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Kinetic Resolution of Secondary Alcohols Using Proline-Derived Bicyclic Iminium Salts

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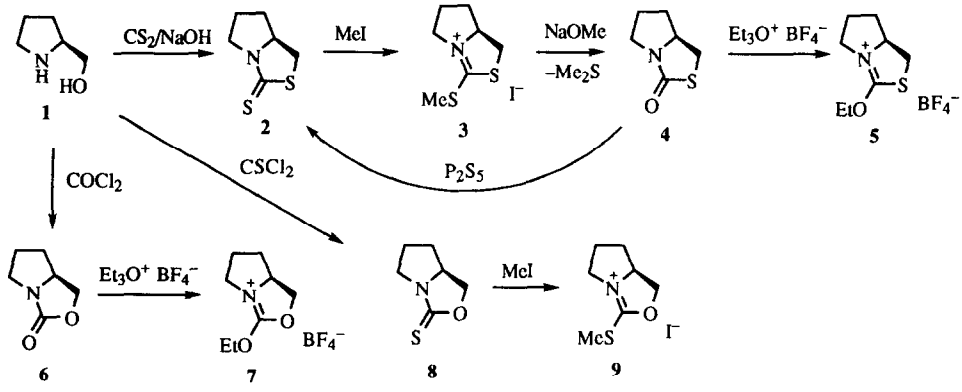
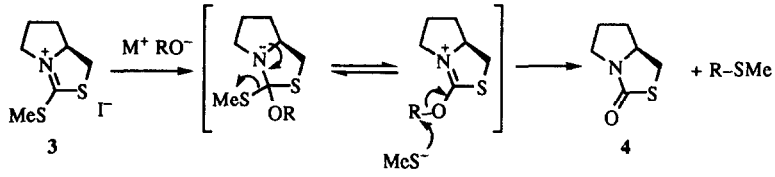
Abstract: The proline-derived bicyclic iminium salt **3** can be used to bring about kinetic resolution in its reaction with salts of secondary alcohols to give the corresponding methyl sulfides. Reaction proceeds most efficiently with sodium 1-phenylethoxide in toluene at RT where either **3** or the benzyl salt **14** give e.e.s of 21–25% and changing the heteroatoms present in the salts, the metal cation used and the solvent and temperature all give similar or lower selectivity. © 1997 Elsevier Science Ltd.

There has been considerable recent interest in the development of simple chiral reagents which will bring about kinetic resolution,[1] and resolution of secondary alcohols by means of acylation has been achieved using *N*-acyloxazolidinones[2] and *N*-acythiazolidinethiones.[3] In the context of a separate study,[4] we wished to convert the proline-derived thiazolidinethione **2** into the corresponding thiazolidinone **4** and were able to achieve this in good yield by a two-step method based on that reported by Roussel and coworkers[5] for conversion of achiral *N*-arylthiazoline-2-thiones to the corresponding thiazolinones. The method involves reaction with methyl iodide in acetone to afford the bicyclic iminium salt **3** followed by treatment of this with sodium methoxide. The sodium methoxide is converted to dimethyl sulfide and consideration of the mechanism of this unusual transformation led to the realisation that it could form the basis for a method of kinetic resolution of racemic secondary alkoxides. As shown in Scheme 1, the reaction proceeds by nucleophilic attack of alkoxide at the iminium carbon to give the



dithioorthocarbamate structure which is in equilibrium with the iminium methanethiolate. Attack of the anion at the alkoxy group then proceeds with inversion of configuration to give the methyl sulfide and **4**. If this reaction were carried out using 2 equiv. of a racemic secondary alkoxide, it seems likely that the chiral salt **3** would show some preference between the two alkoxide enantiomers and so bring about kinetic resolution, with the reacting enantiomer being converted into the methyl sulfide of the same absolute stereochemistry as the unreacted alkoxide due to the inversion involved in the mechanism. We describe here the systematic study of **3** and a variety of related iminium salts as reagents for kinetic resolution of secondary alcohols.



Scheme 1

The first group of salts were derived from (*S*)-prolinol **1** as shown above. The known[6] thiazolidinethione **2** was prepared in moderate yield by reaction of prolinol with CS_2 in aqueous NaOH and then converted into the salt **3** in high yield with MeI.[7] To examine the effect of the heteroatoms present, the oxazolidinone **6**[8] and the previously unknown thiazolidinone **4** and oxazolidinethione **8** were also prepared as shown and converted into their iminium salts, **7**, **5** and **9** respectively, either with MeI or Et_3O^+ BF_4^-.

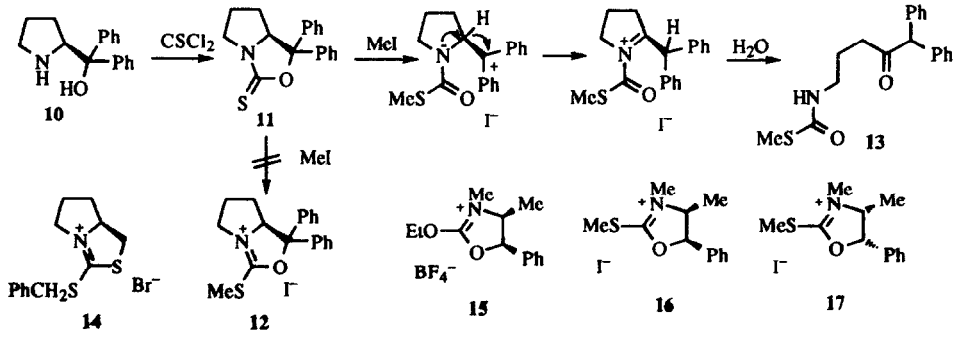
For evaluation of the salts as kinetic resolution agents, a solution of the sodium alkoxide was prepared by boiling the alcohol in toluene with excess sodium metal and then removing the excess of metal and adding 0.5 equiv. of the iminium salt. 1-Phenylethanol was chosen as the standard alcohol and after reaction for 16 h at RT, aqueous work-up followed by extraction and distillation did afford both the unreacted alcohol and methyl 1-phenylethyl sulfide in non-racemic form. By instead working up the reaction by adding hexane and filtering off the precipitated alkoxide and decomposing it with water, the alcohol was obtained free from sulfide and its optical rotation value showed it to be enriched to an extent of ca. 20% e.e in favour of the (*S*)-(–)-enantiomer. Examination of the ^1H NMR spectrum of this sample (CHMe signal) in the presence of $Eu(hfc)_3$ showed baseline separation and a dominance of the lower frequency signal corresponding to an e.e. of 21%. The latter method was then used routinely since it allowed e.e determination in the presence of sulfide. Although no satisfactory method was found to determine the e.e. of the sulfide, it can be assumed from the mechanism that it is formed as the (*S*)-enantiomer in equal e.e to the alcohol in each case.

As shown in the Table, use of other alcohols gave poorer results (entries 2–4) and, while this might be expected in the first two cases, the very poor selectivity for the bulky *tert*-butyl containing alcohol is surprising. The effect of the metal was then examined (entries 5–8) with the lithium and potassium salts being prepared directly and the remaining two by exchange of the sodium salt with the corresponding chloride. Again the other metal counterions all led to poorer selectivity and we may conclude that with sodium the balance between the coordinating nature of the metal and thus the alkoxide reactivity, and steric factors is optimal. Rather surprisingly the bromomagnesium alkoxide, formed either from the alcohol and EtMgBr or from the sodium salt and $MgBr_2 \cdot Et_2O$, failed to react with **3**. Reaction at low temperature and/or using a more polar solvent gave no significant change in selectivity (entries 10–12). The effect of changing the heteroatoms present was now examined by using salts **5**, **7** and **9**. In the first case there was a marginal improvement in the e.e of the alcohol

Table: Kinetic resolution of secondary alcohols using cyclic iminium salts

	Alkoxide	Salt	solvent	temperature	yield of alcohol (%)	e.e. of alcohol (%)
1	$PhCH(Me)O^- Na^+$	**3**	PhMe	RT	50	21 (*S*)
2	$PhCH(Et)O^- Na^+$	**3**	PhMe	RT	27	12
3	$PhCH_2CH(Me)O^- Na^+$	**3**	PhMe	RT	60	6
4	$Bu^tCH(Me)O^- Na^+$	**3**	PhMe	RT	55	0.5
5	$PhCH(Me)O^- Li^+$	**3**	PhMe	RT	82	2 (*S*)
6	$PhCH(Me)O^- K^+$	**3**	PhMe	RT	44	6 (*S*)
7	$PhCH(Me)O^- Cs^+$	**3**	PhMe	RT	50	7 (*S*)
8	$PhCH(Me)O^- Me_4N^+$	**3**	PhMe	RT	56	2 (*R*)
9	PhCH(Me)OMgBr	**3**	PhMe	RT or 110 °C	0	—
10	$PhCH(Me)O^- Na^+$	**3**	PhMe	–78 °C	54	15 (*S*)
11	$PhCH(Me)O^- Na^+$	**3**	CH_2Cl_2	RT	24	18 (*S*)
12	$PhCH(Me)O^- Na^+$	**3**	CH_2Cl_2	–78 °C	52	20 (*S*)
13	$PhCH(Me)O^- Na^+$	**5**	PhMe	RT	50	25 (*S*)
14	$PhCH(Me)O^- Na^+$	**7**	PhMe	RT	60	0
15	$PhCH(Me)O^- Na^+$	**9**	PhMe	RT	36	0
16	$PhCH(Me)O^- Na^+$	**14**	PhMe	RT	88	25 (*S*)
17	$PhCH(Me)O^- Na^+$	**15**	PhMe	RT	54	5 (*S*)
18	$PhCH(Me)O^- Na^+$	**16**	PhMe	RT	50	7 (*R*)
19	$PhCH(Me)O^- Na^+$	**17**	PhMe	RT	24	3 (*S*)

but the ethyl ether was not formed and the monothioorthocarbamate intermediate appears to be stable, in agreement with the early work of Meerwein.[9] This was also the case for the oxazolidionone-derived salt **7**, where a stable orthocarbamate was obtained together with, in this instance, racemic alcohol. The oxazolidinethione-derived salt **9** did afford alcohol and sulfide but in racemic form. An attempt was made to improve the selectivity by increasing the steric bulk of the salts. The α,α-diphenylprolinol **10** which has proved highly effective in directing borane-mediated reduction of ketones,[10] failed to give a thiazolidinethione in



acceptable yield but the oxazolidinethione **11** could be obtained by reaction with thiophosgene. When this was reacted with MeI however, the process took an unexpected course to give not the salt **12** but the acyclic ketone/thiocarbamate **13**. The mechanism for this probably involves a 1,2-hydride shift as shown followed by hydrolysis. Increasing the steric bulk in another way, by reacting **2** with benzyl bromide to give **14**, led to only a marginal improvement in selectivity.

Finally, the monocyclic iminium salts **15–17** were prepared from the corresponding ephedrine-derived oxazolidinone[11] and oxazolidinethiones[12] and these did give non-racemic alcohol in each case, together with the methyl sulfide from **16** and **17** but unfortunately with low e.e. (entries 17–19).

In summary, we have shown that the iminium salt **3** provides the basis for kinetic resolution of secondary alkoxides with the reacting enantiomer being converted into the methyl sulfide, and the resulting thiazolidinone **4** can be recycled by treatment with P_2S_5 and then MeI. However, attempts to improve the selectivity above the 20–25% e.e level by altering a variety of reaction parameters and making some structural changes have so far failed. This suggests that more radical alterations to the structure of the iminium salts may be required and this is currently being examined.

Acknowledgements

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