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Synthesis of and Asymmetric Induction by Chiral Bicyclic Thiazolium Salts

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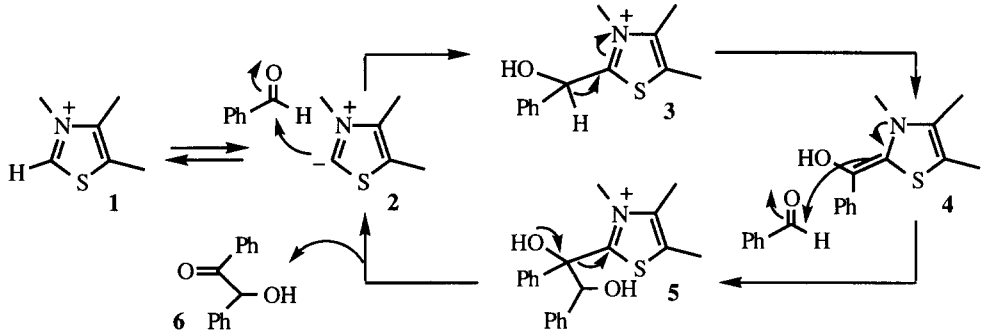
Abstract: Three different chiral bicyclic thiazolium salts, **10**, **16** and **19**, have been synthesised in enantiomerically pure form. These salts all catalysed the formation of benzoin and butyroin from benzaldehyde and butyraldehyde respectively and the product had the *R*-configuration in each case with e.e.'s in the range 10–33%. Possible reasons for these results are discussed. © 1997 Elsevier Science Ltd.

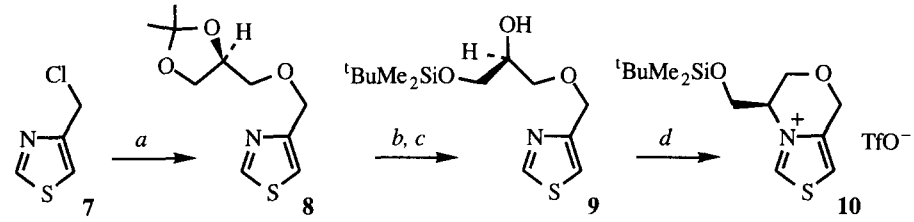
It has been known for a long time that thiazolium salts (*e.g.* **1**) with mild base catalyse the formation of acyloins (*e.g.* **6**) from aldehydes.[1] The generally accepted mechanism, first proposed by Breslow,[1] is shown in Scheme 1. Essentially the same mechanism is believed to operate in thiamin-dependent enzymes such as transketolase, acetolactate synthase and pyruvate decarboxylase.



Scheme 1. The mechanism of the thiazolium salt-catalysed benzoin condensation

Dimerisation of benzaldehyde to give benzoin **6** can also be catalysed by cyanide ions but thiazolium salts have two advantages over cyanide ions: firstly, the reaction proceeds under less basic conditions and so can be used with enolisable aldehydes;[2] secondly, unlike cyanide ions, thiazolium salts offer sites for modification of the catalyst which might be used to introduce various kinds of selectivity into the catalytic process. This paper concerns the introduction of chirality in order to achieve asymmetric induction.

There have been a few previous reports of the synthesis of chiral thiazolium catalysts.[3–6] These have all been simple thiazolium salts with chiral groups attached to the nitrogen atom. In general catalysts which showed even moderate e.e.'s gave very low chemical yields of benzoin. We reasoned that this was because the chiral substituent on N-3, being free to rotate, was hindering the approach of the first benzaldehyde molecule to C-2 of the ylid **2** and then subsequently the approach of the second benzaldehyde molecule to C-2α of the enamine **4**. In order to minimise this steric hindrance, we chose to make thiazolium salts in which free rotation of the chiral centre attached to N-3 is prevented by ring closure onto the C-4 substituent. Our target compounds, **10**, **16** and **19** (Schemes 2 and 3) all have a bulky group (Ph or $CH_2OSiMe_2{}^tBu$) hindering the top face of the thiazolium ring but nothing hindering the bottom face.



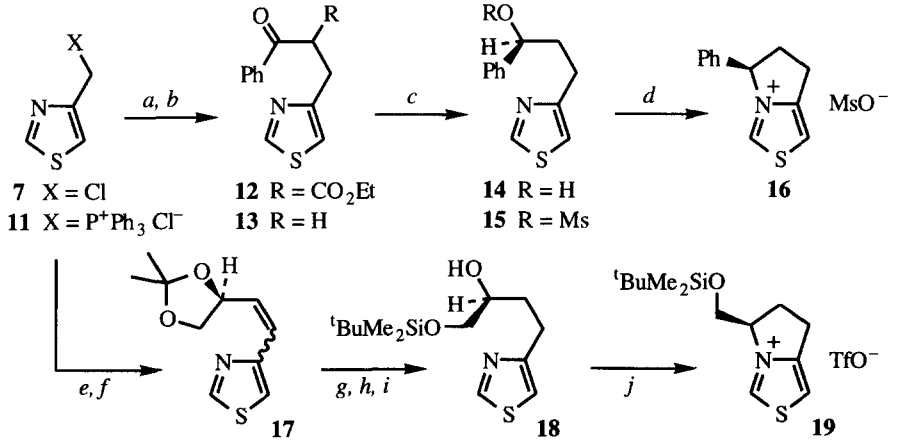
Scheme 2. *Reagents: a*, (*S*)-*O,O*-isopropylideneglycerol, Bu^{t}OK, THF, 65%; *b*, HCl, MeOH, H_2O, 70%; *c*, Bu^{t}Me$_2$SiCl, Et_3N, DMAP, CH_2Cl_2, 86%; *d*, Tf_2O, pyr, CH_2Cl_2, 60%.

RESULTS

The synthesis of the first target, dihydro-oxazinothiazolium salt **10**, is shown in Scheme 2. The oxygen atom in the six membered ring is only present to simplify the synthesis, allowing the ether **8** to be made by coupling the known[7] 4-chloromethylthiazole **7** with (*S*)-*O,O*-isopropylideneglycerol. Hydrolysis of the cyclic acetal and silylation of the primary alcohol gave **9**. The free secondary hydroxyl group was converted into its triflate ester and cyclisation to give the thiazolium salt **10** occurred *in situ*.

The syntheses of the dihydropyrrolothiazolium salts, **16** and **19**, also started with 4-chloromethylthiazole **7**. Reaction with ethyl benzoylacetate followed by de-ethoxycarbonylation of the β-keto ester **12** gave ketone **13**. When this ketone was reduced with (–)-*B*-chlorodiisopinocamphenylborane,[8] a pure borane complex crystallised from the reaction mixture and on decomposition of this complex with diethanolamine, the enantiomerically pure (*S*)-alcohol **14** (by chiral shift reagent and Mosher's ester[9] analysis) was obtained. Mesylation of the alcohol followed by cyclisation of the mesylate **15** *in situ* gave thiazolium salt **16**.

For the synthesis of thiazolium salt **19**, chloride **7** was converted to the phosphonium salt **11** and a Wittig reaction with (*R*)-*O,O*-isopropylideneglyceraldehyde[10] gave alkene **17**, as a 3:2 mixture of *cis* and *trans* isomers. Reduction with diimide,[11] hydrolysis of the cyclic acetal and protection of the primary alcohol gave the silyl ether **18**. Conversion of **18** to its Mosher's ester[9] showed a slight loss of enantiomeric purity had occurred (e.e. 85%) probably by enolisation of the aldehyde during the Wittig reaction (**11** → **17**). Activation



Scheme 3. *Reagents: a*, $PhCOCH_2CO_2Et$, NaOEt, EtOH, 74%; *b*, NaOH, EtOH, H_2O, 86%; *c*, (–)-(Ipc)$_2$BCl, THF, 74%; *d*, Ms_2O, $(C_8H_{17})_3N$, CH_2Cl_2, 60%; *e*, PPh_3, LiI, PhMe, 84%; *f*, (*R*)-*O,O*-isopropylideneglyceraldehyde, Bu^{t}OK, PhMe, 58%; *g*, $TsNHNH_2$, NaOAc, DME, 73%;

h, HCl, MeOH, H_2O, 91%; *i*, Bu^tMe_2SiCl, Et_3N, DMAP, CH_2Cl_2, 92%; *j*, Tf_2O, pyr, CH_2Cl_2, 60%.

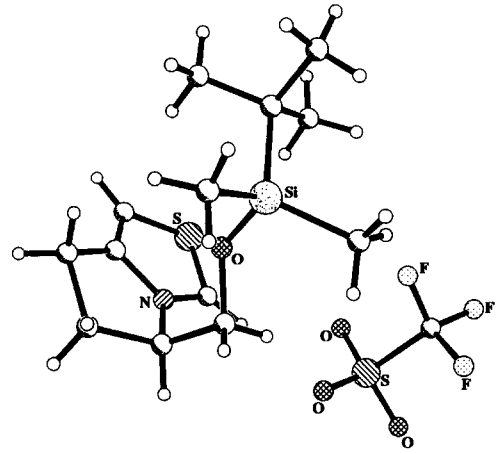


Fig. 1. X-ray crystal structure[12] of thiazolium salt **19**

of the secondary alcohol as its triflate and cyclisation *in situ*, as before, gave the final thiazolium salt **19**, which gave crystals of sufficient quality for an X-ray structure determination,[12] shown in Fig. 1.

In order to check their enantiomeric purity, thiazolium salts **10** and **16** were converted into their (–)-camphor-10-sulfonate salts. The ^1H NMR spectra of these salts in $CDCl_3$ showed only a single peak for 2-H, whereas the same thiazolium salts in racemic form showed two distinct peaks. Thus we can be confident that the cyclisation reaction proceeds by an S_N2 (rather than S_N1) mechanism, with inversion of configuration.

Each of the thiazolium salts were tested as catalysts for the formation of benzoin from benzaldehyde and butyroin from butyraldehyde (see Table 1). Each catalyst was tested under a standard set of conditions and so the yields have not been optimised. For benzoin e.e.'s were measured by optical rotation,[13] checked in one case by HPLC on a chiral column; for butyroin the e.e.'s were measured by ^1H and ^{19}F NMR analysis of its Mosher's ester.[9] In every case the *R* enantiomer of the product predominated. We believe this is the first report of catalytic asymmetric induction in the formation of an aliphatic acyloin.

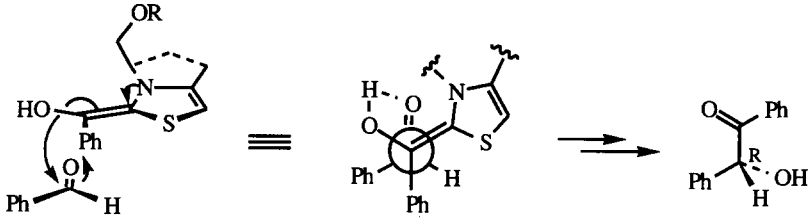
We propose the following explanation for the predominance of the *R* configuration. The double bond of the enamine intermediate **4** will presumably have the *E* configuration in order to avoid steric interactions between the phenyl ring and the N-3 substituent. The second benzaldehyde molecule should then approach from below, again for steric reasons. It is the face of this second benzaldehyde molecule which is attacked which determines the stereochemistry of the benzoin product. The molecules will adopt a staggered

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

Thiazolium salt	Benzoin			Butyroin		
	Yield	Configuration	e.e.	Yield	Configuration	e.e.
10	34%[a]	R	19.5%	75%[c]	R	33%
16	20%[a] (52%[b])	R	10.5% (7%)	86%[c]	R	18%
19	50%[b]	R	20.5%	77%[c]	R	14%

[a] PhCHO (10 equiv.), Et_3N (1.1 equiv.), catalyst (1 equiv.) in dry deoxygenated MeOH, 18 h at 20 °C. [b] As for (a) except

using PhCHO (5 equiv.). [c] PrCHO (5 equiv.), Et_3N (2 equiv.), catalyst (1 equiv.) in dry deoxygenated EtOH, 3 h at 80 °C.



Scheme 4. Proposed transition state for formation of the chiral centre in benzoin

conformation about the C–C bond being formed and we suggest the aldehyde oxygen will prefer to be between the –OH group and the nitrogen atom of the enamine, as shown in Scheme 4, because in that position it can hydrogen bond to the –OH and the positive and negative charges generated during the step (on the nitrogen and oxygen atoms respectively) are close in space. The hydrogen atom of the aldehyde is likely to adopt the position between the two bulky groups attached to C-2α (the phenyl and thiazole rings) thus determining the *R* configuration of the chiral centre being formed.

The above explanation accounts for the production of (*R*)-benzoin [and (*R*)-butyroin] by all three catalysts but it is clear from the moderate enantiomeric excesses that the degree of stereocontrol is not high. This could be because the top face of the catalyst is not sufficiently well hindered to ensure that the second benzaldehyde molecule approaches only from the opposite face. However, on the basis of results with further catalysts discussed in the following paper, we think it is more likely the approach is very largely from the lower face but that this is not sufficient to control the stereochemistry of the product to any great extent.

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