

Selective Cross-Acyloin Condensation Catalyzed by Thiazolium Salt II¹⁾ Selective Formation of 1-Hydroxy-2-ones from Formaldehyde and a Variety of Other Aldehydes, and a Proposal for the Possible Mechanism

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The selective cross-acyloin condensation, where 1-hydroxy-2-ones were obtained selectively from formaldehyde and a wide variety of other aldehydes, was achieved by using 3-ethylbenzothiazolium bromide as a catalyst in the presence of triethylamine. The present reaction is expected to afford a novel and facile method for the synthesis of 1-hydroxy-2-ones. A mechanism accounting for the selective formation of 1-hydroxy-2-one was proposed based on the results obtained by examining the reactions between formaldehyde and p-substituted benzaldehydes. It is of much interest in the mechanism that two catalytic species show an inverse selectivity toward aldehydes.

INTRODUCTION

Formaldehyde has played an important role in the field of C₁ chemistry since it was synthesized on a large scale by Ag₂O catalyzed oxidation of methanol obtained directly from CO and H₂, i. e., syngas. Elemental composition of formaldehyde, CH₂O, is identical with that of such carbohydrates as glucose. Therefore, if a reaction system, where the self-condensation of formaldehyde proceeds with C-C bond formation, can be developed, it becomes possible to synthesize carbohydrates directly from

formaldehyde. This attempt has been made for a long time and the reaction is well-known as "**formose reaction**"²⁾. However, formose reactions catalyzed by inorganic bases such as Ca(OH)₂ in aqueous solution have generally a complex nature, as seen from the large number of products (often over 30)^{3,4)}. Thus, it is highly desirable to develop a selective formose reaction which gives selectively a specific product in high yield.

Recently, we found that in the formose reaction catalyzed by thiazolium salts in organic solvent dihydroxyacetone (a triose existing in nature) was selectively formed in high yield^{5,6)}. Based on some experimental results, we proposed a mechanism accounting for the selective formation of dihydroxyacetone, as illustrated in **Scheme I**. In order to obtain further corroborating evidence for this proposal, the

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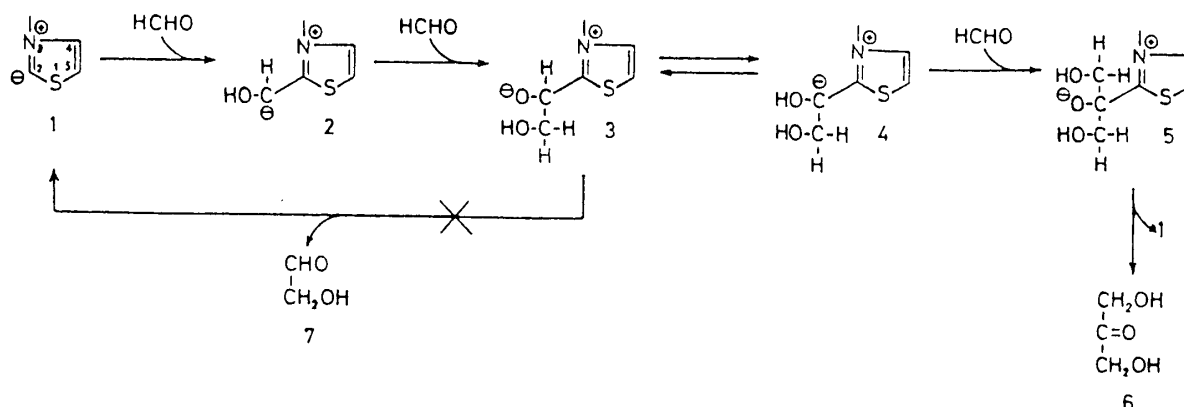
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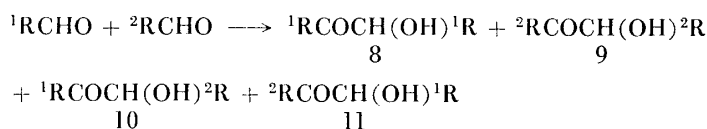
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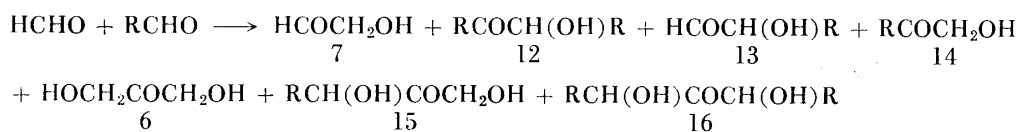
Scheme I



Scheme II



Scheme III



condensation reaction of formaldehyde in the presence of another aldehyde catalyzed by a thiazolium salt was carried out.

Generally, cross-acyloin condensation between different aldehydes is foreseen to give four products, two symmetric (**Scheme II, 8, 9**) and two dissymmetric (**Scheme II, 10, 11**). In the reaction containing formaldehyde, the formation of three other products (**Scheme III, 6, 15, 16**) is also expected by the participation of carbanion **4** in **Scheme I**.

Quite surprisingly, it was found that one product, 1-hydroxy-2-one (**Scheme III, 14**), was formed almost exclusively in the condensation of formaldehyde with another aldehyde catalyzed by 3-ethylbenzothiazolium bromide, and reported this interesting result in the previous paper accompanied with a possible mechanism by taking account into the mole-

cular structure of the product, 1-hydroxy-2-one¹⁾.



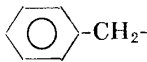


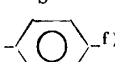
In the present article, possible extension of this cross-acyloin condensation to a wide variety of other aldehydes is described and the reaction mechanism reported previously is discussed again based on some results which have been obtained since then in support of the mechanism.

RESULTS AND DISCUSSION

Cross-Acyloin Condensation between Formaldehyde and a Wide Variety of Other Aldehydes

The condensations of formaldehyde with a wide variety of other aldehydes catalyzed by 3-ethylbenzothiazolium bromide in the presence of triethylamine were examined in ethanol at 60°C for 24 or 42 h. The conversion of alde-

Table 1 Synthesis of 1-hydroxy-2-ones (RCOCH₂OH) from formaldehyde and a variety of other aldehydes (R-CHO)^{a)}

Other Aldehyde R	Reaction Time (h)	Aldehyde Conversion (%)	Selectivity in 1-Hydroxy-2-one (%)
Me	24	76 ^{b)}	100 ^{d)}
Et	24	74 ^{b)}	89 ^{d)}
n-Pr	24	93 ^{b)}	73 ^{d)}
Isopr	42	90 ^{c)}	100 ^{e)}
Isobu	24	87 ^{c)}	94 ^{e)}
Sec-bu	42	82 ^{c)}	75 ^{e)}
	24	94 ^{b)}	64 ^{d)}
	24	96 ^{b)}	100 ^{d)}
 -CH ₂ -	42	92 ^{c)}	75 ^{e)}
	24	88 ^{b)}	81 ^{d)}
	42	60 ^{c)}	90 ^{e)}
 -f)	42	>90 ^{c)}	>90 ^{e)}

a) Paraformaldehyde, 5 mmol (as HCHO); other aldehyde, 5 mmol; 3-ethylbenzothiazolium bromide, 0.5 mmol; triethylamine, 0.5 mmol; ethanol, 5 ml; 60°C; in N₂, b) By chromatropic acid method, c) By ¹H-NMR, d) By GLC, e) By ¹H-NMR, f) Double the molar quantity of formaldehyde.

hydes and the selectivity in the formation of 1-hydroxy-2-ones are summarized in **Table 1**. The all 1-hydroxy-2-ones formed as a main product were isolated by fractional distillation, recrystallization, or column chromatography, and those chemical structures were determined by IR, ¹H-NMR, ¹³C-NMR, and mass spectrometries. The conversion of aldehydes was estimated by two different ways, that is, by determining formaldehyde colorimetrically and other aldehydes spectroscopically with ¹H-NMR. The selectivity was also evaluated by two different techniques, by gas-liquid chromatography (GLC) and by ¹H-NMR spectroscopy. As can be seen from **Table 1**, various 1-hydroxy-2-ones were obtained selectively and in high yield from

formaldehyde and a wide variety of other aldehydes except a few examples such as cyclohexanecarboxaldehyde. Furthermore, such bis-aldehydes as terephthalaldehyde were found to give selectively the corresponding bis(α-ketol)s by using double the molar quantity of formaldehyde.

Although a 1-hydroxy-2-one can be an important intermediate with a keto and a hydroxy groups in organic synthesis, it has so far been synthesized from limited types of diols such as 1,2-butanediol by partial oxidation with expensive palladium catalyst. Therefore, the present reaction is expected to afford a novel and facile method for the synthesis of 1-hydroxy-2-ones.

Reaction Mechanism

In the previous paper, we proposed a mechanism as shown in **Scheme IV** in view of the selectivity observed to form 1-hydroxy-2-one from formaldehyde and another aldehyde¹⁾. In order to ensure this proposed mechanism we examined the reactions between formaldehyde and p-substituted benzaldehydes with different substituent constants in an electrophilic aromatic substitution reaction. The results are summarized in **Table 2**, together with the substituent constants⁷⁾. Electrophilicity of carbonyl carbon

in p-substituted benzaldehydes can be considered to increase with increasing the value of substituent constant. The conversion of aldehydes and the selectivity in the formation of 1-hydroxy-2-ones were estimated by GLC.

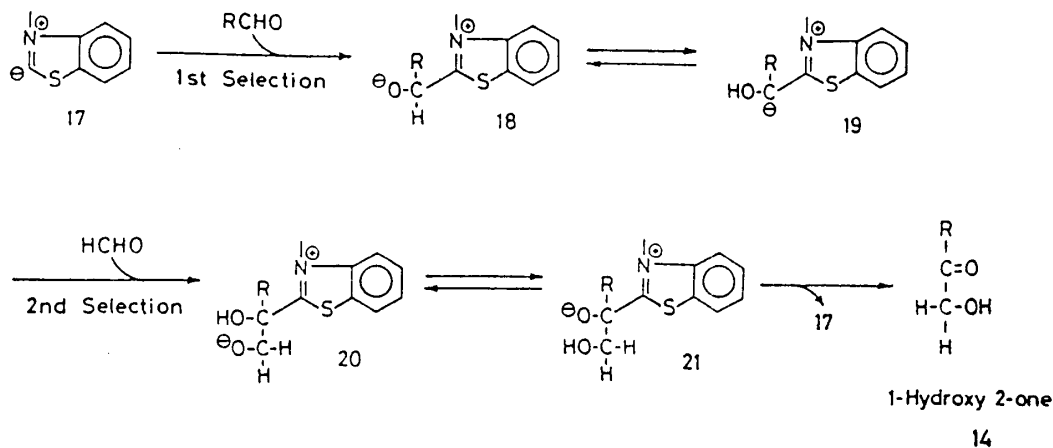
In the reaction between formaldehyde and benzaldehyde in ethanol or methanol, not only the conversion of benzaldehyde but the selectivity was considerably high. In contrast, the reaction by using dimethylformamide as the solvent proceeded scarcely, where formaldehyde remained insoluble as paraformaldehyde

Table 2 The cross-acyloin condensation of formaldehyde with p-substituted benzaldehydes ($X-\langle\bigcirc\rangle-\text{CHO}$)^{a)}

X	Substituent + Constants (σ para)	Aldehyde Conversion (%) ^{b)}	Selectivity in 1-Hydroxy-2-one (%)
H	0	92	97
H ^{c)}	0	94	70
H ^{d)}	0	16	0
H ^{e)}	0	1	—
OCH ₃	-0.778	28	71
Cl	0.114	77	57
NO ₂ ^{f)}	0.790	88	trace
NO ₂ ^{e)}	0.790	69	—

a) Paraformaldehyde, 10 mmol (as HCHO); p-substituted benzaldehyde, 10mmol; 3-ethylbenzothiazolium bromide, 1 mmol; triethylamine, 1 mmol; ethanol, 10 ml; 60°C, 42h, b) GLC, c) Methanol solvent, d) DMF solvent, e) without paraformaldehyde, f) 24 h, g) 24 h, without paraformaldehyde.

Scheme IV



(solid) for a long time from the beginning of the reaction. In the absence of formaldehyde, the reaction did not essentially occur under the conditions examined.

In the codensation of formaldehyde with *p*-methoxybenzaldehyde, the reactivity was fairly low in spite of the selectivity somewhat high.

In the case of *p*-chlorobenzaldehyde, the selectivity was not so high, although the reaction proceeded smoothly.

To our surprise, *p*-nitrobenzaldehyde underwent the self-condensation even without formaldehyde, to produce a benzoin-type compound. Although the reaction also in the presence of formaldehyde occurred readily, it gave trace quantities of the corresponding 1-hydroxy-2-one.

Based on the results described above, here let us discuss again the mechanism for the selective formation of 1-hydroxy-2-ones illustrated in **Scheme IV**. Judging from the different results between the reactions in alcohol and in dimethylformamide, the first selection is due to the difference in the concentration in solution between formaldehyde and another aldehyde. Formaldehyde was supplied as paraformaldehyde, powdery polyoxymethylene, so the amount of monomeric formaldehyde with the practically reacting ability, which is anticipated to have a hemiacetal structure in alcohol, was negligibly smaller than that of another aldehyde in the early stage of the reaction. It can be considered that monomeric formaldehyde is not actually present in such aprotic solvents as dimethylformamide throughout the reaction under the conditions examined, because of the lack of the ability of hemiacetal or acetal formation. Therefore, in the early stage of the reaction, the carbanion **19** formed from **17** and an aldehyde other than formaldehyde exists in larger amount than that from **17** and

formaldehyde, though formaldehyde has higher electrophilicity. On the other hand, in the step corresponding to the second selection, the difference in electrophilicity between the aldehydes affects the selection in a striking manner, as can be seen from the results that benzaldehyde did not undergo the self-condensation which gives benzoin in the absence of formaldehyde and that the self-condensation of *p*-nitrobenzaldehyde proceeded smoothly even in the absence of formaldehyde. The carbanion **19**, formed by isomerization of **18** produced from **17** and an aldehyde other than formaldehyde and resonance stabilized by virtue of the thiazolium ring, attacks predominantly the carbonyl carbon of monomeric formaldehyde (more exactly, the methylene carbon of monomeric formaldehyde hemiacetal) with high electrophilicity, nevertheless the concentration of monomeric formaldehyde is extremely low. Then, a 1-hydroxy-2-one is cleaved off from **20**, via **21**, to regenerate **17**. Electron density on the carbon directly bound to the C-2 carbon of thiazolium ring in **19** is easily predicted to be somewhat lower than that on the C-2 carbon in **17**, so the carbanion **19** is supposed to be practically unable to attack the carbonyl carbon of such aldehydes as benzaldehyde with lower electrophilicity. Even if it should be possible and consequently generate the intermediate corresponding to **20** or **21**, the intermediate may not enable to be cleaved into the 1-hydroxy-2-one and **17**.

EXPERIMENTAL SECTION

Materials

Ethanol, methanol, and triethylamine were refluxed with CaH_2 and then fractionally distilled. Dimethylformamide was dried over CaH_2 , and then fractionally distilled under reduced pressure. Ethyl bromide was refluxed

with P_2O_5 , followed by fractional distillation. Benzothiazole, trimethylchlorosilane, and hexamethyldisilazane were purified by fractional distillation. Paraformaldehyde was commercial grade. The other aldehydes were purified in the usual manners. 3-Ethylbenzothiazolium bromide was synthesized as described in the previous report⁶⁾.

Condensation Reaction

Paraformaldehyde (0.3 g, 10 mmol as HCHO), aldehydes other than formaldehyde (10 mmol), 3-ethylbenzothiazolium bromide (0.244 g, 1 mmol), solvent (10 ml), and triethylamine (0.14 ml, 1 mmol) were placed in a 10 ml flask, and dry nitrogen was bubbled through the mixture. Then the flask was tightly closed with a glass stopper. The reaction was begun by heating the flask in an oil bath adjusted to the required temperature with stirring magnetically. After the fixed time the reaction was quenched by cooling the flask in a solid CO_2 -ethanol or an ice-water bath.

Determination of Amounts of Aldehyde and 1-Hydroxy-2-one

The amount of formaldehyde was determined colorimetrically with chromotropic acid⁸⁾. Those of the other aldehydes and 1-hydroxy-2-ones were estimated by gas-liquid chromatography (GLC) and 1H -NMR spectroscopy. The GLC analysis was made as follows. To an aliquot (0.5 ml) of the reaction mixture 0.02 g of hexamethylbenzene or pentaerythritol as an internal standard was added. The solution was allowed to react with 0.1 g of hydroxylamine hydrochloride in 8 ml of pyridine at 70°C for 1 h, followed by trimethylsilylation by adding 3 ml of a mixture of hexamethyldisilazane and trimethylchlorosilane (2:1 in volume)⁹⁾. The solution containing the trimethylsilylated (TMS)-oxime derivatives was subjected to GLC under the following conditions: glass capillary column

of 30 m \times 0.28 mm id; adsorber, silicone SF-96; column temperature 100~200°C, rising at a rate of 3°C/min. The amount of the reacted aldehyde was evaluated by determining the peak area of TMS-oxime derivative of the aldehyde remaining unreacted. The amount of the 1-hydroxy-2-one formed was estimated in the similar manner. The estimation was also carried out with 1H -NMR as follows. To an aliquot (0.5 ml) of the reaction mixture 0.01 ml of hexamethyldisiloxane was added with a microsyringe as an internal standard, and then the 1H -NMR spectrum of the solution was taken. The amount of the aldehyde was estimated by measuring the signal intensity appearing around 10 ppm assigned to the aldehyde proton, and the amount of the 1-hydroxy-2-one formed was evaluated based on the signal around 5 ppm assigned to the methylene proton of hydroxymethyl group in the 1-hydroxy-2-one.

Instruments

The gas-liquid chromatogram was taken on an OHKURA Model-103 chromatograph equipped with a flame-ionization detector and a HITACHI Model-164 with a thermal conductivity detector. The UV and IR spectra were measured on a JASCO UVIDEC-1 UV/VIS spectrophotometer and a HITACHI 260-30 or a JASCO A-102 infrared spectrophotometer, respectively. The 1H -NMR spectrum was taken on JEOL Model JNM-GX-400 and JEOL Model JNM-PMX 60 SI nuclear magnetic resonance spectrometers. The ^{13}C -NMR spectrum was observed using JEOL Model JNM-PET-100 and JEOL Model JNM-FX-90 Q apparatus. The mass spectrum was taken on a SHIMADZU Model GCMS-7000 gas chromatograph-mass spectrometer.

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