Registry No.—Sodium bisulfite, 7631-90-5; 1-methylcytosine, 1122-47-0; 1,4-dimethylcytosine, 6220-49-1; 4,4-dimethylcytosine, 6220-48-0; 1,4,4-trimethylcytosine, 2228-27-5; 4,5-dimethylcytosine, 62006-34-2; 1-methyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-35-3; 1,4-dimethyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-36-4; 4,4-dimethyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-37-5; 1,4,4-trimethyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-05-7; 4,5-dimethyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-06-8; sodium 1-methyl-5,6-dihydrocytosine-6-sulfonate, 62006-07-9; sodium 1,4-dimethyl-5,6-dihydrocytosine-6-sulfonate, 62006-08-0; sodium 4,4-dimethyl-5,6-dihydrocytosine-6-sulfonate, 62006-09-1; sodium 1,4,4-trimethyl-5,6-dihydrocytosine-6-sulfonate, 62006-10-4; sodium 4,5-dimethyl-5,6-dihydrocytosine-6-sulfonate 62029-61-2; 5,6-dihydrocytidine-6-sulfonic acid, 29725-37-9; sodium 5,6-dihydrocytidine-6-sulfonate, 62006-11-5.

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Coordinative Role of Alkali Cations in Organic Reactions. 1. Selective Methylation of the Alcoholic Group of Kojic Acid

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There is no method in the literature which describes methylation of an alcoholic group of an organic compound in the presence of its phenolic group. Kojic acid, 5-hydroxy-2-hydroxymethyl-γ-pyrone (HkH), can be methylated to 5-methoxy-2-hydroxymethyl-γ-pyrone (MkH) with diazomethane[1,2] or by treating a 1:1 mixture of HkH and KOH with a stoichiometric amount of dimethyl sulfate (DMS).[3] Both the hydroxyl groups of HkH can be methylated using an excess of KOH and DMS[2,4] to produce MkM.

There is no rationalized method of methylating HkH to obtain 5-hydroxy-2-methoxymethyl-γ-pyrone (HkM). However, the latter is reported[5] produced along with MkM when an aqueous solution of HkH (1 mol) and KOH (6 mol) is treated with DMS (3.7 mol). We feel that HkM is produced in this reaction because the amount of KOH overweighs that of DMS and the phenoxy site gets protected against the incipient CH_3^+ by K^+. This suggested to us the synthesis of HkM employing an excess of LiOH as alkali for a 1:1 reaction mixture of HkH and DMS. It was found that a threefold excess of LiOH could perfectly protect the phenoxy site (through the formation of partly covalent lithium kojate, $Li^+ {}^-kH$) in water against a stoichiometric amount of DMS at and below 40 °C.

Synthesis of HkM. Take 2.84 g (0.01 mol) of HkH and 2.60 g (0.03 mol) of $LiOH \cdot H_2O$ in 15 mL of water and maintain the reaction mixture at 35–40 °C. Add dropwise 1.7 mL (0.013 mol) of DMS in about 20 min while stirring constantly. Keep the reaction mixture for 30 min and add 2 N HCl to pH 6 and evaporate the solution to a semisolid employing a rotary evaporator. Extract HkM with six lots (10 mL) of benzene and crystallize it by expelling the latter at room temperature, yield ca. 55% (mp 72–74 °C, lit. mp 75–76 °C). The product can be recrystallized from ethyl acetate.[5]

Below 35 °C the reaction appears to be too slow whereas at 35–40 °C a fraction of DMS gets destroyed owing to alkali present in excess. Consequently, the yield of HkM is promoted by using a slight excess of DMS at 35–40 °C; DMS exceeding the recommended amount favors the formation of MkM. The product and an authentic sample of HkM both give a red color with ferric chloride. Infrared spectra of both show a broad band at 3300 cm^{-1} indicative of a free phenolic hydroxyl group ($-CH_2OH$ of HkH and MkH absorbs at about 3200 cm^{-1}). ^1H NMR spectra (80 MHz in D_2O) of both show an absorption at 2.7 ppm which is characteristic of the $-CH_2OCH_3$ methyl protons ($-OCH_3$ protons of MkH and MkM produce a singlet around 3 ppm).

Discussion

Methylation of $-CH_2OH$, obviously, is due to coordination of this group with Li^+, for this aids polarization of the alcoholic proton and its elimination with OH^-. The resulting oxide directly associates with the incipient CH_3^+ instead of Li^+ to produce $-CH_2OCH_3$. If ion pairing of the oxide with Li^+ should have taken place preferentially then conversion of $-CH_2OLi$ to $-CH_2OCH_3$ should have not been possible, for Li^+ cannot be replaced with CH_3^+ even from the more delocalized phenoxy site under these conditions as seen from the possibility of obtaining HkM. The idea of coordination of Li^+ derives its justification from the fact that even the low charge density K^+ and Cs^+ have been found to be coordinated (x-ray analysis) to $-CH_2OH$ in the compounds KI (phenacyl kojate)$_2$[6] and CsNCS(phenacyl kojate),[7] respectively.

Previous workers[5] failed to obtain the dienol by opening the γ-pyrone ring of HkH; we note that HkH and HkM do not undergo ring opening. This is probably because electron depletion (and hence bond weakening) of the ring through the carbonyl oxygen is overcompensated by the electron supply from the phenoxide created by the alkali. This should be true, in principle, for any γ-pyrone ring carrying an ionizable hydroxyl group.

The Ar(OH)(CH_2OH) type of compounds, which do not polymerize in alkaline medium, should in principle be methylated selectively. Optimum conditions may be discovered by keeping in view that (1) methylation of the alcoholic group is favored as the DMS/substrate ratio exceeds 1 and the temperature of the reaction is raised (toward 50 °C), and (2) methylation of the phenolic group, which takes place via salification, can be prevented when LiOH/DMS and LiOH/substrate ratios are at least 3 and the reaction temperature is lowered (toward 20 °C).

Registry No.—HkH, 501-30-4; HkM, 6269-25-6.

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Phase Transfer Catalysis. Preparation of Aliphatic and Aromatic Sulfonyl Fluorides

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We wish to report a very facile and convenient synthesis of organic sulfonyl fluorides employing crown ether catalysis.

Organic sulfonyl fluorides are of interest owing to their insecticidal, germicidal,[1,2] and enzyme inhibitory properties.[3-5] There are many methods available for their preparation, most of which involve halogen exchange (i.e., conversion of the corresponding sulfonyl chloride to the sulfonyl fluoride). One of the original sulfonyl fluoride preparations requires boiling the sulfonyl chloride with an aqueous solution of potassium fluoride.[6,7] This procedure results in only moderate yields (46–83%) and will not work for water-sensitive compounds. Other syntheses include (1) refluxing the corresponding sulfonyl chloride and potassium fluoride in a cosolvent system (e.g., dioxane/water) (70% yield), (2) reacting anhydrous hydrogen fluoride with the sulfonic anhydride (90–95%),[8] (3) addition of sodium nitrite to a solution of the corresponding sulfonamide in anhydrous hydrogen fluoride (53–78%),[9] and (4) heating the sulfonyl chloride with sodium fluoride suspended in tetramethylenesulfone, acetonitrile, or dimethylformamide (62–72%).[3,10]

A recently reported synthesis of sulfonyl fluorides involved conversion of the sulfonyl chloride using a dialkylaminosulfur trifluoride compound as the fluorine/chlorine exchange reagent (72–79%).[11] The reagent, however, must be prepared in two low-yield steps from a secondary amine, trimethylsilyl chloride, and sulfur tetrafluoride.[12]

In recent years, solid–liquid phase-transfer catalysis involving crown ethers has gained widespread use as a tool in organic synthesis.[13] The nucleophilic enhancement of anions by crown ethers in aprotic solvents is well known. The use of 18-crown-6 ether[14] to catalyze fluorine/halogen exchange with a wide variety of substrates has also been documented;[15] however, to the best of the authors' knowledge, no mention has been made in the literature of a crown ether catalyzed fluoride exchange reaction with organic sulfonyl chlorides.

The reaction is conducted by stirring the sulfonyl chloride and excess potassium fluoride at room temperature in acetonitrile solution or neat in the presence of 18-crown-6 ether catalyst. Representative sulfonyl fluorides have been prepared by this method in very high yield (see Table I).

$$RSO_2Cl \xrightarrow[KF,\ CH_3CN,\ RT]{\text{18-crown-6 ether}} RSO_2F + KCl$$

The reaction mixture is heterogeneous at all times, but the appearance of the solid phase changes as the reaction progresses. The reaction is exothermic, and controlled addition is sometimes necessary. The 18-crown-6 ether is catalytic (see Table I); however, the reaction will proceed in the absence of catalyst at a slower rate. All conversions are complete within 4 h and are essentially quantitative, making isolation and purification remarkably simple. Water washing easily separates the sulfonyl fluoride product from the salts. It was found that liquid sulfonyl chlorides make excellent solvents for this phase-transfer catalyzed reaction. These conversions were run neat with the potassium fluoride being phase transferred into the coreactant. For solid sulfonyl chloride reactants, acetonitrile appeared to be the solvent of choice, although other aprotic solvents may work equally well.[17]

Dansyl chloride is of importance as a fluorescent probe, but has a poor shelf life owing to its water sensitivity. This preparation allows one to prepare dansyl fluoride (**7**), which is quite stable and has the same fluorescent probe properties.[5] The

Table I. 18-Crown-6-Ether Catalyzed Conversion of Sulfonyl Chlorides to Sulfonyl Fluorides

Registry no.		Product[a]	Equiv of KF	Solvent	Mp/bp, °C	% yield[b]	Concn of crown, mol %[c]
5558-25-8	1	Methanesulfonyl fluoride	1.2		123–124	84[d]	~0.6
329-98-6	2	α-Toluenesulfonyl fluoride	2.0	CH_3CN	91–92	89	~2.0
368-43-4	3	Benzenesulfonyl fluoride	1.2		84 (8 mmHg)	92.5	~0.7
455-16-3	4	*p*-Toluenesulfonyl fluoride	2.0	CH_3CN	42.5–43.5	100	~1.0
498-83-9	5	*p*-Bromobenzenesulfonyl fluoride	2.0	CH_3CN	64–65	100	~1.0
329-20-4	6	*p*-Acetamidobenzenesulfonyl fluoride	2.0	CH_3CN	175–177	96	~1.0
34523-28-9	7	5-Dimethyl-amino-1-naphthalenesulfonyl fluoride (dansyl fluoride)	2.0	CH_3CN	48–50	100	~3.0

[a] In all cases, conversion to product was quantitative. All spectral data (IR, NMR) are consistent with the assigned structure of the isolated product. [b] Represents isolated yield. [c] In all cases, the 18-crown-6 ether was used as its acetonitrile complex. NMR analysis of the complex indicates a 2:1 ratio of acetonitrile to 18-crown-6 ether. This has been confirmed by an x-ray diffraction study.[16] [d] Yield is not optimized.