Pergamon

Tetrahedron Letters 39 (1998) 2925–2928

TETRAHEDRON LETTERS

CATALYSIS OF BENZOIN CONDENSATION BY CONFORMATIONALLY-RESTRICTED CHIRAL BICYCLIC THIAZOLIUM SALTS

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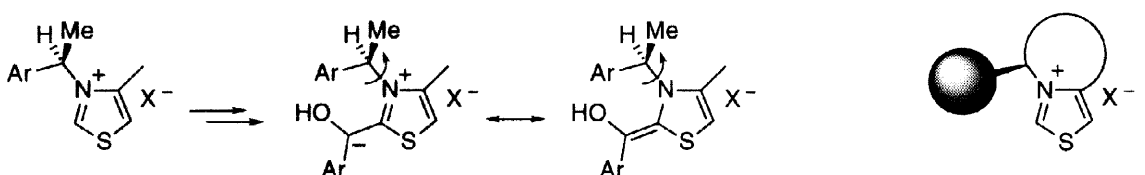
Received 11 August 1997; revised 9 February 1998; accepted 10 February 1998

Abstract: Two new conformationally-restricted chiral bicyclic thiazolium salts have been synthesized by a concise, high-yielding route. These salts are effective catalysts for the benzoin condensation, affording benzoin in 20-30% yield, with a similar range of enantiomeric excesses.

First reported by Ukai et al.,[2] the thiazolium salt catalyzed benzoin condensation has been the subject of considerable investigation.[3] A mechanism for this reaction, which has withstood the test of time, was first proposed in a landmark paper by Breslow.[4] Aside from serving as a good model for the mode of action of the coenzyme thiamine pyrophosphate,[5] thiazolium salts are of interest because they promote the formation of a carbon-carbon bond, with the attendant chiral center, under mild conditions. Several research groups have synthesized thiazolium salts bearing a chiral unit on the nitrogen in an effort to induce asymmetry during the C-C bond-forming step.[6] Among the first and best are the α-aryl-*N*-ethyl thiazolium salts (**1**) reported by Sheehan and Hara,[6e] which yielded benzoin with low to modest ee's. We reasoned that the low ee's obtained by these and other groups resulted from the free rotation available to the chiral side-chain, which provided inadequate discrimination between the two prochiral faces of the presumed nucleophilic intermediate (**2**). We postulated that restricting the rotation of the chiral side-chain, by locking it in a ring (e.g., **3**), would more effectively block just one face of the thiazole and, hence, improve enantioselectivity of the nucleophilic addition step. We describe here the synthesis and catalytic activity of two such conformationally restricted thiazolium salts.[7,8]



1a: Ar = Ph
1b: Ar = 1-Naph

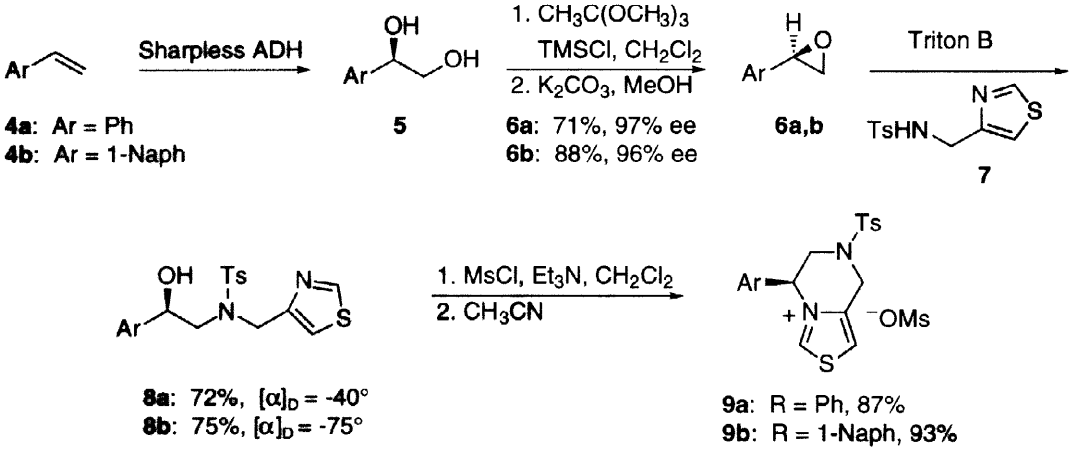
2 **2** **3**

So as to allow a direct assessment of the effect of conformational restriction on asymmetric induction, the phenyl- and 1-naphthyl-substituted catalysts were synthesized. The synthesis of these closely-related thiazolium salts is described in Scheme 1. The chiral units were prepared from styrene and 1-vinylnaphthalene, which were dihydroxylated under the Sharpless protocol, using $DHQD_2PHAL$ as the

0040-4039/98/$19.00
PII: S0040-4039(98)00439-0

chiral ligand, to give the corresponding glycols (**5a,b**) in quantitative yield and 89% and 86% ee's, respectively.[9] Recrystallization increased the ee's to >96%, with very good recovery of material. On treatment with trimethyl orthoacetate and TMSCl followed by K_2CO_3 in methanol the diols were transformed into the respective epoxides (**6a,b**),[10] with >96% ee, as shown by chiral HPLC analysis. The thiazole portion (**7**) was readily prepared by alkylation of *p*-toluenesulphonamide with 4-chloromethylthiazole[11] in aqueous NaOH. The two epoxides were then condensed with sulphonamide **7**[12] using triton B as the base catalyst to give the cyclization precursors **8a,b** in good yield. The alcohols were converted into the corresponding mesylates, which upon warming in CH_3CN underwent cyclization to the desired chiral bicyclic thiazolium salts, **9a** and **9b**.[13]

Scheme 1



The two catalysts were then examined in the benzoin condensation and some of the results are shown in Table 1. The reactions were carried out under an inert atmosphere in either MeOH or a mixture of MeOH and water, generally using triethylamine as the base. The heterogeneous reaction mixtures were stirred vigorously at room temperature for the times indicated, and the benzoin formed was isolated, purified by flash chromatography, and analyzed by HPLC on a chiral stationary phase (Welko-S,S column, Regis). From the several dozen conditions examined, most using the phenyl-substituted catalyst **9a**, it is clear that the yield and ee's of the benzoin is significantly affected by subtle changes in the reaction conditions. Entries 1-4 show that while the yield of benzoin increases with longer reaction times the asymmetric induction diminishes. Several different bases were examined for the reaction using catalyst **9a** (e.g., K_2CO_3, pyridine, Borax), but none were as effective as Et_3N. The one exception was aqueous Na_2HPO_4, which afforded benzoin in a measurable yield and 26% ee (entry 5). When the reaction was carried out at 30 °C (entry 6), conditions employed by Sheehan for his phenyl-substituted catalyst (entry 7), benzoin was obtained in 65% yield with 15% ee. These results are consistent with the initial hypothesis, that restricting the conformation of the phenyl group enhances, albeit modestly, the asymmetric induction in the benzoin condensation.

Based on Sheehan's work, the naphthyl-substituted thiazolium salt (**9b**) was expected to give benzoin in a lower yield but with significantly higher ee than the phenyl-substituted salt (**9a**). In fact, the two catalyst

were found to exhibit similar reactivity, as might have been expected *a priori*. Comparison of entries 2 and 8, and entries 4 and 9, shows that the yield of benzoin is slightly higher and the ee slightly lower with catalyst **9a** than **9b**. As with catalyst **9a**, the reaction with **9b** at 30 °C gave benzoin in higher yield but with lower ee (entry 10). Thus, whereas restricting the rotation of the phenyl-substituted salt resulted in improved asymmetric induction, such restriction of the naphthyl system did not lead to commensurate improvement in the catalyst's effectiveness. The small differences in asymmetric induction observed here for the conformationally-restricted phenyl and naphthyl catalysts would not have been surprising, but for Sheehan's report of large differences in the reactivity of analogous unrestricted salts **1a** and **1b**. It is particularly noteworthy that under our optimized reaction conditions, Sheehan's catalyst **1b** afforded benzoin in 48% ee and with remarkably improved yield (*cf.* entries 11 and 12). To our knowledge this represents the best ee/yield result for a chiral thiazolium salt catalyzed benzoin condensation.

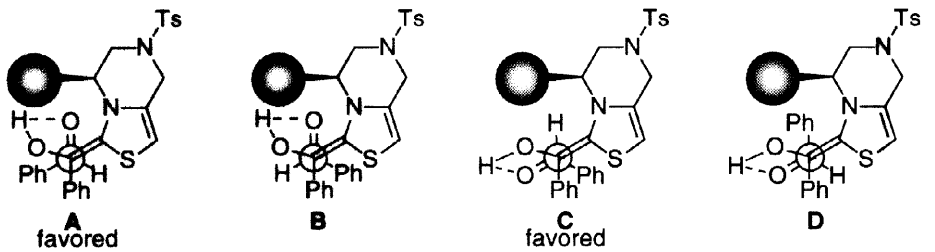
Table 1. Benzoin Condensation Using Chiral Thiazolium Salts

Entry[a]	PhCHO (mmol)	Solvent (ratio, amount)	Catalyst (**9a** or **9b**, mmol)	Base (mmol)	Time (h)	% Yield (isolated)	% ee
1	1.17	MeOH, 0.5 mL	**9a**, 0.12	Et_3N, 0.13	0.6	< 2%	28
2	1.17	MeOH : H_2O 1 : 2.5, 0.5 mL	**9a**, 0.12	Et_3N, 0.12	8	20	24
3	1.17	" "	**9a**, 0.12	Et_3N, 0.14	12	30	23
4	2.15	MeOH : H_2O 1 : 2.5, 1.0 mL	**9a**, 0.22	Et_3N, 0.24	24	27	20
5	1.17	0.5M Na_2HPO_4 0.5 mL	**9a**, 0.14		8	13	26
6[b]	1.36	MeOH, 0.68 mL	**9a**, 0.136	Et_3N, 0.129	24	65	15
7[b,c]	1 eq.	MeOH	**1a**, 0.1 eq.	Et_3N, 0.095 eq.	24	78	7.8
8	2.54	MeOH : H_2O 1 : 2.5, 1.0 mL	**9b**, 0.25	Et_3N, 0.28	8	18	30
9	2.54	" "	**9b**, 0.22	Et_3N, 0.24	24	26	27
10[b]	0.74	MeOH, 0.2 mL	**9b**, 0.075	Et_3N, 0.078	6	45	16
11[b,c]	1 eq.	MeOH	**1b**, 0.1 eq.	Et_3N, 0.095 eq.	6	6.1	51.5
12	2.16	MeOH : H_2O 1 : 2.5, 1.0 mL	**1b**, 0.22	Et_3N, 0.24	6	52	48

[a]Unless indicated, the reactions were carried out at ambient temperature (20-23 °C). [b]Reaction carried out at 30 °C, bath temperature. [c]Data taken from Sheehan and Hara's work, reference 6e.

The benzoin obtained in all of these condensations was enriched in the *R* enantiomer, determined through comparison of its optical rotation with authentic samples. The observed asymmetric induction can be rationalized by invoking a steric model. The enamine formed by the reaction of the thiazolium ylide with benzaldehyde is expected to possess the *E* geometry, which minimizes allylic strain. If it is assumed that one face of the enamine is effectively blocked by the aryl group, then the reaction with the second benzaldehyde should occur from the other, open face. A final requirement to explain the observed preponderance of the R

enantiomer is that the enamine reacts preferentially with the *Si* face of benzaldehyde, possibly via a hydrogen-bonded transition state in which the phenyl group of benzaldehyde is oriented so as to minimize steric interactions (A or C vs. B or D). The low asymmetric induction observed in the reaction suggests that this last point, the orientation of the phenyl group, has not been properly addressed in our catalyst design.



In conclusion, we have developed an efficient, high-yielding route to conformationally-restricted chiral thiazolium salts. These salts catalyze the benzoin condensation, affording benzoin in 20-30% yield, and with a similar range of ee's.

Acknowledgment: We thank the University of Chicago for financial support of this work. Generous financial support from Pfizer and Merck is also gratefully acknowledged. CAD thanks the Department of Education for a GAANN Fellowship.

References and Notes

1. Present address: Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago, IL 60637.
2. Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296-300. (CA: **1951**, *45*, 5148e)
3. (a) Stetter, H. *Angew. Chem. Int. Ed. Engl.* **1976**, *5*, 639-647. (b) For a discussion of recent developments on the use of stable carbenes for benzoin-type condensations see: Teles, J.H.; Melder, J. P.; Ebel, K.; Schneider, R.; Geher, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Helv. Chim. Acta.* **1996**, *79*, 61-83.
4. (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726. (b) Undue attention has been given to the mechanism over the last few years, stimulated primarily by an improbable mechanism proposed by Lopez-Calahorra and coworkers. See: Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241-8242, and references cited therein.
5. Breslow, R.; McNelis, E. . *J Am. Chem. Soc.* **1959**, *81*, 3080-3082.
6. (a) Yamashita, K.; Sasaki, S.; Osaki, T.; Nango, M.; Tsuda, K. *Tetrahedron Lett.* **1995**, *36*, 4817-4820. (b) Marti, J.; Castells, J.; Lopez-Calahorra, F. *Tetrahedron Lett.* **1993**, *34*, 521-524. (c) Zhao, C.; Chen, S.; Wu, P.; Wen, Z.. *Acta. Chimia. Sinica.* **1988**, *46*, 784-790 (CA: **1988**, *110*, 192696r). (d) Tagaki, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478-480. (e) Sheehan, J.C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196-1199. (f) Sheehan, J.C.; Hunneman, D.H. *J. Am. Chem. Soc.* **1966**, *88*, 3666-3667.
7. While this work was being readied for publication, Knight and Leeper reported the only other conformationally restricted thiazolium salts. See, Knight, R.L.; Leeper, F.J. *Tetrahedron Lett.* **1997**, *38*, 3611-3614.
8. Taken from the Ph. D. thesis of C. A. Dvorak, The University of Chicago, 1998. This work was presented at the American Chemical Society 30th Annual Great Lakes Regional Meeting, Loyola University of Chicago, Chicago, IL, 5/30/97.
9. Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483-2547 and references therein.
10. (a) Kolb, H.C.; Sharpless, K.B. *Tetrahedron* **1992**, *48*, 10515-10530. (b) 1% IPA/Hexanes; flow=1mL/min; Welko-S,S column (Regis).
11. Caldwell, W.T.; Fox, S.M. *J. Am. Chem. Soc.* **1951**, *73*, 2935-2936.
12. Johnson, D.A. *J. Am. Chem. Soc.* **1955**, *77*, 2336-2337.
13. No racemization was observed as confirmed by reduction of the salts to the corresponding thiazolidines and HPLC analysis. (10%IPA/Hex, flow=1mL/min).