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Introduction to a Rational Design of Chiral Thiazolium Salts

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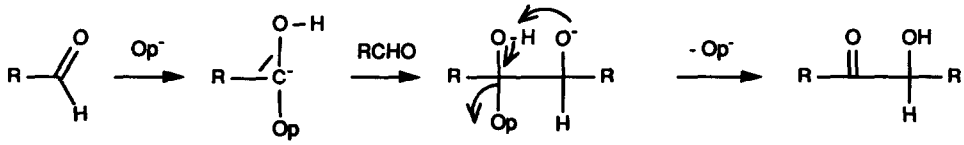
Abstract: A rational design of chiral thiazolium salts to be used in chiral benzoin condensations is possible from the proposal that bis(thiazolin-2-ylidene)s are the actual catalytic species in the benzoin condensation.

Although the importance of thiamine in the biosynthesis of carbohydrates (typical *chiral* metabolites) has been known for many years, the use of chiral thiazolium salts to induce chirality in the benzoin condensation is a problem scarcely studied[1,2,3].

The question is particularly difficult because the chiral center, in benzoin, is the second center formed; in fact, the chiral center generated in the initial reaction step then gives rise to the carbonyl group and, obviously, looses its chirality (Scheme). On the other hand, as we explained in a previous paper[4], in our



Scheme

opinion, the catalytic species or *umpolung* operators in these reactions are the bis(thiazolin-2-ylidene)s and these species are planar structures that can act through the two sides of the plane and from the two equivalent carbon atoms bonded by the central double bond.

Reasoning from the bis(thiazolin-2-ylidene) hypothesis it is clear that if the four different approaches of the aldehyde to the catalyst have the same chances then the reaction will yield racemic benzoin. The only way of inducing chirality is discriminating simultaneously between the two faces and the two carbons and that can be achieved by means of chiral N-substituents with restricted conformational freedom. These N-substituents could block selectively, for instance (Figure 1), the front approach to carbon 2 and the rear approach to carbon

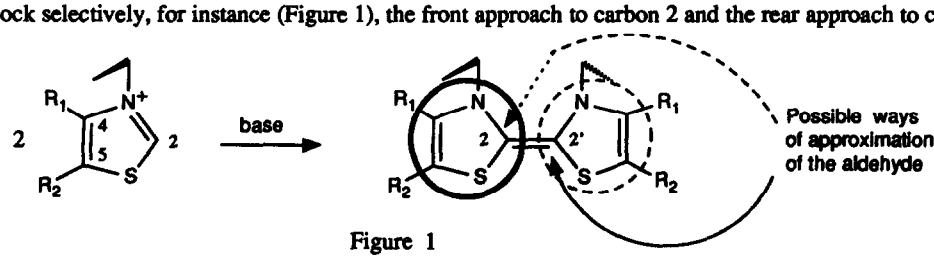


Figure 1

2' of the first aldehyde molecule to the catalytic species. Of course, the steric hindrance thus introduced should not prevent the alternative approaches, that is to say, the front approach to carbon 2' and the rear

approach to carbon 2. This reasoning is valid only for (*Z*)-bis(thiazolin-2-ylidene)s. In *E* isomers the two bulky groups will be in the same side of the planar system, and the asymmetric induction will not have place because the two active positions will be in the same face of the planar systems and both will be equally available; in other words, the discrimination between the positions 2 and 2' disappears. The simultaneous formation of *E* and *Z* bis(thiazolin-2-ylidene)s from thiazolium salt in basic medium is well known[5], but, unfortunately for asymmetric induction purposes, the *E* isomers are, in general, more stable because of the minor steric interactions due to the N-substituents. In other words, isomers *E* are more abundant with the consequent poor enantiomeric excess, only possible in significative amount from *Z* isomers.

In the Table, the chemical yields and enantiomeric excesses in benzoin condensations catalyzed by a variety of thiazolium salts (plus base) are collected. These salts were chosen to evaluate the influence of several structural aspects in the catalytic behaviour; all of them have been characterized by elemental analysis, spectroscopic data, specific rotation and, except **3** and **4**, they were obtained from the corresponding commercial chiral amines by formation of their thioformamides[6] and "construction" of the thiazolium ring by the classic Hantzsch method.

Table. Thiazolium salts, yields in benzoin and obtained enantiomeric excess.

	N-group	R_1	R_2	X^-	yield	e.e.%
1	(*R*)-2-butyl	CH_3	CH_3	I	0	---
2	(*R*)-2-butyl	H	H	I	100	0
3	Ethyl	CH_3	CH_3	Cl	47	---
4	2-hydroxyethyl	CH_3	CH_3	Cl	49	---
5	(*R*)-1-hydroxy-2-butyl	CH_3	CH_3	I	8	10
6	(*S*)-1-phenylethyl	CH_3	CH_3	I	40	7
7	(*S*)-1-phenylethyl	H	H	I	100	0
8	(*S*)-2-hydroxy-1-phenylethyl	CH_3	CH_3	I	5.5	12

N-group, R_1 and R_2 as indicated in Figure 1. Yields calculated in isolated benzoin. Reaction conducted under the following conditions: 1 mmol of benzaldehyde, 0,1 mmol of salt, 0,1 mmol of Et_3N, 5 mL of methanol, 24 h, 30°C. Enantiomeric excess calculated based on the specific rotation of *S*-(+)-benzoin : $_{Na}[\alpha]^{19}$= +115 ° (c=1.5, acetone).

A dramatic difference in behaviour of salts **1** and **2** is observed: the presence of methyl groups in positions 4 and 5 in the thiazole ring reduces the yield of benzoin from a 100% to 0%. Our explanation is that

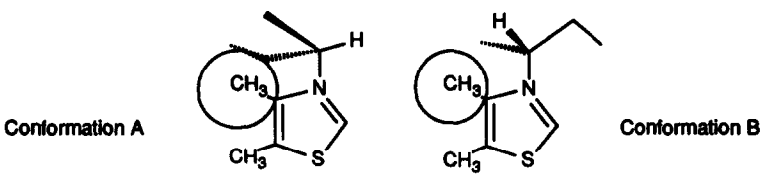


Figure 2

in the case of salt **1** the methyl in position 4 forces the system to exist in conformation B and in such conformation the ethyl groups do not permit the approximation of the two rings to form the bis(thiazolin-2-ylidene)s (Figure 2), which, according to our views[4] is the actual catalytic species. In salt **2**,

however, the absence of a methyl group in position 4 enables the existence of conformation A (or any other) and the catalytic species is formed. The reaction takes place quantitatively but without asymmetric induction because in the resulting (*Z*)-bis(thiazolin-2-ylidene) the two N-groups have a great conformational freedom and the necessary rigid situation to induce chirality is not achieved, and the *E*-isomers do not induce chirality in any case.

A related situation is found in the case of salts **6** and **7**; now differences are not as spectacular as in the case of salts **1** and **2** because the steric hindrance due to a phenyl group is not as strong as the one due to an ethyl group but, in any case, the yield grows from 40% to 100% when the C_4-methyl group is removed. Salt **6** is very similar to one of the salts described by Sheehan[1] and the asymmetric induction observed by us is the same. According to our views, this asymmetric induction is due to some degree of restricted rotation imposed by the blocking action of the C_4-methyl group. In the case of salt **7** (no C_4-methyl group present) no asymmetric induction is observed.

The practically identical catalytic behaviour of salts **3** and **4** proves that, in principle, the effect of a hydroxyl group in a given achiral structure is negligible. However, the presence of an hydroxyl group in salts **5** and **8**, introduces clear differences with regard to the salts **1** and **6**; the introduction of the OH in the N-group in both cases **5** and **8** has similar consequences: the reaction takes place, although with low and similar yields, but the enantiomeric excess is significative and, also, similar. The presence of the OH group in the two salts in the same relative position could explain the similar behaviour: in the two cases the hydroxyl group could form a hydrogen bond capable to form a *pseudo*(bisthiazolium) system with a seven-membered bridge and stabilize in some extension the (*Z*)-bis(thiazolin-2-ylidene) (Figure 3) in spite of the steric

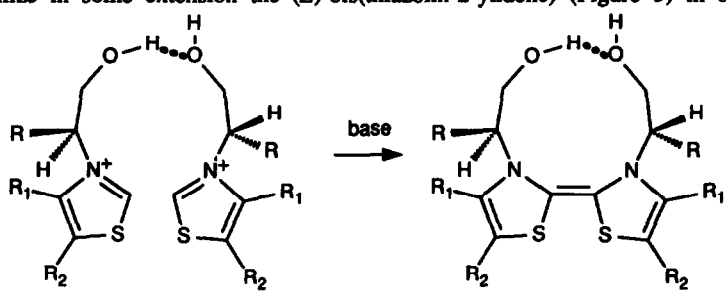
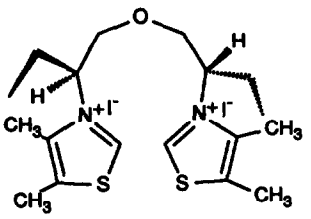


Figure 3

repulsion; this would be sufficient to explain the increment of the yield from 0 to 8 per cent in the case of salts **1** and **5**, respectively, and, due to the similar structure and stability of the catalytic species, the yield from **8** could be analogous. In a previous work[7] we have shown that in the N,N'-polymethylene-bridged bisthiazolium salts the heptamethylene-bridged system is the optimum in terms of yield in benzoin, and now we are in front of a similar case. In relation to the asymmetric induction, the hydrogen bond establish a relative rigidity in the system, coming close to the ideal one described in the Figure 1, with a relatively voluminous blocking group R in the opposite sides of each thiazole moieties. It has been possible confirm the validity of this reasoning by means of the preparation and use of the bisthiazolium salt **9**, derived from (3*R*,7*R*)-2,7-diamino-5-oxa-nonane (Figure 4), an undescribed chiral diamine that has now been synthesized from (*R*)-2-amino-1-butanol, the starting material for salt **5**. Working in the standard conditions (30°C) the yield in benzoin was 87%, and the enantiomeric excess 4%. This means that the bridge in salt **9** forces the formation of the cyclic (*Z*)-bis(thiazolin-2-ylidene), with the consequent much better yield in benzoin. However, stereochemical, no conformational, aspects of this active form are similar to the (*Z*)-bis(thiazolin-



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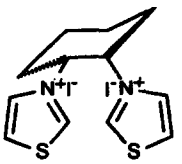

10

Figure 4

-2-ylidene) formed from salt **5** and the enantiomeric excess has the same order of magnitude. The dramatic improvement in the yield permitted us to work at lower temperature (5°C), with a yield of 17 % and enantiomeric excess of 9% after 20 h, and a yield of 54% and enantiomeric excess of 8% after 5 days of reaction.

The above examples show that the hypothesis of rigid chiral (*Z*)-bis(thiazolin-2-ylidene)s is an adequate starting point for a rational design of systems with a good chance of success in terms of asymmetric induction and by using that hypothesis we have prepared a bisthiazolium salt **10**, derived from (1*R*, 2*R*)-1,2-diaminocyclohexane (Figure 4). This salt catalyses the formation of benzoin with 11.5% chemical yield and 27% enantiomeric excess in *S*-(+)-benzoin at 30°C, and 20.6% yield and 26% e.e. at 5°C, values of e.e. of the same order of the best described for this kind of reaction. The poor yield is congruent with the results obtained from the cited N,N'-polymethylene-bridged bisthiazolium salts[7]: ethylene-bridged system is a minimum in terms of yield in benzoin; the yield is higher at 5°C because these bis(thiazolin-2-ylidene)s are very strained systems, more stable at low temperature. The poor enantiomeric excess indicates that the cyclohexane ring has still an insufficient volume to discriminate efficiently between the active positions of the catalytic species, and the conformational characteristics of this rigid structure is not affected by the temperature, and, consequently, the enantiomeric excess is the same. Unfortunately, chiral diamines with the suitable stereochemical characteristics are very scarce, adding a supplementary practical problem to the chemical ones, and preventing a fast screening of the different conceivable chiral bisthiazolium salts. Work in this way is in progress.

Conclusion

A rational design of chiral bisthiazolium salts to be used in chiral benzoin condensations is possible, and this fact reinforces the proposal of bis(thiazolin-2-ylidene)s as the actual catalytic species in the benzoin condensation.

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