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Synthesis of and Asymmetric Induction by Chiral Polycyclic Thiazolium Salts

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Abstract: Polycyclic thiazoles, **6a** and **b**, have been synthesised and the enantiomers resolved. Alkylation gave chiral thiazolium salts which catalyse the dimerisation of benzaldehyde to give benzoin with enantiomeric excesses up to 26%. Reasons for these results are discussed.
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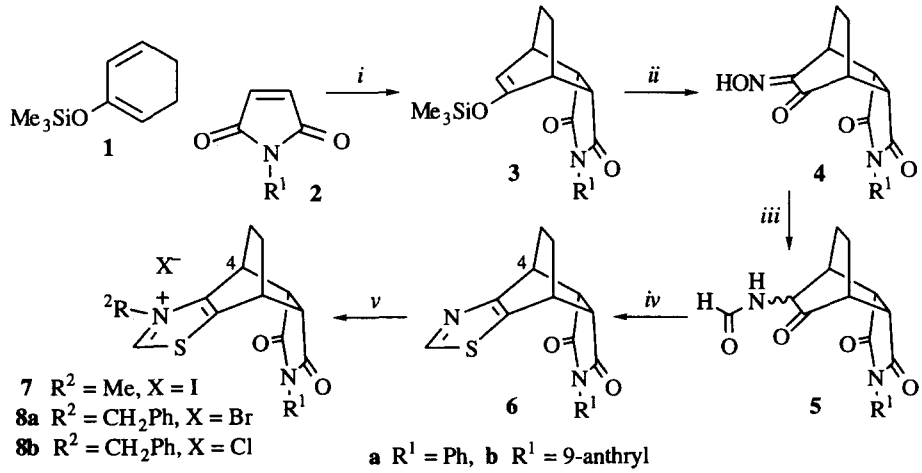
In the preceding paper[1] the synthesis and evaluation of chiral bicyclic thiazolium catalysts were described. The enantiomeric excesses (e.e.'s) achieved in the benzoin condensation using those catalysts were up to 21%. From the structure of the catalysts, it was not obvious whether the e.e. was low because the hindered face of the thiazolium ring was not completely blocked or whether this is the level of e.e. that results from reaction occurring on one face only. In order to answer this question, we set out to synthesise a different type of thiazolium salt in which one face of the thiazolium ring is more effectively blocked. The chosen thiazolium salts, **7** and **8**, were designed to have the chiral centres attached to C-4 and -5 rather than to N-3 so that unwanted hindrance at the site of reaction, C-2, could be minimised. The [2.2.2]bicyclooctane skeleton was chosen as a rigid framework which could be readily formed by a Diels Alder reaction.

The synthesis of the required thiazolium salts is shown in Scheme 1. Initially racemic thiazole **6a**, containing the *N*-phenyl imide, was made. Diels Alder reaction between *N*-phenylmaleimide **2a** and diene **1**[2] gave adduct **3** (84% yield), only the *endo* isomer being detected. The nitrogen atom, destined to be part of the thiazole ring, was introduced by nitrosation of the silyl enol ether **3a** using butyl nitrite and a Lewis acid[3]



Scheme 1. *Reagents: i*, heat; *ii*, BuONO, $TiCl_4$; *iii*, Zn, HCO_2H, $HgCl_2$ (cat.); *iv*, Davy's reagent; *v*, MeI, $PhCH_2Br$ or $PhCH_2OTf$

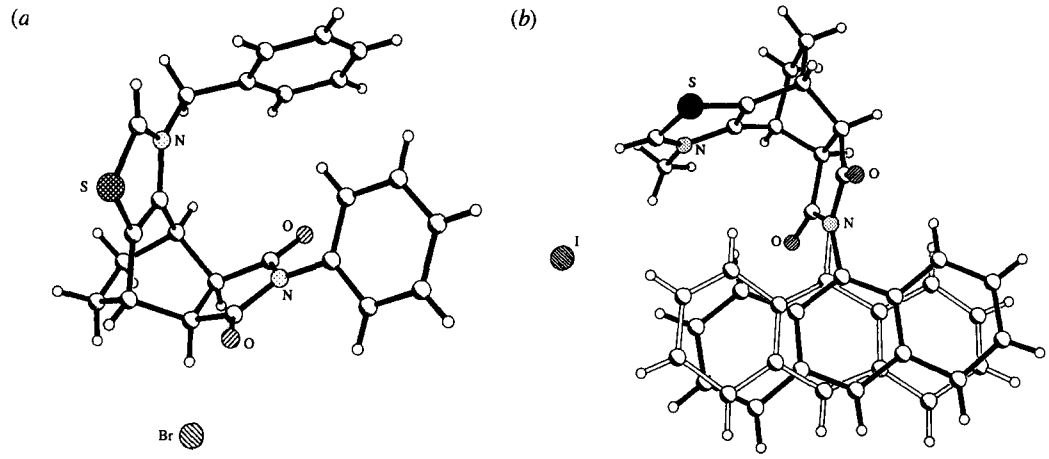


Fig. 1. X-ray crystal structures of (*a*) (4*R*)-(+)-thiazolium salt **8a** and (*b*) (4*S*)-(+)-thiazolium salt **7b**.[5]

(87% yield). Reduction of the resulting oxime **4a** with zinc in formic acid[4] led directly to the formamido ketone **5a** in 78% yield as a mixture of diastereoisomers. Formation of the thiazole **6a** from **5a** was best effected by thionation using Davy's reagent (61% yield, 35% overall from cyclohexenone).

At this stage the thiazole **6a** was resolved by formation of its (–)-camphor-10-sulfonate salt and three recrystallisations from absolute ethanol. Liberation of the free thiazole from its salt gave (–)-thiazole **6a** in 96% e.e., as shown by ^{1}H NMR spectroscopy using a chiral shift reagent. From the mother liquors a similar procedure using (+)-camphor-10-sulfonic acid gave (+)-thiazole **6a** in 98% e.e.. Reaction of the (–)-thiazole with methyl iodide gave the (+)-thiazolium iodide **7a** and with benzyl bromide gave the (+)-thiazolium bromide **8a**. An X-ray crystal structure of (+)-**8a** was obtained (Fig. 1a), which established its absolute configuration [and that of (+)-**7a**] as *R* at C-4,[5] (opposite to the configuration shown in Scheme 1).

The thiazolium salts (4*R*)-(+)-**7a** and (4*R*)-(+)-**8a** were tested as catalysts for the benzoin condensation and the results are given in Table 1. The most notable result is the 26% e.e. and quantitative yield obtained with catalyst **8a**. This was achieved using the catalyst and triethylamine in neat benzaldehyde (method B). The other procedure, employing methanol as the solvent, gave lower yields and, for catalyst **8a**, a lower e.e. also. Catalyst **8a** was also tested in neat benzaldehyde at a lower temperature (0 °C instead of 20 °C) but this had no effect on the e.e. and lowered the yield slightly to 92%. Also the reaction was performed in a two-phase

Table 1. Yields and Enantiomeric Excesses of the Benzoin Produced by each of the Thiazolium Salts

Thiazolium salt	**Method A**[a]			**Method B**[b]		
	Yield	**Configuration**	**e.e.**	**Yield**	**Configuration**	**e.e.**
(4*R*)-**7a**	50%	*R*	5%	88%	*S*	1%
(4*R*)-**8a**	70%	*S*	8%	100%	*S*	26%
(4*S*)-**7b**	47%[c]	*S*	6%	46%[c]	*S*	7%
(4*S*)-**8b**	31%[c]	*S*	13%	91%	*S*	16%

[a] PhCHO (492 μmol), Et_3N (27 μmol, 5.5%) and catalyst (24.5 μmol, 5%) in dry deoxygenated MeOH (1 ml) for 16-22 h at 20 °C.

[b] As for *a* but without any solvent at 20 °C for 1–16h. [c] Using 2.75% Et_3N and 2.5% catalyst.

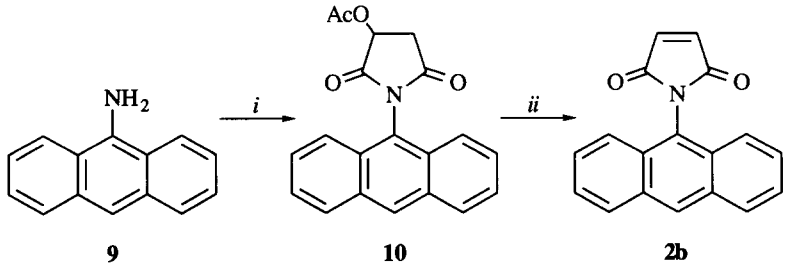
mixture of benzaldehyde and 0.5M aqueous Na_2HPO_4 at 20 °C; the results were very much the same (e.e. 26%, yield 96%), although the reaction was significantly faster, being complete in one hour compared with the 16 hours allowed for the other methods.

The crystal structure of thiazolium salt **8a**, along with molecular modelling, suggested that, during the course of the benzoin condensation, the second benzaldehyde molecule might still approach from either side of the plane of the thiazolium ring (see Scheme 1 of the foregoing paper for the mechanism of the reaction). The benzene ring attached to the imide does not extend far enough across the face of the thiazolium ring to block effectively the lower face of C-2α of the enamine intermediate. Accordingly, we next set out to make the corresponding thiazole **6b** with an anthracene ring blocking the lower face.

A synthesis of the required *N*-(9-anthryl)maleimide **2b** has been reported, involving reaction of 9-aminoanthracene **9** with maleic anhydride.[6] In our hands, however, this reaction gave an excellent yield (97%) of the Diels-Alder adduct and none of the imide **2b**. To avoid the possibility of the unwanted Diels-Alder reaction, the amine **9** was reacted with acetoxysuccinic anhydride[7] to give, after closure of the imide ring using acetyl chloride, the succinimide **10**. Elimination of acetic acid was then effected using triethylamine, giving the maleimide **2b** in 78% overall yield from the amine **9**. This imide proved to be quite stable and there was no evidence of dimerisation by a Diels-Alder reaction. This is understandable as models show that the imide and anthracene ring systems are perpendicular to each other and C-9 of the anthracene is hindered on both sides by the carbonyl groups of the imide.

With the *N*-(9-anthryl)maleimide **2b** in hand, the synthesis of the thiazole **6b** proceeded as in Scheme 1. The Diels-Alder reaction of **2b** with silyl enol ether **1** required a slightly higher temperature (80 °C instead of 60 °C) but still gave a satisfactory yield of 87%. Nitrosation gave the oxime **4b** in 74% yield and finally the reduction/formylation and the thionation/cyclisation steps were performed without purification of the intermediate formamide **5b** to give the thiazole **6b** in only 14% yield. The lower yield in this reaction compared with the corresponding *N*-phenyl series (**4a** → **6a**) is presumably due to steric hindrance from the anthracene system; this at least shows that this group is having the desired effect. The close proximity of part of the anthracene to the thiazole ring could be observed in its ^1H NMR spectrum, in which the proton attached to C-1' appeared at δ 5.81, nearly 2 ppm upfield from its usual chemical shift, due to its location beneath the face of the aromatic thiazole ring.

As previously, the thiazole **6b** was resolved by recrystallisation of its salt with camphor-10-sulfonic acid. Three recrystallisations of the (–)-camphor-10-sulfonate salt from acetonitrile, followed by liberation of the free base, gave the (–)-thiazole **6b** with no detectable amount of its enantiomer (by NMR analysis with a chiral shift reagent). Similar recrystallisation of the (+)-camphor-10-sulfonate salt gave the enantiomerically pure (+)-thiazole **6b**. Alkylation of the thiazole to give thiazolium salts **7b** and **8b** proved to be a problem.



9 **10** **2b**

Scheme 2. *Reagents: i*, acetoxysuccinic anhydride then AcCl; *ii*, Et_3N

Methylation of (+)-**6b** with methyl iodide required heating at 120 °C in a sealed tube for 24 hours, giving (+)-**7b** in 79% yield. An X-ray crystal structure of (+)-**7b** was obtained (Fig. 1b), which established its absolute configuration [and that of (+)-**6b**] as *S* at C-4,[5] the same as shown in Scheme 1. No reaction was observed between benzyl bromide and thiazole **6b**, however, even after heating at 120 °C for 48 hours. Eventually the *N*-benzylthiazolium salt was obtained by reacting (4*S*)-(+)-**6b** with the highly reactive benzyl triflate, formed *in situ* from benzyl alcohol with triflic anhydride and diisopropylaminomethylpolystyrene at –78 °C; the triflate ion was then exchanged for chloride to give the crystalline salt (4*S*)-(–)-**8b**. The difficulty in effecting the alkylation of thiazole **6b** is again evidence of the hindrance caused by the anthracene ring system.

These enantiomerically pure thiazolium salts were then tested as catalysts for the benzoin condensation (see Table 1). Disappointingly, the benzoin produced had even smaller enantiomeric excesses than for the *N*-phenyl catalysts, **7a** and **8a**. However, both (4*S*)-**7b** and (4*S*)-**8b** produce an excess of (*S*)-benzoin and this is in accord with the putative preferred transition state given in the preceding paper.[1] The fact that the same stereochemical trend is observed with the very different thiazolium salts described in the two papers is encouraging. Catalyst (4*R*)-**7a** gave very little asymmetric induction, maybe because the second benzaldehyde molecule can approach from either face. On the other hand, catalyst (4*R*)-**8a** in neat benzaldehyde gave the largest e.e. for benzoin, with a configuration opposite to that expected. One possible reason for this is that the two phenyl rings of **8a** together may form a binding pocket for the second benzaldehyde molecule (see Fig. 1a) which favours its approach from that face rather than the opposite one as intended.

It is now apparent, from the results described in these two papers, that the strategy of blocking one face of a thiazolium ring is not, by itself, sufficient to give high levels of asymmetric induction. Some other means of controlling the orientation of the second aldehyde molecule when it approaches the enamine intermediate is required. This makes the relatively high level of asymmetric induction recently reported[8] for the benzoin condensation catalysed by a chiral triazolium ion[9] all the more surprising, as the explanation offered was simply that one face of the triazolium ring would be more hindered than the other.

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