Reactions of Benzaldehyde with Thiazolium Salts in Me_2SO: Evidence for Initial Formation of 2-(α-Hydroxybenzyl)thiazolium by Nucleophilic Addition and for Dramatic Solvent Effects on Benzoin Formation

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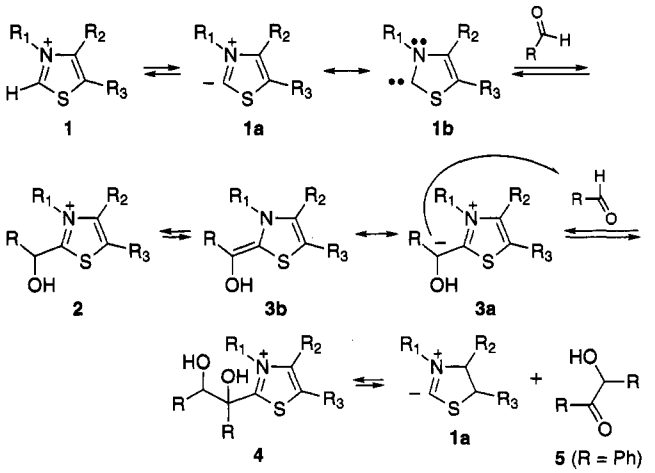
The mechanism of benzoin condensation from benzaldehyde catalyzed by [2-^{13}C]-labeled 3-benzyl- and 3-methylthiazolium salts was examined under a variety of conditions. At ambient temperatures in dry Me_2SO, employing *t*-BuOK as the base, several different combinations of these labeled thiazolium salts and [α-^{13}C]benzaldehyde or [α-^{2}H]benzaldehyde all pointed to the formation of 2-(α-hydroxybenzyl)thiazolium ion, that under these conditions was stable for long periods of time, but was converted to benzoin once even a trace of water or methanol was added to the solution. Analysis of the ^{13}C NMR spectra of the reaction mixtures indicated that the 2-(α-hydroxybenzyl)-thiazolium ion was produced by nucleophilic addition of the C2 carbanion/ylide to the carbonyl carbon, without rearrangement of the benzaldehyde-CαH during the process. ^{1}H NMR experiments suggested that under the conditions employed, the ylide/carbanion, rather than the dimerized bithiazolin-2-ylidene is the reactive species that condenses with the aldehyde. The kinetic isotope effect for a reaction in which the thiazolium ion was allowed to discriminate between [α-^{2}H]-benzaldehyde and [α-H]benzaldehyde was inverse (k_H/k_D = 0.83), also consistent with addition at the benzaldehyde α carbon. When there was nearly 1 equiv of *t*-BuOK added and moisture was not rigorously excluded, 2-(α-hydroxybenzyl)thiazolium ion was still very much in evidence as an intermediate and excellent yields of benzoin resulted. In addition, several other compounds in much smaller yields, probably including 2-benzoylthiazoline also appeared to accumulate to NMR-detectable levels. The reaction of thiazolium salts with the aromatic aldehydes, *p*-anisaldehyde and cinnamaldehyde, in MeOH/MeONa, led to the formation of significant amounts of the corresponding dimethyl acetals, rather than to the benzoin products. Some of the conditions identified in this mechanistic study could be of synthetic utility as well.

Introduction

Several benzoin-type condensation reactions of aldehydes leading to α-ketols are catalyzed by enzymes that have an absolute requirement for thiamin diphosphate (ThDP, the vitamin B_1 coenzyme).[1-4] On the basis of model chemical reactions, it was proposed by Breslow that the C2-conjugate base of the thiazolium ring of ThDP is the active nucleophile in such reactions,[5-8] although it is still unclear whether such a conjugate base (usually called the ylide) exists as a discrete intermediate on the relevant enzymes. For thiazolium salt-catalyzed benzoin condensations,[9] Breslow suggested that the thiamin ylide behaves analogously to cyanide ion, as proposed by Lapworth (Scheme 1; R = Ph).[10-12] According to this proposal, the thiazolium ylide/C2 carbanion **1a** reacts with benzaldehyde to yield a 2-(α-hydroxybenzyl)thiazolium salt (HBT) **2**. The C2α proton in **2** is then ionized to yield an "active benzaldehyde" or enamine **3**. The C2α atom in turn is also a good nucleophile that reacts with a second molecule of benzaldehyde followed by release of benzoin **5** and regeneration of the ylide. Breslow and his co-workers did not isolate the intermediate **2** from

Scheme 1. Mechanism of Benzoin Condensation Proposed by Breslow



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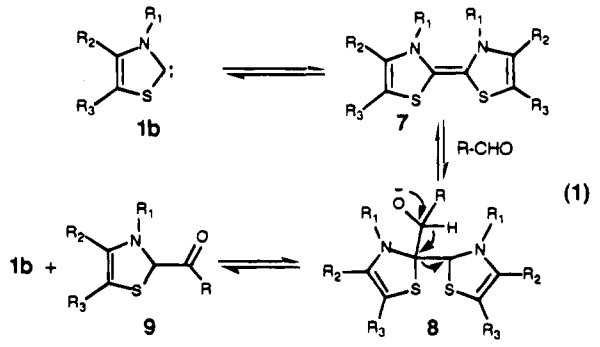
the reaction mixture of benzaldehyde and the thiazolium salt, presumably for lack of stability. Later, a 2-(α-hydroxybenzyl)-3,4-dimethylthiazolium salt was synthesized and was found not to decompose to benzaldehyde and 3,4-dimethylthiazolium ion under mild conditions; rather, it proceeded to benzoin in the presence of excess benzaldehyde under the typical conditions used for the benzoin condensation. Krampitz and co-workers showed that in a similar fashion 2-(α-hydroxyethyl)thiamin will react with acetaldehyde to produce acetoin **6**.[13]

Prompted in part by a number of reports on the formation of bithiazolin-2-ylidenes upon addition of base to thiazolium salts in aprotic media,[17–20] benzoin condensations have also been claimed to be catalyzed by bithiazolin-2-ylidenes[14,15a,b] and 1,1′,3,3′-tetraalkylbiimidazolin-2-ylidene.[16] It had also been reported that a considerable amount of 2-benzoylthiazoline is generated, when benzaldehyde and certain thiazolium salts are refluxed in methanol in the presence of triethylamine,[19,20] and it was argued that these 2-benzoylthiazolines should be considered as intermediates in the formation of benzoins, perhaps according to eq 1:



(1)

According to this mechanism the bithiazolin-2-ylidene symmetrical dimer **7** generated from the ylide by direct dimerization of two conjugate bases, reacted with benzaldehyde to form intermediate **8**, which released a molecule of ylide to form 2-benzoylthiazoline **9**. This appeared to be a plausible hypothesis, since the C2 carbanion could be considered as a resonance hybrid of a carbene and a zwitterionic resonance contribution. In 1991 we reported evidence that the mechanism of formation of the bithiazolin-2-ylidenes **7** in Me_2SO is best accounted for by nucleophilic addition of the C2 carbanion/ylide to a second thiazolium ion leading to an unsymmetrical dimer, that is further deprotonated to the bithiazolin-2-ylidene symmetrical dimer, not by direct dimerization of two C2 carbanions.[21]

Structures analogous to **2** and **3** are of additional biochemical importance since their existence is often invoked on the pathway of α-keto acid decarboxylases, as exemplified by the decarboxylation of pyruvate to acetaldehyde catalyzed by brewers' yeast pyruvate decarboxylase (PDC). Breslow[5] proposed that the addition of the C2-carbanion of ThDP to pyruvate forms 2-α-lactylthiamin **10**, followed by decarboxylation to generate "active aldehyde" (enamine or C2-α-carbanion **3**), which is protonated to lead to 2-(α-hydroxyethyl)thiamin **2**. Finally, the C2α-OH of **2** is ionized to yield acetaldehyde and ThDP (Scheme 2). Kluger's group[2] studied the chemistry of both 2-α-lactylThDP and 2-(α-hydroxyethyl)-ThDP, while the structure and chemistry of the highly conjugated enamine has been investigated in our laboratories both on pyruvate decarboxylase[22] and in models.[23]

We undertook this study to reexamine the chemical reactivity of the thiazolium C2-carbanion/ylide vis-à-vis benzaldehyde, and the course of benzoin condensation, as a sequel to our study concerning the mechanism of self-dimerization of thiazolium ions in Me_2SO.[21] Extensive NMR studies monitoring the fate of [2-^{13}C]thiazolium ion and [α-^{13}C]benzaldehyde during their reaction in Me_2SO induced by a strong nonnucleophilic base, provide evidence for the initial formation of HBT under all conditions used, whereas bithiazolin-2-ylidene and 2-benzoylthiazoline are not always present in detectable amounts under these same conditions.

In addition, it was found that from certain aromatic aldehydes thiazolium salts in methanol can catalyze acetal rather than benzoin formation.

Results and Discussion

A. Mechanism of the Reaction between Benzaldehyde and Thiazolium Salts at Low Percent Conversion to Product in Dry Aprotic Me_2SO. Mixtures of benzaldehyde and thiazolium ion, labeled with ^{13}C at Cα and/or at C2, were treated with *t*-BuOK in Me_2SO and the course of the reaction was monitored by broad-band proton-decoupled ^{13}C NMR. The ^{13}C resonances

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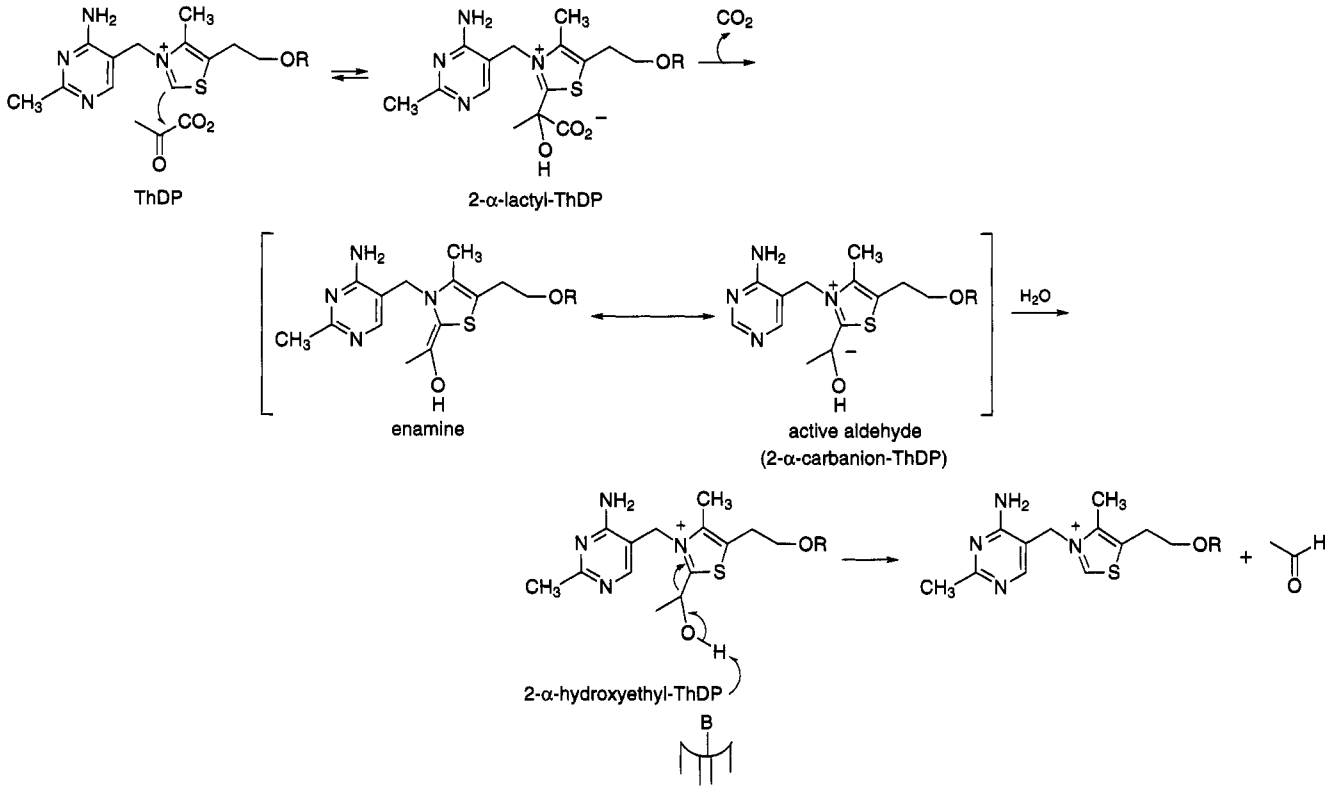
Scheme 2. Pyruvate Decarboxylation Catalyzed by the Thiamin-Dependent Enzyme Pyruvate Decarboxylase



corresponding to the C=O of benzaldehyde, and the C=O and C−OH of the benzoin product are at δ 193.13, 199.25, and 75.37, respectively. Also, to assist assignment of resonances in the reaction mixtures, the chemical shifts of the resonances for authentic 2-(α-hydroxy-*p*-bromobenzyl)-3,4-dimethylthiazolium salt **11** were determined at δ 68.86 at C2α and 178.02 at C2.

The first set of experiments (Scheme 3) was designed to identify the initial compound formed on reacting benzaldehyde with thiazolium salts and *t*-BuOK. Compounds resulting from nucleophilic addition, or the presence of 2-benzoylthiazoline, would be evident from the spectra. In all five experiments the concentration of base was limiting, so as not to convert all of the thiazolium salt to a catalytic form, thereby enabling us to observe the early reaction product.

In an experiment typical of this series, a mixture of excess unlabeled benzaldehyde **12** (ca. 2 mmol) and 3-benzyl-5-(β-ethoxyethyl)-4-methyl[2-^{13}C]-thiazolium bromide **13** (0.09 mmol) in Me_2SO was treated with *t*-BuOK (0.05 mmol) (Scheme 3A, Figure S1). In addition to benzaldehyde and **13**, a new resonance appeared at δ 178.01, that was assigned to 2-(α-hydroxybenzyl)-[2-^{13}C]-thiazolium ion **14.** From the result we deduce that the 2-benzoylthiazoline **15** is not generated in detectable amounts under these conditions. The adduct **14** is stable in aprotic solution for more than three weeks without any further reaction. Once the solution was exposed to moisture from the air, in four days two additional resonances at δ 198.75 and 75.38 appeared, corresponding to benzoin (Figure S2). The benzoin coexists with benzaldehyde and thiazolium ion in solution, as well as with the HBT analog **14**. It is important to emphasize that a proton source, such as water or methanol, was required to convert **14** to benzoin. Dry *tert*-butyl alcohol could not convert **14** to benzoin.

Additional experiments (3-benzylthiazolium bromide **17** with [α-^{13}C]benzaldehyde **16** in Scheme 3B, results in Figure S3; [α-^{13}C]benzaldehyde **16** and 3-benzyl-5-(β-ethoxyethyl)-4-methyl-[2-^{13}C]thiazolium bromide **13** in Scheme 3C, Figure S4, then with a drop of methanol added in Figure S5; benzaldehyde **12** with 3,4,5-trimethyl-[2-^{13}C]thiazolium nitrate **22** in Scheme 3D, results in Figure S6; [α-^{2}H]benzaldehyde **25** and 3,4,5-trimethyl-[2-^{13}C]thiazolium nitrate **22** in Scheme 3E, Figure S7, an experiment based on the observations that a deuterium either directly attached or two bonds away will induce an upfield chemical shift of the ^{13}C resonance,[26] and with a small amount of benzaldehyde in Figure S8) *all* gave results consistent with the product expected under "Nucleophilic Addition" in Scheme 3. The chemical shifts of ^{13}C enriched positions in these compounds are summarized in Table 1.

Under the conditions used in these experiments we conclude the following: 1. The deuterium or hydrogen is still attached to C2α of HBT in aprotic solution in the presence of a base, nor is this proton undergoing tautomerization to the 2-benzoylthiazoline, or being removed to form the enamine under the conditions. Subsequently, this proton must be removed to enable further reaction with a second benzaldehyde to form benzoin. The thermodynamic pK_a of this C2α-H has been reported[23d] in Me_2SO (ca. 12.4 for a methoxy analog of **14**), and is lower than that of the OH, yet a strong base such as *t*-BuOK (pK 33) is apparently unable to catalyze the entire benzoin condensation. 2. The addition of a small

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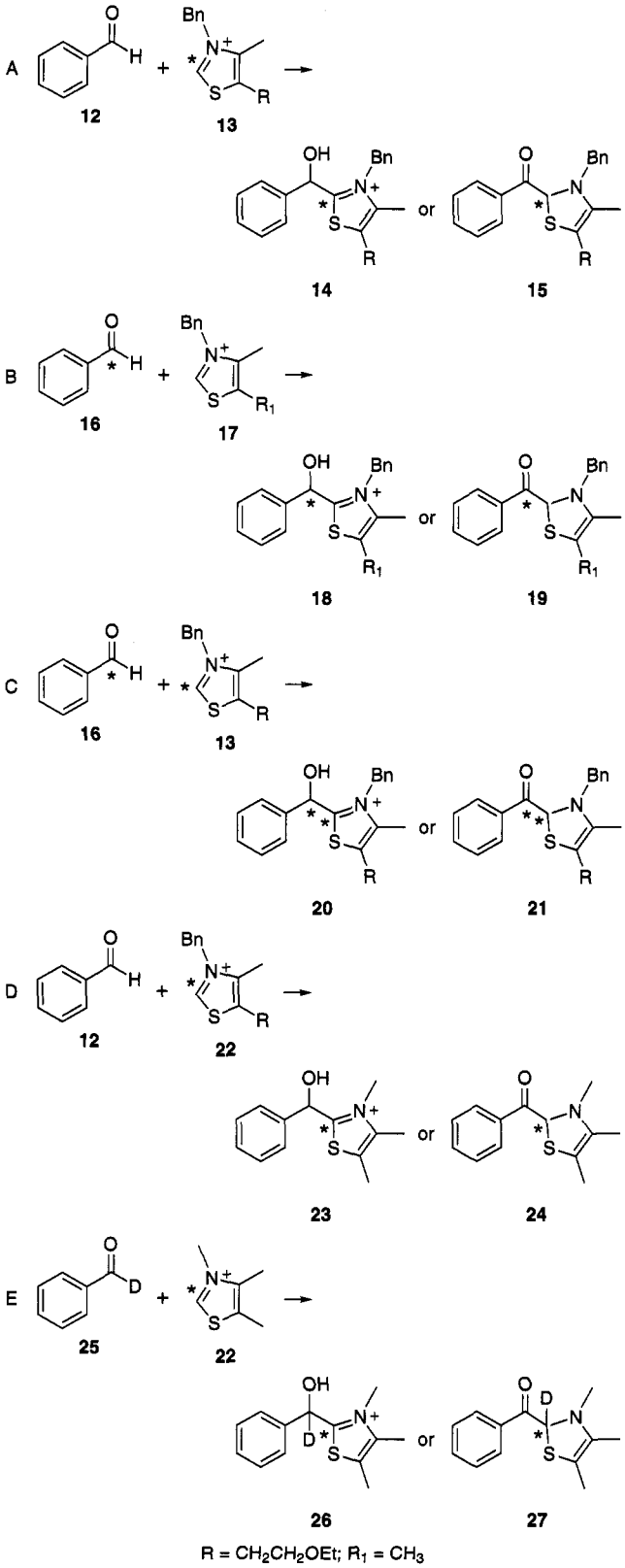
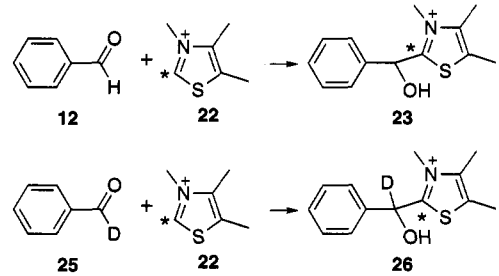
Scheme 3. Intermediates Expected during Benzoin Condensation



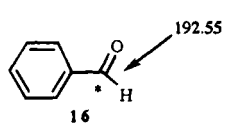
concentration of methanol or moisture to the dry DMSO solutions of HBT analogs readily leads to benzoin formation. 3. The behavior of 3-methyl- and 3-benzylthiazolium salts under these conditions is similar. 4. In these experiments we could not observe the two singlets at δ 116 and 113 characteristic of the bithiazolin-2-ylidene symmetrical dimer and/or the two doublets at δ 173, 174 and 65, 66 characteristic of the unsymmetrical dimer that are formed in the absence of the benzaldehyde acceptor.[21] Apparently, the *benzaldehyde competed effectively with the thiazolium dimerization reaction*. Under the conditions of these experiments, there is no evidence to support the mechanism for benzoin formation suggested by Metzger[19,24] and Castells[15] and their co-workers. Diederich and Lutter[25] synthesized a supramolecular cyclophane with a thiazolium ring covalently attached to it that catalyzed the benzoin condensation. The thiazolium ion in this catalyst is located inside the macrocyclic cavity, and it is unlikely that this cyclophane-bound thiazolium could form a symmetrical dimer (in either aqueous or nonaqueous solution) prior to catalyzing the benzoin condensation, also inconsistent with the alternative mechanisms suggested in refs 15 and 19.

Kinetic Isotope Effect for the Competition of 3,4,5-Trimethyl-[2-^{13}C]thiazolium Nitrate for a Mixture of Benzaldehyde and [α-^{2}H]Benzaldehyde. The nucleophilic adduct **2** is stable enough in the presence of a nonnucleophilic base enabling a kinetic analysis of its formation and estimation of the α-deuterio kinetic isotope effect (KIE) resulting from discrimination between [α-H]- and [α-^{2}H]benzaldehydes in the condensation reaction. We hypothesized that addition at the benzaldehyde α-carbon will be reflected by a different magnitude of the KIE than insertion. The initial ratio of benzaldehyde **12** (0.051 mL, 0.50 mmol) to [α-^{2}H]-benzaldehyde **25** (0.074 mL, 0.72 mmol) in 0.6 mL of dry Me_2SO-d_6 was determined to be equal to 0.689:1 according to integration of the 300 MHz ^{1}H NMR spectrum at δ 10.053 (the aldehydic hydrogen) and 7.934 (two hydrogens ortho to the aldehyde group). Next, 3,4,5-trimethyl-[2-^{13}C]thiazolium **22** (7.0 mg, 0.037 mmol) was added to this solution, along with *t*-BuOK solution (1.46 N, 0.05 mL, 0.07 mmol), and the ^{13}C NMR spectrum was recorded using the inverse-gated decoupling technique with a recycle delay of 7 s. The ^{13}C NMR spectra are shown in Figure 9A after three weeks, and in Figure 9B after four weeks of incubation at room temperature. A singlet at δ 155.72, a singlet at δ 193.11, a 1:1:1 triplet at δ (192.45, 192.81, 193.17) correspond to **22**, **12**, and **25**, respectively. Two singlets at δ 175.24 and 175.20 were observed, corresponding to C2 of **23** and **26**, respectively. The two bond deuterium shift on the ^{13}C resonance is upfield by 3.3 Hz, as shown above. The integrated intensities of these two resonances relative to 1/10000 of the ^{13}C resonances of Me_2SO-d_6 were 22.423 and 32.187 for **26** and 16.194 and 21.804 for **23** after three and four weeks, respectively. Since we are observing small percent conversion to product, initial velocity conditions can be assumed to hold, and we can estimate the isotope effect from changes in concentrations of the two products between the third and fourth week of incubation of the same sample (more accurate than the initial ratios), leading to a kinetic isotope effect k_H/k_D for the formation of **23** to **26** of 0.83, i.e. inverse.

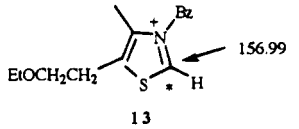


(2)

Table 1. ^{13}C NMR Chemical Shifts of C2 and C2α Atoms in Starting Materials and Intermediates in Benzoin Condensation Produced by *t*-BuOK in Me_2SO-d_6



16



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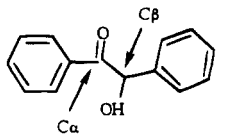
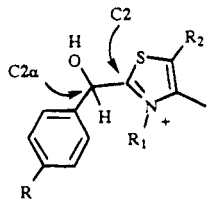


Cα	Cβ	δ at Cα	δ at Cβ
		198.759	75.37
*	*	199.360, 198.792	75.428, 74.853



compd	R	R_1	R_2	C2	C2α	δ at C2	δ at C2α	Figure
11	Br	CH_3	H			178.016	68.857	
18 (Scheme 3B)	H	Bz	CH_3		*		69.334	3
14 (Scheme 3A)	H	Bz	C_2H_4OEt	*		178.010		1
20 (Scheme 3C)	H	Bz	C_2H_4OEt	*	*	177.938, 177.259	69.674,68.995	4

While the error in such an approximation may be significant, there is little doubt based on the integrals measured that the isotope effect is indeed inverse, and not very much smaller than unity. Some literature precedents for addition reactions to benzaldehyde are k_H/k_D = 0.78 for the addition of hydrogen cyanide to 4-methoxybenzaldehyde[27] and k_H/k_D = 0.74 for the addition of hydroxylamine to benzaldehyde.[28] Kinetic isotope effects for insertion of CH_2 into C–H bonds are reported to result in k_H/k_D ranging from 1.3 to 3.9.[29] Our estimated value for k_H/k_D is more consistent with those found for nucleophilic addition to benzaldehyde, than for insertion into C–H bonds, and its inverse magnitude is also consistent with theoretical estimates for a carbon undergoing change in hybridization from sp^2 to sp^3.[27,28]

B. Nature of the Active Thiazolium Species Condensing with Benzaldehyde and the Course of the Reaction with 1 Equiv of Base and Traces of Water or Methanol (test for the intermediacy of bithiazolin-2-ylidene). We next addressed the question as to which form of the thiazolium species, the ylide or the bithiazolin-2-ylidene symmetrical dimer reacts with benzaldehyde. First, to a solution of 3,4,5-trimethylthiazolium tetrafluoroborate (0.11 mmol) dissolved in dry Me_2SO was added increments of *t*-BuOK ranging from 0 to 0.12 mmol (Figure S10) and the ^1H resonances corresponding to the unsymmetrical and symmetrical dimer could be detected. As the base was added, the C2H resonance of starting material near δ 10 diminished, while that of the C2H corresponding to the unsymmetrical dimer near δ 6.4 first increased and then disappeared as all of the material was converted to bithiazolin-2-ylidene symmetrical dimer, consistent with the ^{13}C spectra reported earlier.[21] Next, 0.15 mmol of benzaldehyde was added to the solution indicating *no new products being formed*. Finally, the base was partially neutralized with DCl and the spectrum was rerecorded indicating that the thiazolium starting material was not regenerated. Formation of the bithiazolin-2-ylidene symmetrical dimer is also evident from the appearance of a new characteristic visible absorption band centered at 424 nm.

In a different experiment, to 0.09 mmol of 3,4,5-trimethylthiazolium tetrafluoroborate were added first 0.05 and then an additional 0.12 (for a total of 0.062) mmol of *t*-BuOK, followed by 0.1 and then an additional 0.2 mmol of benzaldehyde. The proton NMR spectrum was recorded after each addition. Under these conditions there was clear indication of the formation of the symmetrical and unsymmetrical dimers and of unreacted thiazolium salt prior to addition of benzaldehyde. Within a few minutes after addition of benzaldehyde, there was a new resonance formed near δ 6.4, with chemical shift characteristic of the C2αH of HBT (not shown). Also, from the characteristic chemical shift of the 3-methyl group in the starting material (δ 4.04) and in HBT (δ 3.78) both could be discerned. After 15 h plenty of benzoin (presumably resulting from release of benzoin with the help of moisture that was not rigorously excluded) along with unreacted thiazolium salt and HBT was apparent in this solution, but no 2-benzoylthiazoline.

While it is difficult to rule out a catalytic role for bithiazolin-2-ylidene unequivocally, our results indicate that when the unsymmetrical dimer and the bithiazolin-2-ylidene symmetrical dimer are preformed, they do not react with benzaldehyde if moisture is rigorously ex-

(27) do Amaral, L.; Cordes, E. H. *J. Am. Chem. Soc.* **1972**, *94*, 7579–7580.
(28) do Amaral, L.; Bastos, M. P.; Bull, H. G.; Cordes, E. H. *J. Am. Chem. Soc.* **1973**, *95*, 7369–7374.
(29) (a) Jones, M. Jr.; Moss, R. A. *Carbenes*; Wiley: New York, 1973; Vol. 1. (b) Jones, M., Jr.; Moss, R. A. *Carbenes*; Wiley: New York, 1975; Vol. 2.

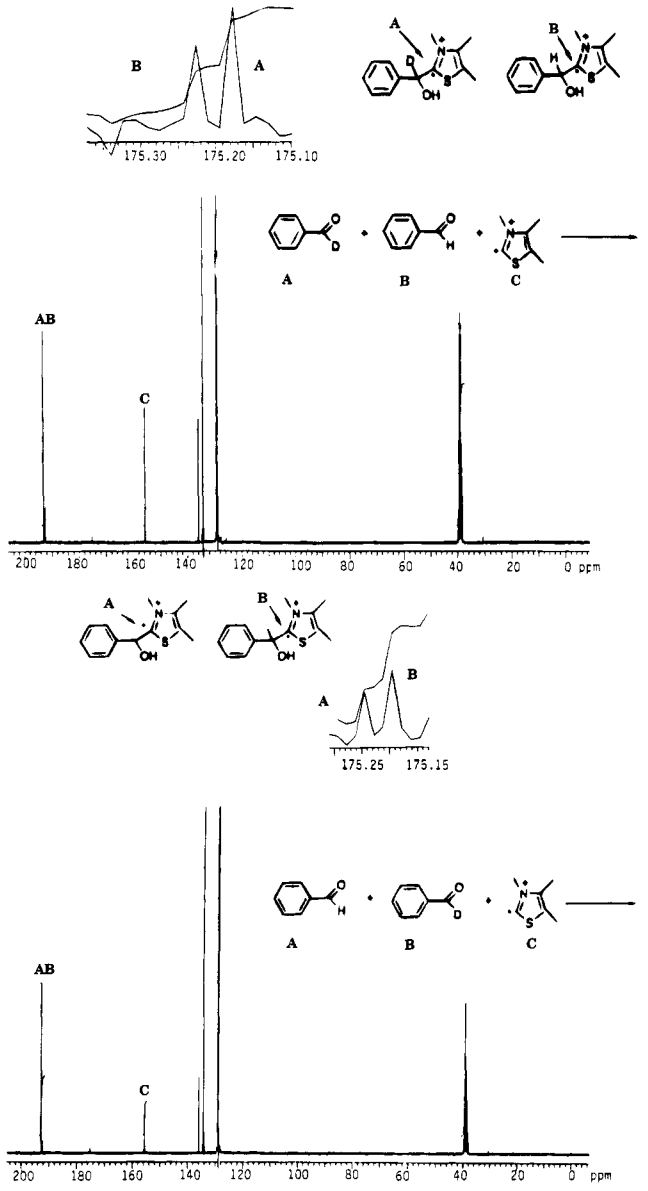


Figure 9. (A) Broad-band proton decoupled ^{13}C NMR spectrum (75 MHz) of a mixture of **12, 25,** and **22** in Me_2SO-d_6 with *t*-BuOK added after three weeks; inset: the resonances corresponding to **26** and **27**. (B) Broad-band proton decoupled ^{13}C NMR spectrum (75 MHz) of a mixture of **12, 25,** and **22** in Me_2SO-d_6 with *t*-BuOK added after four weeks; inset the resonances corresponding to **26** and **27**.

cluded. When there is unreacted thiazolium salt still in solution, HBT will be formed. An inspection of several experiments suggests that in the absence of water or methanol, benzoin is clearly not formed via bithiazolin-2-ylidene, but conceivably HBT is. We conclude that the unsymmetrical dimer and the bithiazolin-2-ylidene indeed are formed under some of our experimental conditions, but are most likely side products, not related to benzoin formation.

Reaction Products when Thiazolium Salt and Benzaldehyde are Premixed. In order to identify other potential side reactions, next the fate of reaction mixtures in which the thiazolium salt and the benzaldehyde were premixed prior to the addition of base was examined (as contrasted with premixing of thiazolium salt and base, as in the experiments immediately above). First, to a mixture of 0.09 mmol of 3,4,5-trimethylthiazolium tetrafluoroborate (Figure S11) and 0.15 mmol of benzaldehyde, increments of *t*-BuOK ranging from 0.05 to 0.20 mmol was added. The most prominent proton resonance on first addition of the base was HBT again (δ 6.45), along with some benzoin (δ 6.07) and perhaps 2-benzoylthiazoline (a proton resonance at δ 6.17, similar to that reported for 2-benzoyl-5-carbethoxy-3,4-dimethylthiazoline by Doughty[20b,e]) being produced. As additional base was added, the solution turned dark and the amount of HBT diminished, while the concentration of benzoin and the putative 2-benzoylthiazoline increased. The deep color produced on addition of base had a λ_{max} at 380 nm, an absorbance that we have shown to pertain to the enamine.[23g] This deep color faded to a much lighter one within minutes, presumably as the condensation was completed. After 15 h there was virtually no thiazolium or benzaldehyde starting material left, but benzoin, the putative 2-benzoylthiazoline, and perhaps two other altered forms of thiazolium: the ring-opened form with δ 5.4 (appropriate for the Cα-H of the mandelamide, that would result from the hydroxide-catalyzed ring opening of HBT) and two closely-spaced singlets at δ 4.95, perhaps pertaining to the diastereotopic C2α-Hs of a C2-C2α "spiro-epoxide" (eq 3 below and ref 20e), resulting from ring closure of the alkoxide of HBT.

This experiment was repeated with a double labeled [α-^{13}C, α-^{2}H]benzaldehyde. The advantage of this compound is that both the directly coupled deuterium-leading to a 1:1:1 triplet for the ^{13}C to which it is attached, as well as the residual 2% hydrogen at this position (reflected by a doublet in the proton spectrum with the characteristic one bond $^1J^{13}_{C-H}$ between 130–160 Hz) provide useful information. After mixing 0.09 M of 3,4,5-trimethylthiazolium salt with 0.2 M of this doubly labeled benzaldehyde (Figure S12), we added *t*-BuOK incrementally resulting in 0.05–0.20 M total concentrations. The first ^{13}C spectrum on addition of base showed the formation of HBT (δ 68–70), and of some benzoin (δ 199 and 75). *As more and more base was added,* the HBT diminished, as did the benzaldehyde (δ 193), forming predominantly benzoin (doublet at δ 199 due to $^{13}C-^{13}C$ coupling, multiplets in the aliphatic region showing both carbon and deuterium coupling). The initial formation of HBT followed by formation of benzoin is clearly evident. There were found minor ^{13}C resonances under broad band decoupling conditions, that became more prominent once most of the benzaldehyde was consumed. A small resonance was seen in the aliphatic chemical shift region, first near δ 78, and then, with more base added, an additional one near δ 87. In the trigonally hybridized chemical shift region was found a resonance near δ 169 due to benzoic acid (demonstrated by addition of authentic compound), that may result from air-oxidation of the enamine, a known and documented reaction both on ThDP-dependent enzymes.[22h,i] This resonance grew with time and two days after the start of the experiment was the only resonance remaining in the trigonal carbon region, aside from the benzoin. There was a resonance near δ 189.5 that existed for the first few additions, but did not survive for two days. The chemical shift of this resonance, and the observation that the δ 6.17 resonance in the proton spectrum showed parallel temporal behavior, prompts us to tentatively assign these resonances to the C2α and C2H of 2-benzoylthiazoline, respectively. There was a smaller resonance at δ 165 (dd, J = 17.4 and 4.3 Hz), that eventually was converted to either benzoin or to benzoic acid and

remains unassigned. There was also observed formation of considerable amounts of the *syn–anti* symmetrical dimers at δ 114.4 and 116.4 and these persisted for all four additions of the base, but did not survive long term, suggesting that they reverted to thiazolium salts.

It should be emphasized that in this series of experiments no special effort was made to dry the Me_2SO-$^2H_6$, and unlike in the first series, HBT was now clearly an intermediate and benzoin was the major product resulting from HBT. Benzoin was formed in excellent yields; benzoic acid was the only side product derived from benzaldehyde. No special effort was made to exclude air from the solutions, either.

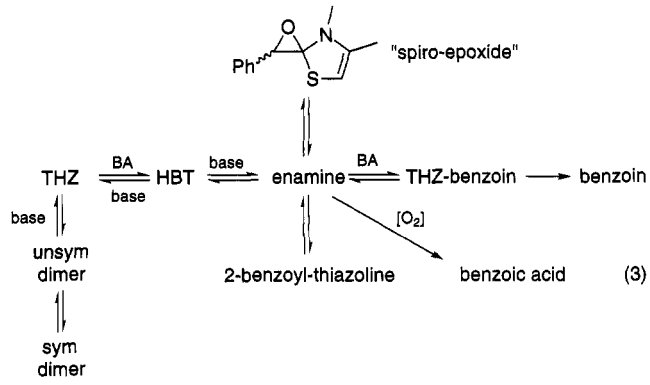
The doubly labeled benzaldehyde also helped to confirm several ^1H NMR assignments: δ 6.45 (d, $^1J_{C-H}$ = 150 Hz, HBT C2α-H), δ 6.17 (s, 2-benzoylthiazoline C2-H), δ 6.09 (dd, $^1J_{C-H}$ = 146 Hz, $^2J_{C-H}$ = 2.7 Hz, benzoin Cα-H), δ 5.4 (d, $^1J_{C-H}$ = 150 Hz, the mandelamide-type ring-opened form of the thiazolium salt observed in some experiments after the solution was exposed to traces of water, C2α-H).

The ^2H NMR spectrum of a solution similar to that shown in Figure S12 confirmed initial formation of HBT, followed by its conversion to benzoin. Also, the ^2H spectrum reconfirmed the proton resonances detected at δ 4.95, with two closely-spaced doublets now centered at δ 4.8 showing $^1J_{C-^2H}$ = 17 Hz, and a separation of 0.054 ppm.

In a further control experiment it was shown that none of the carbon and proton resonances discussed resulted from incubation of authentic benzoin under the reaction conditions.

We conclude from these experiments that under all of the conditions examined HBT is the first and most prominent compound to be detected. On addition of more base, deprotonation either at C2α-oxygen or at C2α results giving the alkoxide (that perhaps closes to an epoxide) or the enamine, respectively. The evidence for the "spiro-epoxide" is not air-tight, but the appearance of two proton resonances near δ 4.95 and the above mentioned deuterium NMR results are consistent with C2α protons in diastereotopic environments. The evidence for the presence of some enamine is the absorbance at 380 nm. The enamine is tautomeric with 2-benzoylthiazoline, and the latter is apparently more stable (sometimes even isolable).[20b,e] Spectral assignments for these compounds are tentative, since such compounds with electron-donating substituents are difficult to isolate. While benzaldehyde is still present in solution, the enamine is converted to benzoin. Once the benzaldehyde concentration is significantly depleted, the modified forms of the thiazolium ring begin to dominate and persist. Equation 3 summarizes the various species mentioned and their places in the overall reaction, based on the combined evidence in this study where BA is benzaldehyde, THZ is the thiazolium salt, and the relative magnitude of the arrows has no significance.

Benzaldehyde Methyl Acetal is a Side Product in Methanol Solvent. When the experiment outlined in Scheme 3C was run in MeOH/Me_2SO-d_6 using two ^{13}C labels (in the thiazolium ion **13** and in benzaldehyde **16**), two doublets at δ 175.12, 174.33 and 77.62, 76.82 with a coupling constant of 59.2 Hz were observed, in addition to the doublets at δ 177.94, 177.26 and 69.67, 69.00 (see Table 1) corresponding to 2-(α-methoxy[2α-^{13}C]benzyl)-*N*-benzyl-[2-^{13}C]thiazolium ion, **20**, and a distinct singlet at δ 96.5 corresponding to benzaldehyde dimethyl acetal,



(3)

or benzaldehyde methyl hemiacetal (Figures S5A and S5B). These new species coexist with starting material and benzoin, implying that unsubstituted benzoin is not the exclusive product in this reaction. It was shown[21b] that under the reaction conditions in methanol *p*-anisaldehyde and *trans*-cinnamaldehyde are converted predominantly to their dimethyl acetals, rather than to the respective benzoin products, in a reaction clearly catalyzed by thiazolium salts. It had been shown by others that *trans*-cinnamaldehyde is not a substrate for benzoin condensation by thiazolium salts.[20a,30]

Summary and Conclusions

The substrate structure, the solvent system used, and the nature and concentration of the base all influence the product distribution in the benzoin condensation catalyzed by thiazolium salts, while the reactivity of the C2α carbanion will be modulated by different substituents. Benzoin is not the exclusive product of the thiazolium-catalyzed reaction in the presence of methanol, it is the predominant one from benzaldehyde. The presence of the side products shows that a kinetic analysis, based solely on the rate of formation of benzoin, can lead to erroneous deductions.

The identification by ^{13}C and ^1H NMR of 2-(α-hydroxybenzyl)thiazolium ion as a likely intermediate in all experiments on reaction of thiazolium salts with benzaldehydes provides evidence for thiazolium C2-carbanion/ylide with nucleophilic behavior, as was also found in the companion study on the dimerization of thiazolium salts under similar conditions.[21] On addition of base, this intermediate or its alkoxide then proceeds to the enamine or C2-α-carbanion (evidenced by the deep color with λ_{max} at 380 nm, that fades within minutes), that would condense with a second benzaldehyde molecule. The existence of such enamines in both chemical models[23] and enzymatic reactions has been amply demonstrated by this group from a variety of alternate substrates/inhibitors of PDC.[22] Competition between deprotonation at C2αH or C2α-OH leading to aldehyde expulsion has been documented before. For example, Sable and co-workers used proton NMR to demonstrate proton–deuterium exchange at the α-position of 2-(α-hydroxyethyl)thiamin and 2-(α-hydroxyethyl)thiamin diphosphate.[31] Breslow[5] demonstrated that 2-(α-hydroxybenzyl)thiazolium ion is a good model to study the details of the benzoin conden-

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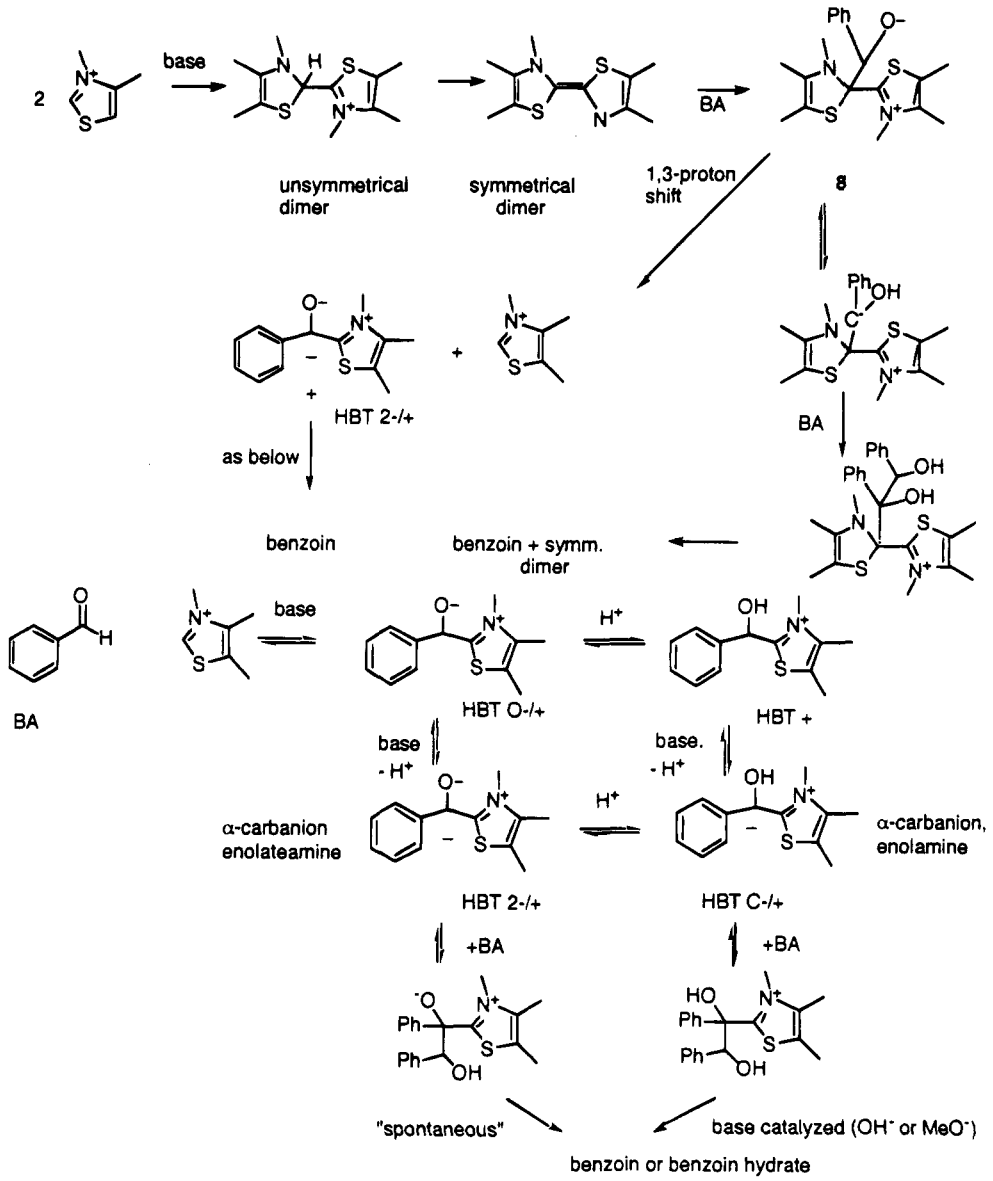
(31) (a) Mieyal, J. J.; Bantle, G.; Votaw, R. W.; Rosner, I. A.; Sable, H. Z. *J. Biol. Chem.* **1971**, *246*, 5213–5219. (b) Mieyal, J. J.; Votaw, R. W.; Krampitz, L. O.; Sable, H. Z. *Biochim. Biophys. Acta* **1967**, *141*, 205–209.

Scheme 4. Mechanisms for Thiamin-Catalyzed Benzoin Condensations



sation, because it doesn't eliminate aldehyde under mild conditions, while later Kluger[2] reported that 2-(α-hydroxyethyl)thiamin released aldehyde in nonenzymatic reactions only at pH > 10. In aprotic media Rios had shown that C2αH deprotonation in 2-(α-hydroxyethyl)-thiazolium ions can successfully compete kinetically with other pathways requiring OH deprotonation,[23f] while Barletta in unpublished results has confirmed such results even in Me_2SO–water mixtures. The enamine thus has significant lifetime in aqueous,[23g] as well as in nonaqueous solutions. As was demonstrated by Risinger and Doughty[20] there is 2-benzoylthiazoline being formed in detectable amounts in the presence of excess base, in their case with an electron withdrawing substituent at the thiazolium C5, in ours with a H or Me group. We also emphasize the difference between the postulate presented by Doughty and Risinger,[20b] in which the 2-benzoylthiazoline is the first product of the reaction between the 2-carbanion/ylide and benzaldehyde, and our results, showing strong evidence for the initial formation of **2** exclusively in the absence and predominantly in the presence of traces of moisture.

It appears that the t-BuO^-/t-BuOH system is too bulky to allow completion of the condensation reaction. This would explain why we can observe **23** and **26** in solution for more than 4 weeks without any trace of benzoin being found, when moisture is rigorously excluded. We wish to speculate about this marked solvent/base effect (i.e. t-BuOH/t-BuOK vs t-BuOH/MeONa or MeOH/MeONa) on the benzoin condensation.

Mechanism 1. If the so-called symmetrical dimer is preformed (according to the mechanisms elucidated in the companion study),[21] according to Wanzlick,[17] Metzger,[19] and Castells[15] and their co-workers, it can react with neat benzaldehyde to form **8**, that has at least two options for benzoin formation (Scheme 4, top). According to Castells et al., **8** can be ionized at C2α and then condense with benzaldehyde and finally release benzoin.[15] This would require significant acidity at the C2α atom in **8**, a rather ordinary benzylic position that is also attached to a tetrahedral center. According to a report by Lemal and co-workers,[32] it is more likely that an intermediate such as **8**, if it is formed, would undergo concerted 1,3-prototropic shift that produces the "enolateamine", that condenses with benzaldehyde and releases benzoin from

(32) Lemal, D. M.; Lovald, R. A.; Kawano, K. I. *J. Am. Chem. Soc.* **1964**, *86*, 2518–2519.

the thiazolium ring. This, we believe is a more likely scenario, given the demonstrated facility for C2α-H ionization leading to this intermediate under aprotic conditions. Our results do not support this mechanism.

Mechanism 2. Under conditions used in the present study, the condensation appears to be taking place according to the "traditional" Breslow mechanism, and 2-(α-hydroxybenzyl)thiazolium ion can be clearly identified on the pathway, *in the presence of both limiting and excess base and in the absence and presence of traces of water*. All of our observations are consistent with the thiazolium ylide **1a** reacting with benzaldehyde by a nucleophilic addition to form adduct anion (Scheme 4, lower half). This adduct must undergo prototropic shift to the enolamine (HBT C-/+) or enolateamine (HBT 2-/+) to complete the benzoin condensation. Why is *t*-BuOK even in the presence of some *t*-BuOH ineffective in converting HBT to benzoin, whereas addition of even traces of water or methanol (the latter may contain traces of water) can achieve this conversion? This is observed in spite of the fact that the acidities of water, methanol, and *t*-BuOH in Me_2SO are nearly the same, and certainly their conjugate bases are all equally adequate to deprotonate either the C2α-H or the C2α-OH, the latter to initiate benzoin release.[23]

Formation of benzoin from HBT according to eq 3 requires both excess benzaldehyde and base. One possibility is that there is steric hindrance to release of benzoin from THZ-benzoin, perhaps because the C2α-OH proton is in a highly sterically hindered environment in this species, such that *t*-BuO^- cannot access it, but HO^- and MeO^- can. A second scenario is that formation of either the enolateamine or enolamine needed as a nucleophile, or of the C2α-O^- species of THZ-benzoin needed for release of benzoin, requires solvation and because of its steric bulk *t*-BuOH and Me_2SO cannot solvate the rather high energy incipient alkoxides or carbanion.

So far as biochemical relevance is concerned, the three X-ray structures solved to date of ThDP-dependent enzymes[33] show no evidence for two molecules of ThDP being proximal enough to allow formation on the enzyme of a "symmetrical dimer", even if that compound turned out to be a benzoin catalyst under some conditions.

Experimental Section

General. ^{13}C and ^1H NMR spectra were carried out on a Varian Model XL-200 or Gemini-300 or VXR-400 spectrometers and ^2H spectra on the VXR-400. NMR data are reported in ppm downfield relative to (a) TMS, using $CDCl_3$ or Me_2SO-d_6; (b) DSS, using D_2O as an internal reference. All NMR samples that required anhydrous conditions were prepared in Atmos-Bags with dry He or N_2 purging. Mass spectra were obtained on a Varian Model MAT 312 spectrometer and exact mass measurements were carried out by a VG Analytical Model ZAB-SE spectrometer. In the fast atom bombardment (FAB) technique thioglycerol or 3-nitrobenzyl alcohol were used as matrix. In the chemical ionization (CI) technique NH_3, CH_4, or isobutane was used as carrier gas. In the electron ionization (EI) technique the eV was 70 V. Microanalyses were performed by the Physical and Analytical Department of Schering-Plough Corp., Bloomfield, NJ. All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Flash chromatography refers to the method described by Still *et al.* using Baker 40 mm silica gel with a pressure of 8 psi.[34]

Materials. All chemicals were reagent-grade and used without further purification unless otherwise stated. *t*-BuOK (97%) (Aldrich) was dried in a desiccator with P_2O_5 under high vacuum prior to use. 4,5-Dimethylthiazole and 4-methylthiazole were purchased from Pyrazine Specialties, Inc. ^{13}C-Thiourea (enriched 91.2% and 99.9%), [α-^2H]benzaldehyde and [α-^{13}C]benzaldehyde were purchased from ICON Services, Inc. and were used in the reactions without further purification. Chloroform-*d* ($CDCl_3$), Me_2SO-d_6 (99.9% D) and D_2O (99.9% D) were purchased from Merck Sharpe and Dohme Isotopes, Canada. The 4 Å molecular sieves were washed with anhydrous Me_2SO (Aldrich) and stored in the oven at 127 °C prior to use. The [2-^{13}C]thiazolium salts were dried under high vacuum for at least one week prior to use; their synthesis was reported elsewhere.[21]

Sample Preparation for ^{13}C NMR and ^1H NMR. Solutions were prepared by dissolving the thiazolium compounds in 0.8 mL of Me_2SO-d_6 and adding to it 10 mL aliquots of 1.46 N *t*-BuOK (prepared by dissolving 0.5 g of 97% *t*-BuOK in 3 mL of Me_2SO-d_6). Other details are presented in the text and in the figure legends.

Benzoin (2-hydroxy-2-phenylacetophenone) (5).[5] To a solution of benzaldehyde (freshly distilled) (1.0 g, 9.4 mmol) in methanol (10 mL) with *t*-BuOK (20 mg, catalytic amount) was added a catalytic amount of thiazolium **17** at room temperature. After stirring for 10 h, the solution was concentrated. The residue was flash-chromatographed over silica gel (pretreated with 1% triethylamine/hexane) eluting with a gradient of (0-40%) ether/hexane to yield **5** (0.80 g, 3.77 mmol, 40%): ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 7.936 (d, 2H), 7.540–7.276 (m, 8 H), 5.972 (d, 1H, J = 6.12 Hz), 4.577 (d, 1H, J = 6.12 Hz); ^{13}C NMR (75 MHz, Me_2SO-d_6/TMS, broad band proton decoupled) δ 199.233, 139,580, 134.555, 133.041, 128.637, 128.394, 128.261, 127.497, 127.062, 75.275.

2-(α-Hydroxy-*p*-bromobenzyl)-3,4-dimethylthiazolium Tetrafluoroborate (11). Synthesis was reported elsewhere:[23h] ^1H NMR (300 MHz, Me_2SO-d_6/TMS) δ 7.978 (s, 1H), 7.695 (d, 2H, J = 8.4 Hz), 7.649 (d, 1H, J = 4.7 Hz), 7.447 (d, 2H, J = 8.4 Hz), 6.437 (d, 1H, J = 4.7 Hz), 3.778 (s, 3H), 2.509 (s, 3H); ^{13}C NMR (75 MHz, Me_2SO-d_6/TMS, broad band proton decoupled) δ 178.016, 147.902, 137.045, 131.870, 129.728, 118.760, 122.476, 68.856, 36.883, 12.890.

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Supplementary Material Available: Figures S1–S8 and S10–S12, illustrating ^{13}C NMR spectra (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(34) Still, W. S.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.