

Further Evidences About the Role of Bis(thiazolin-2-ylidene)s as the Actual Catalytic Species in the Generalised Benzoin Condensation.

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Abstract. Applying our mechanistic hypothesis about the real catalytic species in the benzoin condensation catalysed by thiazolium salts plus bases, we have succeeded in the extension to aldehydes different from formaldehyde of a previously described method of synthesis of α -aminoketones combining Mannich reaction and benzoin condensation. Copyright © 1996 Published by Elsevier Science Ltd

In the last twenty years, a variety of reactions related with the benzoin condensation^{1,2} have been described: the addition of aldehydes to conjugate double bonds,³ the oxidative benzoin reaction,⁴ the formoin reaction⁵ and the synthesis of hydroxymethylketones⁶ from formaldehyde and other aldehydes.

For all these reactions, as in benzoin condensation, essentially identical mechanisms have been proposed:^{7,8} the catalyst (1) reverses the reactivity (*umpolung*) of an aldehyde's carbonyl group; this forms an active species (2), equivalent to an acyl anion, which attack an electrophile, also containing a carbonyl group. In 1988 we described⁹ a new process combining Mannich's reaction¹⁰ and benzoin condensation (figure 1), in which the electrophile is an aza-analogue of a carbonyl group: an iminium salt generated *in situ* by the reaction between a secondary amine and formaldehyde (R' = H in figure 1). The resulting product is an α -aminoketone.

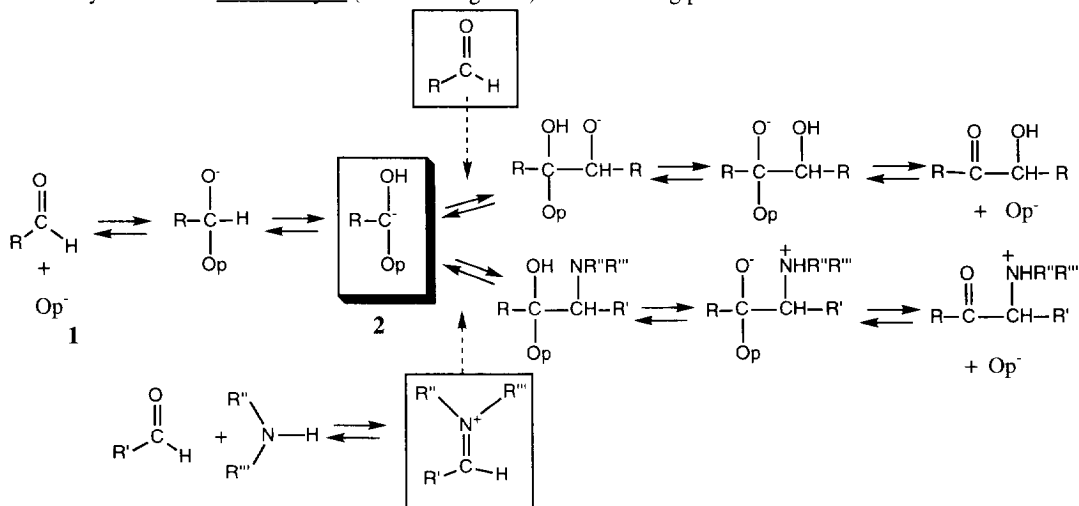


Figure 1. Generalised mechanisms of benzoin condensation and related synthesis of α -aminoketones.

However, the same reaction applied to aldehydes different from formaldehyde did not take place.

According to Breslow's mechanism⁷ (figure 2) for the generalised benzoin condensation catalysed by thiazolium salts in basic medium, the catalytic species (Op^- in figure 1) would be the conjugated base of the thiazolium cation or thiazolin-2-ylidene (1_B) and the active intermediate would be the enol-enamine 2_B .

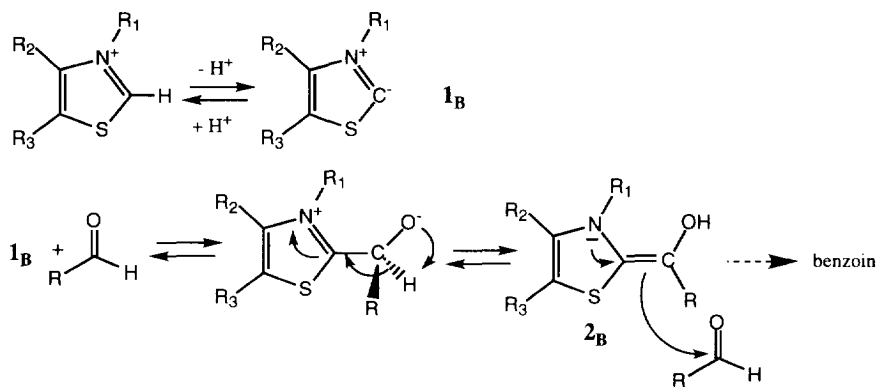


Figure 2. Breslow's mechanism of the benzoin condensation

Here it is important to remember^{11,12} that the thiazolin-2-ylidenes, species 1_B , are unavoidably coexistent with bis(thiazolin-2-ylidene)s, 1_N (figure 3) in protic, basic, conventional conditions, because they are formed *in situ* by nucleophilic attack of the nascent thiazolin-2-ylidenes on the surrounding thiazolium cations.

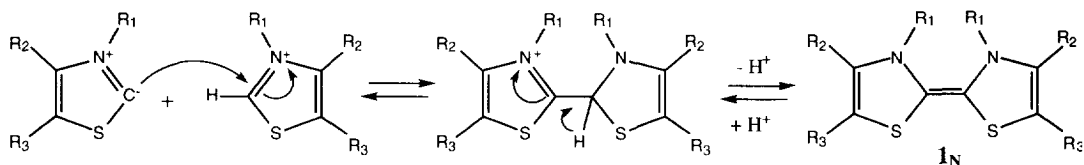


Figure 3. Formation of bis(thiazolin-2-ylidene)s from thiazolin-2-ylidenes and thiazolium cations.

As a logical consequence of several experimental and theoretical observations, we have proposed^{8,13} a new mechanistic hypothesis. Such observations are, briefly, the following ones:

a) the bis(thiazolin-2-ylidene)s 1_N catalyse⁸ the benzoin condensation better than the thiazolium salts in the presence of base;

b) the thiazolin-2-ylidenes 1_B prepared in an irreversible way by decarboxylation of thiazolium-2-carboxylates¹⁴ have little, or no, catalytic capacity;

c) when thiazolin-2-ylidenes 1_B are generated by desilylation in aprotic medium of 2-(trimethylsilyl)thiazolium cations¹⁵ with fluoride anion, conditions that preclude the formation of bis(thiazolin-2-ylidene)s, the benzoin condensation does not take place; however, on adding a little amount of thiazolium salt, making possible the formation of bis(thiazolin-2-ylidene)s 1_N , benzoin is produced in good yield;

d) polymethylene-bridged thiazolium and benzothiazolium salts were synthesised;^{16,17} when these are used as catalysts, the yield of benzoin depends strongly on the methylene bridge length, showing that the magnitude of the bridge must influence the formation, stability and/or evolution of the bis(thiazolin-2-ylidene)s;

e) a theoretical study^{17,18} of both Breslow's proposal and ours has led us to the conclusion that the intermediate 2_B is a final point in the reaction and that our hypothesis is thermodynamically and kinetically reasonable;

f) the last and probably the most important data: a kinetic study¹⁹ of benzoin condensation has shown that it is a second order process in both aldehyde and thiazolium cation.

Shortly, the key steps of our mechanistic proposal are the ones indicated in figure 4.

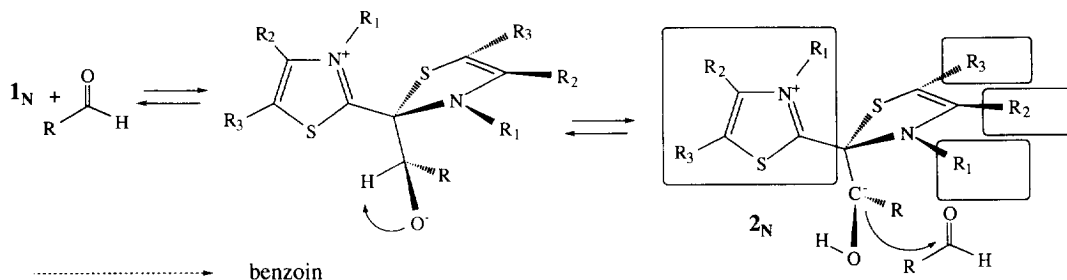


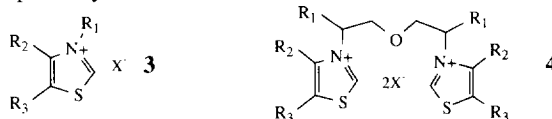
Figure 4. Key steps of the benzoin condensation in agreement with our mechanistic proposal.

The examination of intermediate 2_N evidences: **a)** the two thiazole ring are in almost perpendicular planes, and **b)** the groups R_1 , R_2 and R_3 have a strong influence²⁰ in the approximation of the two rings (specially R_1 , see figure 3) and in the approximation of the second unit of aldehyde to the intermediate (see figure 4).

The consequence of these geometric characteristics is that intermediates 2_N are bulky with the reactive centre (the carbon with carbanionic character) surrounded by several groups in different relative planes, affecting the approach of the electrophile in the next step of the process.

In the context of other complementary study we have prepared several thiazolium salts varying the groups linked to the heterocyclic system and we have used them as pre-catalyst in the benzoin condensation. The results have been very interesting and we report here a representative sample (table).

Table. Sterically enhanced thiazolium salts with and without methyl groups in 4 and 5 positions and yields in benzoin when used as precatalyst.



Salt	R_1	R_2	R_3	X^-	yield (%)
3a	(<i>R</i>)-2-butyl	CH ₃	CH ₃	I	0
3b	(<i>R</i>)-2-butyl	H	H	I	100
3c	(<i>S</i>)-1-phenylethyl	CH ₃	CH ₃	I	40
3d	(<i>S</i>)-1-phenylethyl	H	H	I	100
4a	(<i>R</i>)-benzyl	CH ₃	CH ₃	I	4
4b	(<i>R</i>)-benzyl	H	H	Br	100

From the previous yield values - taken as a diagnostic of the difficulty of the approach between species- it is easily deduced: **a/** the combined influences of a bulky group linked at nitrogen atom and methyl groups at 4 and 5 supposes a situation of maximum steric hindrance and the yield in benzoin is very low or none (salts **3a**, **3c**, and **4c**); **b/** the absence of methyl groups at 4 and 5 has as consequence the complete lack of steric hindrance in the approach between the intermediate 2_N and the second aldehyde unit and, having as a consequence quantitative yields (salts **3b**, **3d** and **4b**).

All these facts are easily justified by our mechanistic proposal and impossible by Breslow's one. We can explain the steric hindrance provoked by the methyl groups as a consequence of their geometric characteristics (see figure 4), but the intermediate 2_N is a completely flat structure that would not justify the different catalytic behaviour of thiazolium salts with or without methyl groups at 4 and 5 positions, because these cannot affect the approach of the aldehyde to the reputed reactive centre.

According to the above results, we thought that the failure in the syntheses of α -aminoketones when aldehydes other than formaldehyde are used, could also be of steric nature. Therefore, it was decided to test as catalyst 3-methylthiazolium cation in basic medium, the minimum size structure with catalytic activity not substituted at 4 and 5 (figure 5).

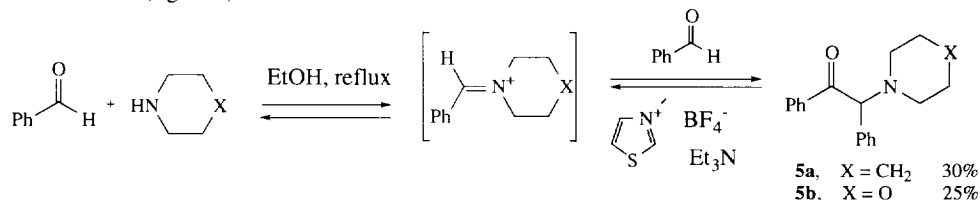


Figure 5. Synthesis of α -aminoketones derived of benzaldehyde using 3-methylthiazolium cation as precatalyst.

In the conditions previously reported⁹ 1,2-diphenyl-2-(1-piperidinyl)ethanone (**5a**) was obtained in 30 % yield, and 1,2-diphenyl-2-(4-morpholinyl)ethanone (**5b**)²¹ in 25 % yield. *From a synthetic point of view these are modest yields, but they really constitute a qualitative change in respect to the former situation - not reaction at all - and, on the other hand, they fulfil the prediction based on our mechanistic hypothesis, affording a new proof about the role of the bis(thiazolin-2-ylidene)s as the real catalytic species in the benzoin condensation and related reactions catalysed by C-2 thiazolium salts in basic medium, at least in conventional conditions.*

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