An alternative approach could utilize diethylaluminum cyanide to obtain the cyanohydrin. See "The Use of Aluminum Alkyls in Organic Synthesis", The Ethyl Corporation, Baton Route, La., 1969–1972 Supplement, p 108.
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Coordinative Role of Alkali Cations in Organic Synthesis. 3.[1] Selective Methylations of 5-Hydroxy-2-hydroxymethyl-γ-pyrone

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Methylation of 5-hydroxy-2-hydroxymethyl-γ-pyrone (kojic acid, **1**) has been investigated using dimethyl sulfate and caustic alkalis to obtain 5-methoxy (**2**), 2-methoxymethyl (**3**), and 5-methoxy-2-methoxymethyl (**4**) methyl ethers free of each other. The phenolic OH of **1** is methylated through salification, whereas the alcoholic one is methylated due to its coordination with the alkali cations (M^+); the former can be selectively methylated using a stoichiometric amount of an alkali of a low charge density M^+(KOH), the latter by employing excess alkali of a high charge density M^+(LiOH), and both with the alkali of a medium charge density M^+(NaOH). When KOH is the alkali and excess methylating reagents are used, a large amount of the substrate is lost as K^+–**2** complexes in the aqueous phase. Opening of the γ-pyrone ring is attributed to the coordination of its carbonyl with H^+ (in acidic medium) or M^+ (in alkaline medium); in alkaline medium, **1** and **3** do not undergo ring opening due to the creation of an electron-supplying phenoxide.

Methylation of kojic acid (**1**) with dimethyl sulfate (DMS) in aqueous caustic alkalis (MOH) leads[2–4] to all three possible ethers **2**, **3**, and **4**. However, selective preparation of **3** and **4** in high yields was never achieved and it is not convenient to separate them. Coordination of neutral organic nucleophiles with alkali cations (M^+) is becoming known,[5–11] so we attribute their low yields to the formation of water-soluble complexes with M^+; we indeed isolated a number of alkali sulfate complexes of **2** from the aqueous phase of reaction mixtures involving use of excess DMS and KOH.[12] This paper reports the results of a detailed systematic study leading to procedures by which each of the three ethers can be obtained free of the other in 60 to 75% yields.

The reactants of a reaction mixture are written in the order **1**, DMS, MOH such that the reaction mixture 142 denotes 1–DMS–MOH (1:4:2). Experimental conditions of a reaction are also described by notations; 132 (KOH), 10 aq, DMS (↓), 25 °C reads that 1–DMS–KOH (1:3:2) was the reaction mixture in 10 mL of water where DMS was added to the 1–KOH system maintained at 25 °C.

Results and Discussion

The results of selected experiments are shown in Table I and synthetic routes in Scheme I. Employing 111 reactions, only phenolic OH was methylated to obtain **2** (Scheme I, reaction a). Methylation, however, was hampered and M^+–OkH (metal kojate) instead of **2** was mainly recovered for LiOH and

Scheme I. Routes of Methylation Reactions of Kojic Acid

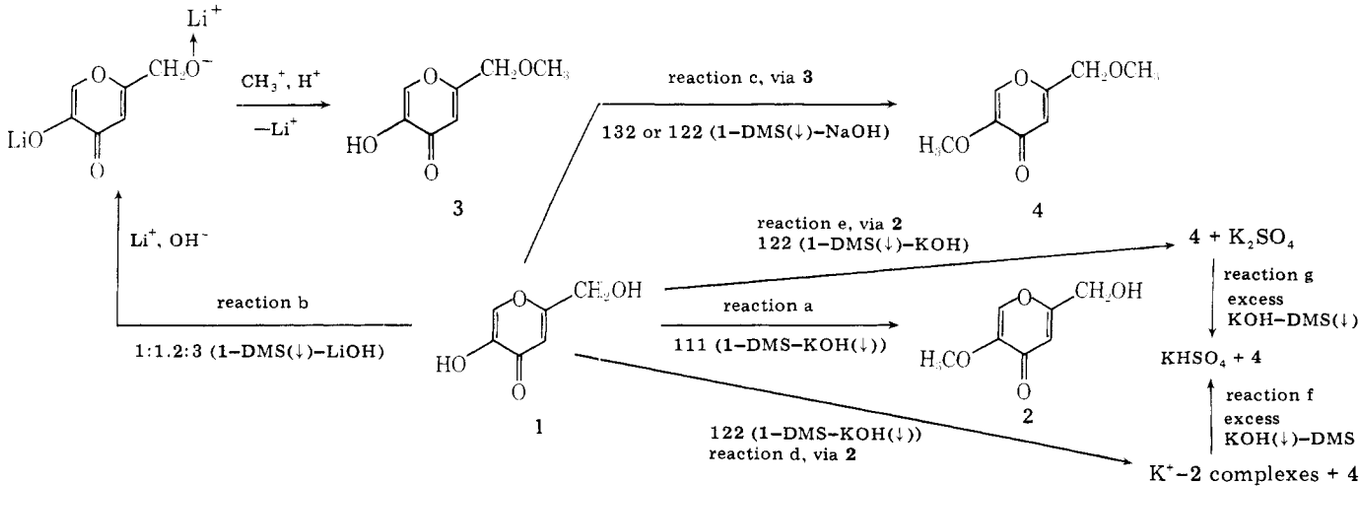

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Table I. Results of Selected Methylation Experiments

Reaction conditions	Recovery Procedure	Methylation product (s) (% yield)	Remarks
111 (NaOH), 10 aq, NaOH (↓), 20–5 °C	cy	2 (75)	Recommended for prep. of 2
111 (NaOH), 10 aq, DMS (↓), 40–45 °C	cy (2), ex (4)	2 (62) + 4 (5)	*a*
111 (KOH), 10 aq, KOH (↓), 20–25 °C	cy	2 (74–76)	Recommended for prep. of 2[b]
123 (LiOH), 10 aq, DMS (↓), 20–25 °C	ex	3 + 4	Low yields[c,d]
113 (LiOH), 10 aq, DMS (↓), 20–25 °C	ex	3 + some 4	Low yields[e]
1:1.2:3 (LiOH), 10 aq, DMS (↓), 40–45 °C	ex	3 (60)	Recommended for prep of 3; see ref 13
122 (NaOH), 10 aq, NaOH (↓), 20–25 °C	cy(2) + ex (4)	2 (18) + 4 (12)	*e*
122 (NaOH), 10 aq, DMS (↓), 40–45 °C	ex	4 (48)	
132 (NaOH), 25 aq, DMS (↓), 40–45 °C	ex	4 (58–60)	Recommended for prep of 4[f]
144 (NaOH), 10 aq, DMS (↓), 40–45 °C	ex	4 (46) + some 3	*g, h*
144 (KOH), 10 aq, DMS (↓), 25–30 °C	cy ($KHSO_4$), ex (4)	$KHSO_4$ + 4 (22)	*h*

[a] High temperature of the reaction favors methylation of $-CH_2OH$ (even in 111 reaction mixture). [b] Contrary to expectations, yield of 2 using KOH is not better than the one with NaOH which is understandable because some 2 is lost as K^+–2 complexes. [c] Yields are low because excess alkali hampers methylation of phenolic OH and reaction temperature is not high enough to favor methylation of $-CH_2OH$. [d] Not possible to know the respective yields of 3 and 4. A rough assessment is possible because the 3–4 oil affords partial crystallization of 4 in about a week. [e] Methylation of $-CH_2OH$ is not favored because reaction temperature is low and the entire alkali has not been taken right from the start of the reaction. [f] The yield of 4 is boosted by using a dilute reaction mixture because methylation of the phenolic OH is favored due to loosening of the $Na^+{}^-OkH$ ion pair and that of $-CH_2OH$ due to a decreased association of $Na_2{}^+SO_4{}^{2-}$ and hence availability of Na^+ for $-CH_2OH \rightarrow Na^+$ coordination. [g] Although NaOH and DMS are stoichiometric and are used in excess, methylation of phenolic OH is not efficient. This is because (i) the reaction starts with a high NaOH/1 ratio and (ii) due to high temperature of the reaction excess NaOH destroys a substantial amount of DMS. [h] Too much of MOH and DMS is unfavorable to the yield of 4 due to mutual destruction of MOH and DMS and destructive reactions of 4.

when in the use of NaOH the reaction mixture was processed below 20 °C or contained nonaqueous solvent (methanol).

Employing excess MOH and DMS, the main product was 4. When the amount of MOH outweighed that of DMS, especially in the case of NaOH and LiOH (reactions b and c), the phenoxide of 1 was protected by M^+ against incipient $CH_3{}^+$ and 4 was produced contaminated with 3. This observation ultimately led us to discover a procedure for the selective methylation of alcoholic groups[13] to obtain 3 and explains why 3 was obtained[2] from the 1–DMS–KOH (1:3.7:6) reaction mixture which involves the use of excess methylating agents.

When the amount of DMS exceeded that of MOH, 4 was obtained at the expense of 3 because due to the availability of $SO_4{}^{2-}$ ions from DMS the equilibrium

$$2M^+{}^-OkMe + SO_4{}^{2-} \rightleftharpoons {}^-OkMe + M_2SO_4$$

is shifted to the right and unprotected phenoxide of ^-OkMe was methylated (reaction c). This explains how 4 uncontaminated with 3 could be obtained from 198 1–DMS–KOH[4] inspite of KOH being used in eightfold excess. When methylating agents are in excess and MOH is KOH, production of 4 and 3 still depends on the DMS/KOH ratio but K^+–2 complexes are also produced due to which yield of the ethers is lowered. The side reaction is pronounced especially when KOH is added to 1–DMS (reaction d), for production of 2 as an intermediate is favored which functions as a ligand for K^+ and diverts the reaction to produce K^+–2 complexes. If only KOH is present along with 1 from the start (reaction e), methylation of $-CH_2OH$ of the intermediate is promoted and so is the yield of 4 at the expense of complexes.

The 144 or 166 1–DMS–KOH reactions produce 4 plus $KHSO_4$ irrespective of the sequence in which KOH and DMS are used (reactions f and g). Obviously, the K^+–2 complexes produced via reaction d are ultimately methylated and due to the weak ligating power of the organic counterpart in the methylation product are decomposed to yield 4 and $KHSO_4$.

Recovery and Yield of Methyl Ethers. The yield of 2 (~75%) employing the recommended procedure is comparable to the reported one (72%) with the same method[3] but less comparable to the diazomethane method;[14,15] the latter method is, however, inconvenient and, due to the insolubility of 1 in the nonpolar medium of synthesis, is applicable to a few grams of the sample at a time.

The recovery of 3 and 4 employing benzene extractions is inefficient due to their high hydrophilicity and due to extraction being pH dependent. Their yield and quality become poor as solution pH falls below 2 and extraction temperature exceeds 50 °C. Extraction is not possible from alkaline solutions where ethers exist as anions: 3 due to salification of the phenolic OH and 4 due to ring opening followed by salification of the enole. Extraction takes place best at a pH which ensures maximum stability of the γ-pyrone ring and in the case of 3 prevents ionization of the molecule; pH 7 for 4 and 5.5–6 for 3.

Mechanism of Methylation. Methylation of the phenolic OH is favored when MOH is added slowly to 1–DMS and methylation of the alcoholic OH is favored when MOH is taken along with 1 from the start of the reaction. This indicates that (i) for methylation of the phenolic OH the MOH/DMS ratio should be minimum at every stage of the reaction so that ionization of the $M^+{}^-OkH$ pair and hence $M^+/CH_3{}^+$ exchange is favored and (ii) for methylation of the alcoholic OH the MOH/DMS ratio should be high throughout the reaction so that "activation" of this group through the formation of

$$-CH_2OH^+ \cdots M^+$$

I

and hence elimination of the polarized proton is facilitated.

The validity of I coordination during methylation of $-CH_2OH$ appears justified because (i) the M^+–2 complexes are actually isolated which do not show the infrared and ^1H NMR characteristics of the ligand[12] and (ii) x-ray analysis has revealed coordination of the $-CH_2OH$ group with M^+ in $KI(PkH)_2$[8] and $CsNCS(PkH)$[16] where PkH is phenacylkojate.

On Opening of the γ-Pyrone Ring. It is known that γ-pyrone ring normally opens in an alkaline medium.[17] We note that the same is "damaged" even in an acidic solution. This suggests that the Lewis acid part of the inorganic species (H^+ or M^+) gets coordinated to the carbonyl of the ring and aids its electron depletion. Due to stabilization of the Lewis acid with the ring, the base counterpart becomes available in a comparatively destabilized state for the nucleophilic attack on the pyrone oxygen; coordination of the carbonyl of the kojate moiety of phenacylkojate has been revealed (by x-ray analysis) for the water proton in PkH, H_2O[18] and for M^+ in $KI(PkH)_2$[8] and $CsNCS(PkH)$[16] whereas electrostatic destabilization and hence an enhanced nucleophilicity of X^- after complexation of the counter M^+ has been demonstrated during the coordination studies of the alkali salts, MX.[7,19,20]

Experimental Section

General Procedure for Methylation. To a solution of **1** (1.77 g, 12.5 mmol) in the concerned medium (10 mL) was either added the desired amount of DMS and the solution was titrated with the desired amount of 50% aqueous MOH or a weighed amount of MOH was added and the solution was slowly treated with DMS. In either case the titrant was added slowly in about 30 min while the reaction mixture was shaken and the latter was then allowed to rest for another 30 min before subjecting it to the recovery of the products.

Recovery of Methylation Products. (i) From Stoichiometric Reaction Mixtures. NaOH (at 20–25 °C) and KOH (20 °C) reaction mixtures produced only **2** which was crystallized by cooling and collected by filtration. After removal of the first crop (c_1), the filtrate was concentrated to 3–4 mL and the second crop (c_2) was collected similarly—procedure cy. LiOH reaction mixtures and those of NaOH processed below 20 °C produced metal kojates, $M^+{}^-OkH$, as c_1 so that **2** was recovered from the filtrate as c_2.

(ii) From Reaction Mixtures Employing Excess Methylating Reagents. A mixture of LiOH or NaOH (which produces **4** or **4** plus **3**) was adjusted at pH 6–7 employing 2 N H_2SO_4 or NaOH and was evaporated to a slurry employing a rotary evaporator. The methyl ether was extracted employing seven 20-mL lots of benzene (the best extractant we found) at 70–80 °C. About 120 mL of the collected extracts was recovered by distillation and recovery of the ether(s) was attempted from the concentrate after its dehydration (with molecular sieve 4 Å pores), decolorization (with activated charcoal), and evaporation to dryness at room temperature—procedure ex. Crystals (mp 85–88 °C) were obtained in case the product was pure **4** but only oil was obtained when the latter was contaminated with **3**.

A mixture of KOH, in addition to **4** (or **4** + **3**), produced also one or more complexes of K^+. Either the ether(s) was removed first employing procedure ex and then the complex(es) was removed employing procedure cy (procedure ex–cy) or first the complex was removed and then the ether—procedure cy–ex.

Characterization of Methyl Ethers. **1** (mp 154 °C; 8.38, 6.83, 4.80 ppm), **2** (mp 165 °C; 8.35, 6.82, 4.80, 4.07 ppm), **3** (mp 75 °C; 7.88, 6.38, 4.55, 4.26, 3.32 ppm), and **4** (mp 90 °C; 7.80, 6.35, 4.50, 4.78, 3.65, 3.33 ppm) were characterized employing (i) 80 MHz ^1H NMR in Me_2SO-d_6, (ii) $FeCl_3$ test which is responsive in neutral medium by **1** and **3**, and (iii) by comparing their melting points with those reported in the literature.[2-4,14,15]

Recommended Procedures for Preparation of Methyl Ethers. (i) Synthesis of 2 by taking **1** (1.77 g), DMS (1.57 g), and KOH (0.7 g) and employing a 111 (KOH), 10 aq, KOH (↓), 20 °C reaction. After addition of KOH is complete, crops c_1, c_2, and c_3 were collected employing procedure cy. The yield of the yellowish crude product is ~1.48 g (75–76%; mp 158–62 °C). The product was recrystallized after decolorization with activated charcoal from ethanol. The colorless crystals melted at 164–65 °C.

(ii) Synthesis of 3 by taking **1** (1.77 g), DMS (1.89 g), and LiOH, aq (1.57 g), and employing a 1:1.2:3 (LiOH), 10 aq, DMS (↓), 40–45 °C reaction. After addition of DMS was complete and the reaction solution had been allowed to rest for another 30 min, the pH was adjusted at 5.5–6 with 2 N H_2SO_4 and the ether was recovered employing procedure ex. The yield of the brownish crystals was ~1.25 g (60%; mp 70–2 °C). Recrystallization, after decolorization with activated charcoal, from benzene yielded colorless crystals melting at 74–5 °C.

No effort was made to make the conditions drastic to promote methylation of the alcoholic group for this cannot be done without simultaneous methylation of the phenolic OH.[13]

(iii) Synthesis of 4 by taking **1** (1.77 g), DMS (4.72 g), and NaOH (1.0 g) and employing a 132 (NaOH), 20 aq, DMS (↓), 40–45 °C reaction. After addition of DMS was complete and the reaction solution had been allowed to rest for another 30 min, the pH was adjusted at 7 using 1 N NaOH. **4** was extracted employing procedure ex. The yield was ~1.27 g (60%; mp 88 °C). The product was recrystallized after decolorization with activated charcoal from benzene to obtain colorless crystals melting at 90 °C.

No effort was made to favor methylation of the two hydroxy groups by raising the reaction temperature beyond 45 °C for this leads to the mutual destruction of NaOH and DMS as well as that of **4** with NaOH.

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