February, 1980] © The Chemical Society of Japan NOTES Bull. Chem. Soc. Jpn., 53, 569—570 (1980) 569

Coordinative Role of Alkali Cations in Organic Reactions. IV. Benzoylation, Phenacylation, and Benzylation of Kojic Acid

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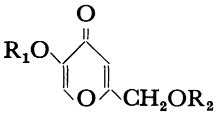
(Received April 21, 1979)

Synopsis. Using kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone) as a substrate, the title reactions were carried out with various alkali metal hydroxides. Whereas phenacylation (with KOH or NaOH) and benzylation (with KOH, NaOH, or LiOH) are possible only on the phenolic hydroxyl, benzoylation can be carried out selectively as well as collectively on both the hydroxyl group (in 80% aq EtOH). The results were discussed in terms of the interactive role of alkali cations with the substrate.

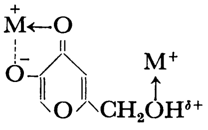
In earlier communications[1,2] we reported that an organic reaction involving the use of alkali hydroxide (MOH) is triggered by the alkali cation (M^+) and that the efficiency and the course of the reaction can be controlled by changing either M^+ or the conditions which influence the coordinative role of the latter. In this article we introduce, in addition, that during benzoylation (with benzoyl chloride), phenacylation (with phenacyl bromide), and benzylation (with benzyl chloride) of kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone, abbr. HO**k**CH_2OH, **1**), (i) MOH is not present just to neutralize the acid byproduct of the reaction but reacts with the substrate (**1**) (see **5**[3,4]) and determines the invitation to the electrophilic reagent, and (ii) the ion-association (insolubility) of the leaving alkali halide ion pair in the reaction medium determines the efficiency of the reaction.

The synthetic procedures for the derivatives of kojic acid, namely, 5-benzoyloxy-2-hydroxymethyl-4-pyrone (**2a**), 5-hydroxy-2-benzoyloxymethyl-4-pyrone (**2b**), 5-benzoyloxy-2-benzoyloxymethyl-4-pyrone (**2c**), 5-phenacyloxy-2-hydroxymethyl-4-pyrone (**3**) and 5-benzyloxy-2-hydroxymethyl-4-pyrone (**4**) have been standardized to maximize the product yields.



(R_1O**k**CH_2OR_2)

1, $R_1=R_2=H$
2a, $R_1=PhCO$; $R_2=H$
2b, $R_1=H$; $R_2=PhCO$
2c, $R_1=R_2=PhCO$
3, $R_1=PhCOCH_2$; $R_2=H$
4, $R_1=PhCH_2$; $R_2=H$



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Results and Discussion

Benzoylation. As against the laborious procedures adopted earlier,[5] we provide herein one-step procedures involving the rather convenient use of MOH in EtOH–H_2O medium for obtaining **2a** (81%), **2b** (65%), and **2c** (79%) in higher yields (see Table 1).

Benzoylation reactions on **1** are possible on the phenolic or both the hydroxyl groups using appropriate amounts of PhCOCl and MOH; the reactions fail in the absence of MOH. The reactions are most favored when MOH of the lowest charge density M^+ (KOH) is used in an ionizing medium (EtOH–H_2O), *i.e.*, under the conditions favoring formation of the loose $K^{+-}O$**k**$CH_2O^-K^+$ ion pairs which allow a facilitated M^+/PhC^+O exchange at each negative site.

With an excess MOH of a high charge density M^+ (NaOH and especially LiOH), which can ensure an effective protection of the phenoxide through M^+, benzoylation of the $-CH_2OH$ group can be carried out using **1** and PhCOCl in equimolecular proportions. This reaction is novel. When the high charge density Li^+ is used, the reaction appears to involve $Li^{+-}O$**k**$CH_2\underset{\underset{Li^+}{\downarrow}}{O}H$ coordinated species as an intermediate because **2b** can also be synthesized (in 32% yield) employing one mole each of **1**, LiOH, $LiClO_4$, and PhCOCl wherein whole LiOH is expected to be consumed by the phenolic hydroxyl while Li^+ ions of $LiClO_4$ carry out the reaction on the alcoholic hydroxyl. If $-CH_2O^-Li^+$ should have formed as an intermediate (alkoxide mechanism), the Li^+/PhC^+O exchange becomes rather difficult to visualize because such an exchange is not possible even at the comparatively delocalized phenoxide as evident from the lack of benzoylation of the phenolic hydroxyl under these conditions. Various sugars coordinate[6] with alkali and alkaline earth cations in water through the $-CH_2OH$ groups (NMR studies) and X-ray diffraction analysis reveals coordination of the cation with the $-CH_2OH$ group in the complexes $KI(\mathbf{3})_2$,[4a] $NaI(\mathbf{3})_2\cdot2H_2O$,[4b] and $NaClO_4$(1,4-anhydroerythritol).[7]

Phenacylation. As in methanol,[8] the direct product of the reaction in ethanol or acetone is the complex $MBr(\mathbf{3})_2$ instead of **3**; on decomposing the complex with water, **3** is recovered in a hydrated form (mp 90 °C and not 144—145 °C as reported earlier[9,10]) which can be dehydrated (mp 145 °C) by recrystallization from absolute ethanol. Using KOH in EtOH–H_2O (4: 1) the reaction efficiency is maximum with 77% yield of **3** (liberated from the complex).

In the presence of MOH only phenolic hydroxyl undergoes phenacylation as known earlier.[8] In the absence of MOH, **1** and $PhCOCH_2Br$ are recovered unreacted under all conditions. Condensation also fails when pyridine is used instead of MOH; the direct $PhCOCH_2Br$–pyridine reaction,[11] was avoided by mixing pyridine with **1** and adding $PhCOCH_2Br$ later. These observations indicate that MOH does not only function to neutralize HBr but reacts with the substrate to produce the reactive $M^{+-}O$**k**CH_2OH and that the nature of M^+ determines the reactivity of the phenoxide with $PhCOCH_2Br$.

The yield of **3** increases as media of increasing polarity and M^+ of decreasing charge density are used. This indicates that the C–Br bond is attacked in accordance with the "liberation" of the cation-controlled

Table 1. Reaction of **1** with PhCOCl, $\mathrm{PhCOCH_2Br}$, and $\mathrm{PhCH_2Cl}$ in the presence of different MOH[a)]

Reaction mixture (proportions)		Medium	Product (yield/%)		
			KOH	NaOH	LiOH
		Benzoylation			
1-MOH-PhCOCl (↓)[b)]	(1:1:1)	$\mathrm{EtOH-H_2O}$ (4:1)	**2a**(81)[c)]	**2a**(75)	c_1 **2a**(54) c_2 **2c**(21)
		EtOH	c_1 **2a**(19) c_2 **2c**(25)	**2c**(37)	**2c**(23)
	(1:2:1)	$\mathrm{EtOH-H_2O}$ (4:1)	**2c**(66)	**2b**(41)	**2b**(65)[c)]
		EtOH	**2c**(15)	**2d**(82)[d)]	**2d**(58)
	(1:2:2)	$\mathrm{EtOH-H_2O}$ (4:1)	**2c**(79)[c)]	**2c**(69)	**2c**(31)
		Phenacylation[e)]			
1-MOH-$\mathrm{PhCOCH_2Br}$ (↓)	(1:1:1)	Acetone-Water (4:1)	**3**(49)[c)]	**3**(43)[e)]	—
		EtOH	**3**(56)	**3**(46)	—
		$\mathrm{EtOH-H_2O}$ (4:1)	**3**(77)[c)]	**3**(60)	—
		$\mathrm{EtOH-H_2O}$ (3:2)	**3**(57)	**3**(48)	—
1-MOH (↓)-$\mathrm{PhCOCH_2Br}$	(1:1:1)	$\mathrm{EtOH-H_2O}$ (4:1)	**3**(43)	**3**(34)	—
	(1:2:2)	$\mathrm{EtOH-H_2O}$ (3:2)	**3**(45)	**3**(38)	—
		Benzylation			
1-MOH-$\mathrm{PhCH_2Cl}$ (↓)	(1:1:1)[f)]	$\mathrm{EtOH-H_2O}$ (4:1)	**4**(68)[c)]	**4**(61)	**4**(57)

— poor or no reaction. c_1 and c_2 stand for the first and the second crop; in case crops are not mentioned, product was the same in both. a) Each reaction has been investigated extensively under varied conditions but only those experiments are included here which either afforded the highest yield or threw light on the reaction mechanism. b) The reagent preceding the arrow was added to the mixture of the other two. c) Optimum conditions recommended for synthesis. d) **2d** represents $\mathrm{M^{+-}}$**Ok**$\mathrm{CH_2OH}$. e) Derivative recovered from the complex—$\mathrm{M^+}$(**3**)$_2\mathrm{Br^-}$. f) When 1:1:2 or 1:2:2 reaction mixture was employed or water was eliminated, yield of the product was decreased for each MOH; when both the changes were made at a time then particularly for NaOH and LiOH phenolic hydroxyl also failed to react and $\mathrm{M^{+-}}$**Ok**$\mathrm{CH_2OH}$ was recovered.

phenoxide through loosening of the $\mathrm{M^{+-}}$**Ok**$\mathrm{CH_2OH}$ ion pair; if the sequence of addition of the reactants is varied and **1**-MOH complexation is not allowed to occur prior to the addition of $\mathrm{PhCOCH_2Br}$, the yield of the product is decreased.

Benzylation. Only phenolic hydroxyl can be benzylated (*cf.* phenacylation) and the **1**-$\mathrm{PhCH_2Cl}$ reaction fails in the absence of MOH. Compound **4** is obtained in the highest yield (68%) when KOH is used and the reaction medium (EtOH) contains water. In a less ionizing medium (EtOH) the reaction is poor (KOH) or is completely stopped (NaOH or LiOH) especially in the presence of excess MOH due to the protection of phenoxide with the cation. This and that the reaction is favored in the order LiOH, NaOH, and KOH indicate that $\mathrm{M^+/PhC^+H_2}$ exchange is facilitated as $\mathrm{M^{+-}}$**Ok**$\mathrm{CH_2OH}$ ion pair loosens. The reaction on the phenolic hydroxyl in the presence of LiOH is possible with $\mathrm{PhCH_2Cl}$ but not with $\mathrm{PhCOCH_2Br}$ (see Table 1). The enhanced reactivity of $\mathrm{PhCH_2Cl}$ with respect to that of $\mathrm{PhCOCH_2Br}$ on a common substrate ($\mathrm{Li^{+-}}$**Ok**$\mathrm{CH_2OH}$) is interestingly significant because $\mathrm{PhCH_2Cl}$ is expected to be a relatively inert reagent due to $\mathrm{Ph^+}$ being a less electron withdrawing agent than $\mathrm{PhC^+O}$ and the C–Cl bond being a stronger bond than the C–Br one. The facilitated benzylation can only be because insolubility[14)] and hence[15)] solution stability of the leaving ion pair for $\mathrm{PhCH_2Cl}$ (*i.e.*, LiCl) is higher than that for $\mathrm{PhCOCH_2Br}$ (*i.e.*, LiBr) which forces an $\mathrm{SN^1}$ contribution of $\mathrm{PhCH_2Cl}$ to aid displacement of $\mathrm{Li^+}$ from phenoxide.

Experimental

Recommended Procedure for Benzoylation, Phenacylation, and Benzylation. To a solution of **1** (1.42 g, 10 mmol) in $\mathrm{EtOH-H_2O}$ (4: 1, v/v) (15 ml) was added the required amount of MOH. The clear reaction mixture was treated with the reagent concerned, and refluxed for 1 h on steam-bath. The product was crystallized by cooling, collected and authenticated. Specific conditions for the synthesis of compounds **2**—**4** are outlined below.

Synthesis of ***2a****.* Compound **1** was taken in $\mathrm{EtOH-H_2O}$ (4: 1) and treated with KOH (0.56 g, 10 mmol) followed by benzoyl chloride (1.41 g, 10 mmol). Yield 1.99 g (81%), mp 143 °C. *Synthesis of* ***2b****.* Compound **1** was taken in $\mathrm{EtOH-H_2O}$ (4: 1) and treated with excess LiOH (0.84 g, 20 mmol) followed by benzoyl chloride (1.41 g). Yield 1.59 g (65%), mp 174—175 °C. *Synthesis of* ***2c****.* Compound **1** was taken in $\mathrm{EtOH-H_2O}$ (4: 1) and treated with KOH (1.12 g, 20 mmol) followed by benzoyl chloride (2.81 g, 20 mmol). The isolated product was recrystallized from 10 ml acetone-water (1: 1, v/v) to remove the traces of the by-product (benzoic acid). Yield 2.76 g (79%), mp 133—134 °C.

Synthesis of ***3****.* Compound **1** was taken in $\mathrm{EtOH-H_2O}$ (4: 1) and treated with KOH (0.56 g) followed by phenacyl bromide (1.99 g, 10 mmol). The isolated product was a crystalline complex $\mathrm{K^+}$(**3**)$_2\mathrm{Br^-}$ (mp 208 °C). The complex was decomposed with boiling water (20 ml) to get the hydrated form of **3** (mp 90 °C) which was recrystallized from ethanol to obtain anhydrous **3** (mp 145 °C). Yield 2.00 g (77%).

Synthesis of ***4****.* Compound **1** was taken in $\mathrm{EtOH-H_2O}$ (4: 1) and treated with KOH (0.56 g) followed by benzyl chloride (1.27 g, 10 mmol). Yield 1.57 g (68%), mp 133 °C.

Authentification of the Products. All the products are known compounds. They were authenticated with the help of elemental analysis, hot stage microscopic examination of melting points and IR spectroscopy. Absorption characteristics of $>$C=O in **2a**, **2b**, and **2c** deserve a mention in that the pyrone carbonyl of each compound absorbs at $\approx$1670 cm^{-1} whereas carbonyl of the benzoyl moieties absorbs at a higher position probably due to the presence of an oxygen in the vicinity. The benzoyl carbonyl near the phenolic oxygen absorbs at the highest —**2a** at 1755 cm^{-1}, **2b** at 1735 cm^{-1}, and **2c** at 1740 and 1667 cm^{-1}.

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