strongly on the absence of marked solvent and temperature effects on chemical shifts and the ability to obtain narrow line widths and hence resolve nearly degenerate resonances. Fortunately, solvent and temperature effects have thus far been insignificant. Quadrupole broadening of $^{17}O$ resonances poses a more serious problem. Significant line narrowing can in general be obtained, however, by lowering solution concentrations and hence lowering viscosity, using solvents having low viscosities, and raising solution temperatures (see Table I).

Having established a quantitative chemical shift scale, we are now in a position to utilize $^{17}O$ NMR for the structural elucidation of polyoxomolybdates having unknown structures. The results of such studies will be reported in the near future.

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(1) A. D. English, J. P. Jesson, W. G. Klemperer, T. Mamouneas, L. Messerle, W. Shum, and A. Tramontano, *J. Am. Chem. Soc.*, **97**, 4785–6 (1975).
(2) The spectrum of $Mo_6O_{19}^{2-}$ shown in Figure 1b of ref 1 was obtained by pulsing between the resonances at −927 and −559 ppm, resulting in the folding over of the −927 ppm resonance to an apparent −829 ppm. In addition, the labels for the solvent resonance and bridging oxygen resonance were permuted. The correct spectrum is shown in Figure 1a of this communication. The resonances tentatively assigned to $V_{10}O_{26}^{6-}$ oxygens in ref 1 are also in large part erroneous due to the folding over of a resonance at −1155 ppm.
(3) H. T. Evans, Jr., *Perspect. Struct. Chem.*, **4**, 1–59 (1971).
(4) The hexamolybdate ion in **6** has the same configuration as the hexaniobate ion shown in ref 3: H. R. Allcock, E. C. Bissell, and E. T. Shawl, *Inorg. Chem.*, **12**, 2963 (1973).

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## Quaternary Ammonium Enolates as Synthetic Intermediates. Trimethylsilylacetate: A New Class of Silylating Reagent for Ketones and Alcohols

*Sir:*

Among various silylating reagents,[1] e.g., base-chlorosilane, silylamide, silylamine, etc., the combination of base and chlorosilane has been used as a standard method for the silylation of ketones.[2] Nevertheless, product yields in such a silylation method are not always very high, and a large amount of inorganic salt or HCl-amine salt accompanies the reaction. Further, aqueous workup usually needed has often made the preparation of moisture-sensitive silyl ethers difficult. We report here a new type of silylation reagent, ethyl trimethylsilylacetate-tetra-*n*-butylammonium fluoride (ETSA-TBAF), which circumvents these difficulties.

**Table I.** Silylation of Ketones and Alcohols with ETSA Catalyzed by TBAF[a]

| RR'C=O or ROH | % yield,[b,c] | Bp, °C (mmHg) |
|---|---|---|
| Acetophenone | 98 | 144 (90)[d] |
| Cyclopentanone | 74 | 99 (140)[d] |
| Cyclohexanone | 98 | 86 (40)[d] |
| Cycloheptanone | 94 | 147 (150) |
| Cyclooctanone | 86 | 106 (25) |
| Cyclododecanone | 94 | 142 (18) |
| 3-Phenylpropanol | 92 | 90 (4)[e] |
| Diisopropylphenylcarbinol | 92 | 110 (7) |

[a] The reaction (10–30 mmol scale) was carried out at room temperature for 1–3 h with 0.01–0.003 equiv of TBAF. [b] Yield of distilled product. [c] Consistent NMR, ir, and mass spectral data have been obtained on all new compounds. [d] Reference 2b. [e] Bath temperature.

An investigation into the reactivities of quaternary ammonium enolates[3] introduced a mild and operationally simple procedure for the silylation of ketones and alcohols which proceeds under nearly neutral conditions,[4] and allows easy isolation of pure products under nonaqueous conditions. We found that, in the presence of a catalytic amount of tetra-*n*-butylammonium fluoride (TBAF),[5] ethyl trimethylsilylacetate (ETSA)[6] silylates ketones and alcohols in excellent yields (Table I). The reaction proceeds smoothly at a temperature around 25° and essentially needs no solvent. The amount of the catalyst, TBAF, can be as small as 0.003 equiv in the silylation of ketones, and about several times more is needed in that of alcohols. In addition to the formation of the Si–O bond, this procedure may also be applied to the Si–C bond formation. Thus phenylacetylene is silylated in 88% yield. The reaction pathway of this silylation reaction

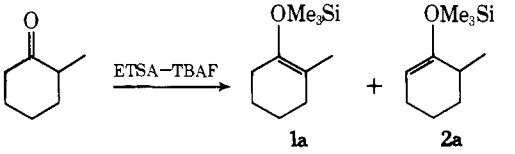
$$C_6H_5C{\equiv}CH + ETSA \xrightarrow[THF]{TBAF,\ room\ temp} C_6H_5C{\equiv}CSiMe_3$$

is explicable in terms of the deprotonation by an ester enolate and the subsequent silylation by trimethylfluorosilane ($Me_3SiF$).

$$Me_3SiCH_2COOEt \xrightarrow[-Me_3SiF]{+TBAF} [^-CH_2COOEt] \xrightarrow{R-H} R^- + CH_3COOEt$$

$$R^- \xrightarrow[-TBAF]{+Me_3SiF} R{-}SiMe_3$$

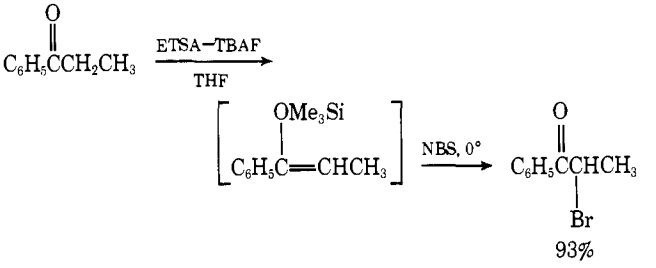
Relatively high regioselectivity was attained in the silylation of unsymmetrical ketones (Table II). The silylation of 2-methylcyclohexanone at −78° and at 0° (entries 1 and 2) indicates that the kinetic deprotonation by the enolate anion predominated, and that the fluoride catalyzed equilibration of enolates (vide infra) was slow in this temperature range. The regioselectivity of the kinetic silylation was as high as 93% with methyl isopropyl ketone, and 90% with methyl isobutyl ketone (entries 4 and 5).[7] When carried out at elevated temperatures, this procedure was found to be an effective method to obtain an equilibrium mixture of a silyl enol ether (entry 3).[8] The silylation of 2-methylcyclohexanone in refluxing dioxane showed a final product ratio, **1a**:**2a** = 82:18, which is essentially identical with those previously reported.[9] As for conjugated ketones, β-ionone was deprotonated in very high regioselectivity at the terminal methyl position,[10] while mesityl oxide was silylated in poor regioselectivity.




**1a** **2a**

The general procedure of the silylation is as follows. To a weighed amount of TBAF[11] (0.03–0.003 equiv) kept under argon is added at 0° a mixture of a ketone or an alcohol and ETSA (1.0–1.1 equiv) with the aid of a hypodermic syringe, which is washed with a small amount of dry tetrahydrofuran. The reaction takes place immediately, accompanied by slight evolution of heat, and the color of the reaction mixture changes to brown. After stirring for a requisite period[12] at room temperature, the reaction mixture is freed of volatile material, or diluted with *n*-hexane, filtered, and concentrated. Short-path distillation of the remaining material, which is usually almost pure, gives the desired silylated product.

The only side product being volatile ethyl acetate, the silylation process which is described herein should also be useful for large molecules, and should exalt the synthetic utility of silyl enol ether itself to a great extent. Addition of an aldehyde[3b] or *N*-bromosuccinimide,[13] for instance, to the crude reaction mixture resulting from silylation of ketones afforded an aldol or a brominated product in good yield.



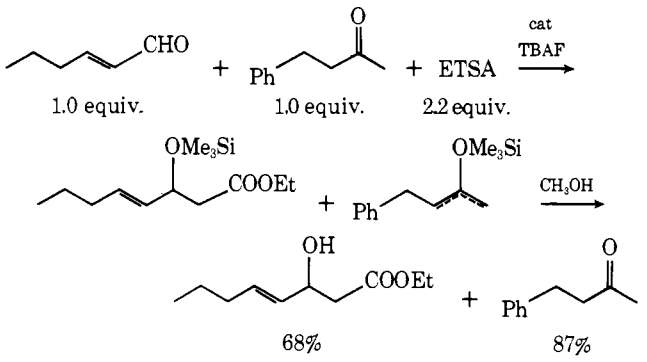

In contrast to the standard silylating reagent, chlorosilane, ETSA–TBAF does not react with epoxides, and the silylation can be performed in their presence. While esters and nitriles[14] are almost inert to the reagent, aldehydes and

**Table II.** Silylation of Unsymmetrical Ketones by ETSA–TBAF

| Entry | RR'C=O | Condn[a] | TBAF, equiv | % yield[b] | Isomer ratio,[c] % 1 | 2 |
|---|---|---|---|---|---|---|
| 1 | 2-Methylcyclohexanone | A | 1/30 | – | 20 | 80 |
| 2 | | B | 1/100 | 98 | 30 | 70 |
| 3 | | C | 1/50 | 75 | 60 | 40 |
| 4 | Methyl isopropyl ketone | B | 1/200 | 84[d] | 7 | 93 |
| 5 | Methyl isobutyl ketone | B | 1/200 | 79[d] | 10 | 90 |
| 6 | Benzylacetone | D | 1/100 | 88[d] | 38 | 62 |

[a] (A) −78°, 5 h; (B) 0°, 2 h; (C) refluxing THF, 1.5 h; (D) −30°, 1.5 h. [b] Distilled yields. [c] Determined by GLC or NMR: **1**, an isomer with more highly substituted olefin; **2**, one with less highly substituted olefin. [d] Consistent NMR, ir, and mass spectral data have been obtained.

reactive halides are not. Especially aldehydes react with ETSA-TBAF as smoothly as ketones to afford β-trimethylsiloxy ester adducts:[15] for example, *trans*-2-hexenal, benzaldehyde, and β-phenylpropionaldehyde reacted with ETSA at −30° in the presence of a catalytic amount of TBAF to give the corresponding adducts in 82, 76, and 24% yields, respectively. Namely, when this silylation procedure is applied to aldehydes, it offers us a simple and selective way of introducing carboalkoxymethyl groups which discriminate between aldehydes and ketones. The following example illustrates this selectivity.

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(2) (a) G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4462 (1968); (b) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(3) (a) I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3257 (1975). (b) Quaternary ammonium enolates underwent aldol reactions with aldehydes: unpublished results by the authors and Professor R. Noyori, Nagoya University.

(4) TBAF has been proved to be a relatively weak base. For example, 0.03 equiv of TBAF in THF caused only very slow base-catalyzed reactions of alkyl thiols and diethyl malonate; it catalyzed no condensation between cyclohexanone and benzaldehyde, either: unpublished results. In addition, under the reaction conditions described here, β-trimethylsiloxy esters remained unchanged: cf. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

(5) (a) Neutralization of commercial 10% aqueous tetra-*n*-butylammonium hydroxide with dilute aqueous HF gave TBAF. The bulk of water was removed, and the paste was dried at 90°, 0.5 mm for 15 h. The resulting hygroscopic mass was pulverized and stored over $P_2O_5$. (b) With KF (0.02 equiv) and dicyclohexyl-18-crown-6 (0.01 equiv) in THF, this catalyzed reaction proceeded well at room temperature, but it took about 1 week for completion.

(6) Trimethylchlorosilane and ethyl bromoacetate reacted in the presence of zinc dust to give ETSA in 70–75% yield, which was practically stable: R. J. Fessenden and J. S. Fessenden, *J. Org. Chem.*, **32**, 3535 (1967).

(7) On silylation of acetoin, the silylation proceeded regiospecifically, and gave none of the isomer, 2,3-bis(trimethylsiloxy)-2-butene (NMR and GLC), while the yield was fair.

(8) Because of some reaction path which may consume fluoride ion, an increased amount of TBAF was required at elevated temperatures in order to obtain a fully equilibrated mixture of a silyl enol ether.

(9) The ratios, 1a:2a = 81:19 and 91:9 were reported by House and Stork, respectively.[2]

(10) The NMR spectrum of the silylated product was completely consistent with the silyl enol ether with a less highly substituted olefinic bond; δ 4.21 (s, 2 H), 5.73 (d, $J$ = 16 Hz, 1 H), 6.36 (br d, $J$ = 16 Hz, 1 H). Treatment of the crude reaction mixture with NBS gave solely the expected bromomethyl ketone in 71% overall yield.

(11) While the reactivity of TBAF rapidly diminishes on exposure to moisture, rapid manipulation in air meets with success.

(12) With 0.003 equiv of TBAF, ketones were silylated in 3 h at ca. 20°.

(13) R. H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).

(14) On silylation in 1 M $CH_3CN$, cyclododecanone was silylated in 86% yield.

(15) L. Birkofer, A. Ritter, and H. Wieden, *Chem. Ber.*, **95**, 971 (1962); L. Birkofer and A. Ritter, *Angew. Chem.*, **77**, 414 (1965).



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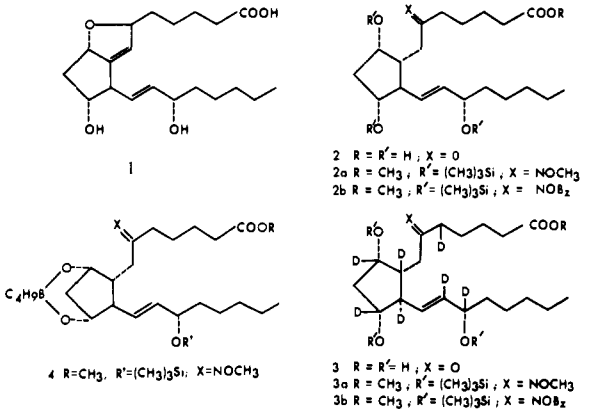
## Isolation, Structure, and Biosynthesis of 6-Ketoprostaglandin $F_{1\alpha}$ in the Rat Stomach

*Sir:*

During our studies of the mechanism of biosynthesis of 6(9)-oxy-11,15-dihydroxyprosta-7,13-dienoic acid (**1**), which was isolated and characterized by us several years ago,[1-3] we discovered the presence of another compound (**2**). This communication deals with evidence supporting its proposed structure i.e., 6-keto-$PGF_{1\alpha}$, evidence arising from biosynthetic studies using as substrates undeuterated as well as 5,6,8,9,11,12,14,15-octatritio-(and octadeuterio)-arachidonic acid and 5,6,8,9,11,12,14,15-octatritio-(and octadeuterio)-15-hydroxy- and -15-hydroperoxyprosta-5,13-dienoate 9,11-cyclic endoperoxide ($PGH_2$ and $PGG_2$, respectively).[4-6]

Substrate (100–200 μg) was incubated (10 min, 37°, $O_2$ atmosphere with arachidonic acid substrate or 2 min with $PGG_2$ and $PGH_2$ substrate) with a homogenate (w/v 1/20) of the rat stomach fundus (12 male Wistar rats, 200–250 g) prepared in 0.05 M $KH_2PO_4$–NaOH buffer (pH 7.4) containing EDTA (20 mM). Incubations were terminated by the addition of water (2 vol) and diethyl ether (10 vol) and the mixture was acidified to pH 3 with 0.5 N HCl. The ether phase was separated, washed to neutrality with water and evaporated under vacuum. The extract was methylated with ethereal diazomethane and the resulting methyl ester was purified by thin layer chromatography (silica gel G/chloroform:methanol:acetic acid:water 90:9:1:0.65 v/v).




The purified TLC zone ($R_f$ 0.45; $PGE_2$ = 0.43) was only slightly reactive to sodium borohydride or 0.5 N sodium hydroxide in methanol. Both of these reactions convert $PGE_2$ formed in small amounts during incubation and present in this TLC zone to $PGF_{2\alpha}$ and $PGF_{2\beta}$ and $PGB_2$, respectively. Compound **2**, however, reacted with methoxylamine hydrochloride (derivative a) and benzylhydroxylamine hydrochloride (derivative b) in pyridine and these derivatives were analyzed as the trimethylsilyl ether derivatives by mass spectrometry.[7] Derivative **2a** (retention time 25.2 carbons; $PGE_2$ = 23.8, 24.3 carbons—3% SE-30 on Gas Chrom Q, 260°) showed intense fragment ions at *m/e* 629 ($M^+$), 614 (M − $CH_3$), 598 (M − $OCH_3$), 558 (M − $C_5H_{11}$), 539 (M − $(CH_3)_3SiOH$), 508 (M − ($OCH_3$ + $(CH_3)_3SiOH$)), 468 (M − ($C_5H_{11}$ + $(CH_3)_3SiOH$)), 449 (M − (2 × $(CH_3)_3SiOH$)), 418 (M − ((2 × 90) + 31)), 378 (M − ($C_5H_{11}$ + (2 × $(CH_3)_3SiOH$ + $OCH_3$)) 217 ($(CH_3)_3$ $Si^+O$=CHCH=CHOSi$(CH_3)_3$), 191 ($(CH_3)_3Si$-$^+O$=CHOSi$(CH_3)_3$), 173 ($(CH_3)_3Si^+O$=$CHC_5H_{11}$), and 115 (C(1)-C(5) fragment, base peak).[8] The benzylhydroxylamine derivative **2b** (retention time 29.5 carbons first isomer; 29.9 carbons second isomer—3% OV-1 on Gas Chrom Q, 240°) showed fragment ions containing the benzyloxime group (first isomer) observed at *m/e* 690 (M − $CH_3$), 615