Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 5, pp. 817-820, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)E0112-N

Asymmetric Supported Reactions : Synthesis Of Chiral Amines

Monique Calmes, Jacques Daunis, Ahmad Hanouneh and Robert Jacquier

URA 468 - Amino Acides et Peptides - Université Montpellier II
Place E. Bataillon, 34095 Montpellier cedex 5, France

Abstract : Deracemization of amines, linked via Schiff bases to a chiral polyacrylic polymer has been studied. An enantiomeric excess of 72% has been obtained with α-methyl benzylamine.

We reported previously[1] the advantages of using a polyacrylic resin as chiral auxiliary in the asymmetric protonation or alkylation of supported α-amino acid enolates, in particular (i) the molecular mobility of substrates linked to a sterically hindered backbone should be strongly reduced even at room temperature, (ii) the reaction can go to completion owing to an excess of reagent which can be easily removed by filtration, (iii) because of the polarity of the polymer surrounding the substrate, some reactions should be facilitated even with non-polar solvents, (iiii) the solid chiral auxiliary can be easily recovered and re-used.

Since use of this method affords amino acids in good enantiomeric excess[1], we decided to extend the field of application to the case of amines. Asymmetric synthesis of amines is generally achieved by stereoselective alkylation of chiraly derivatized Schiff bases[2-13]. To our knowledge, no deracemization reaction has ever been attempted.

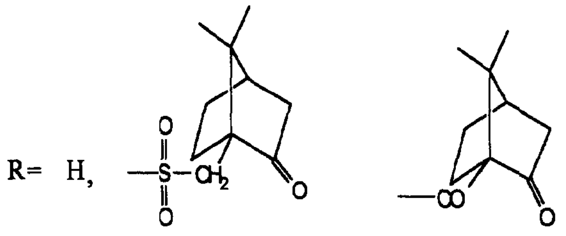
Therefore, we set out to deracemize some amines linked via an imine bond to a polyacrylic support used as chiral auxiliary. The functionalized polyacrylic support **1a** has been previously prepared in our laboratory[14] for use in solid phase peptide synthesis. It was obtained by radical copolymerization of the three monomers, acryloyl pyrrolidine, N,N'-ethylene bisacrylamide and N-methacryloyl-1,5-diaminopentane, and it possesses a loading of 1.2 meq of amine function per gram. Next, this support was made chiral by coupling a bifunctionnal chiral molecule to its arm. Two chiral molecules widely used in asymmetric synthesis were selected : commercially available (+) camphosulfonyl chloride and (+) ketopinic acid which is easily obtained by oxidation of the former compound. The acid function is used for attachment to the supported amine via an amide bond, the ketone being used to link reversibly the racemic amine by a Schiff base. These molecules were chosen because of the possibility of an interaction between the lithium salt of the corresponding supported Schiff base and amide or sulfonamide groups thus providing transition-state rigidity.

Ketopinic acid was easily coupled to the supported amine **1a** in the presence of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU). Unfortunately in the case of camphosulfonyl chloride, the yield of **1b** was never quantitative regardless of the experimental conditions and coupling agent used, probably owing to the bulkiness of the backbone. Therefore we increased the arm length of the resin **1a** by first coupling β-alanine. Under these conditions coupling of camphosulfonyl chloride became quantitative (negative ninhydrin test). With the ketopinic auxiliary, the chemical yields and enantiomeric excesses were unaffected by change in arm length, so we used the same polymer **2a** in all our experiments.

The five readily available (R,S) amines, α-methyl benzylamine, α-methyl naphthylamine, 1,2,3,4-tetrahydro-naphthylamine, 1-amino indane and 1-methyl 3-phenyl propylamine, were selected and each was linked as Schiff base to the support **2b** or **2c** in quantitative yield (yields were measured according to the method of Smith and Bryant[15]). We verified also that these bases can readily be cleaved in 80-85% yield with 1N HCl in THF for 24h at room temperature.

$$\text{Ⓟ}-CONH-(CH_2)_5-NHR \longrightarrow \text{Ⓟ}-CONH-(CH_2)_5-NH-CO-(CH_2)_2-NHR$$

1 **2**



a **b** **c**

With the aim of estimating the influence of the support under homogeneous conditions, we prepared Schiff bases by condensation of the same substituted amines with camphor or N-butyl ketopinic amide. In all cases, yields were always less than 10% (except, surprisingly, with benzyl amine where the coupling yields were almost quantitative as already noted by other authors[5,6,10]). Replacement of camphor by thio-camphor or camphor imine only slightly increased the yields. Additionally, hydrolysis was very difficult: the Schiff bases remained unchanged even when treated with 6N HCl for 24h. Only treatment with hydroxylamine hydrochloride at room temperature resulted in cleavage in good yield. Thus, use of a polyacrylic support attached to camphor derivatives markedly improve both formation and cleavage of Schiff bases of substituted amines.

Next, the supported Schiff bases were deprotonated with LDA in THF and then re-protonated with water, all steps taking place at the same temperature. After hydrolysis with 1N HCl in THF at room temperature, the substituted amines were recovered[16]. Enantiomeric excesses, collected in Table 1, were measured by HPLC or NMR after derivatization with Marfey's reagent[17] (1-fluoro 2,4-dinitrophenyl 5-(L)alanine amide).

Substrate	Polymer	T°C	ee% (S)
α-methyl benzylamine	**2b**	20	0
		-10	12
		-78	53
	2c	20	0
		-10	34
		-78	72
1-naphthyl ethylamine	**2c**	-10	21
		-78	63
1,2,3,4-tetrahydro-1-naphthylamine	**2c**	-10	22
		-78	63
1-amino indane	**2c**	-10	0
		-78	0
1-methyl-3-phenyl propylamine	**2c**	-10	6
		-78	23

Table 1

It can be noted that in the case of α-methyl benzyl amine, enantiomeric excess was lower for the supported camphosulfonyl auxiliary **2b** than for the ketopinic polymer **2c**. For this reason, with other amines we only used the ketopinic derivatized polymer **2c**. The enantiomeric excess is very dependent on the temperature and the nature of amines. Regretably, when reactions were carried out at room temperature no asymmetric induction was observed. With temperature decrease we observed a partial deracemization, the best excess being obtained at -78°C, with the exception of 1-amino indane. The behaviour difference between 1-amino indane and 1,2,3,4-tetrahydro-naphthylamine could be the result of an equilibrium between two isomeric imines in the indane case.

It has not been possible to compare our results with those obtained in homogeneous phase because of the difficulty of formation of the corresponding Schiff bases. However, enantiomeric excesses appear to be close to those resulting from the asymmetric alkylation of chiral Schiff bases formed by benzyl amine with camphor or ketopinic acid[5,6,10].

These initial results concerning amine deracemization show the advantages of the use of a supported chiral auxiliary which (i) favours Schiff base formation, (ii) simplifies work-up, and (iii) allows easy recovery of the chiral auxiliary which we have re-used without any loss of either chemical yield or enantiomeric excess.

REFERENCES AND NOTES

[1] M.Calmes, J.Daunis, H.Ismaïli, R.Jacquier, J.Koudou, G.Nkusi, A.Zouanate, *Tetrahedron*, 1990, 46, 6021

[2] M.Kob, J.Barth, *Angew. Chem. Int. Ed. Engl.*, 1980,19,725

[3] M.Kob, J.Barth, *Liebigs Ann. Chem.*, 1983, 1668

[4] S.Solladié, D.Farkhanj, *Tetrahedron Lett.*, 1986,12,1331

[5] Y.Jiang, G.Liu, J.Liu,C.Zhou, *Synth. Commun.*,1987, 17, 1545

[6] Y.Jiang, G.Liu, J.Deng, *Synth. Commun.*,1988, 18, 1291

[7] Y.Jiang, C.Zhou, L.Gao, G.Liu, *Synth. Commun.*,1989,19,1297

[8] Y.Chen, A.Mi, X.Xiao, Y.Jiang, *Synth. Commun.*,1989,19,1423

[9] A.Mi, J.Wang, Y.Chen, G.Yang, Y.Jiang, *Synth. Commun.*,1989,19, 3337

[10] Y.Jiang, P.Guo, G.Liu, *Synth. Commun.*,1990, 20, 15

[11] A.Mi, Y.Chen, J.Wang, G.Yang, Y.Jiang, *Chin. J. Chem.*, 1990, 6, 561

[12] Y.Jiang, J.Deng, W.Hu, G.Liu, A.Mi, *Synth. Commun.*,1990,20,3077

[13] A.Mi, X.Xiao, L.Wu, Y.Jiang, *Synth. Commun.*, 1991,21,2207

[14] J-C.Alfred, J.Daunis, R.Jacquier, to be published

[15] W.Bryant, D.Smith, *J. Am. Chem. Soc.*, 1935, 57, 57

[16] In a typical experiment, a stirred slurry of supported Schiff base (5g, 6 meq of amine) in THF (80ml) was treated under N_2 at the required temperature with a solution of LDA (3 eq) in THF and allowed to stand at this temperature for 2h. A solution of H_2O (0.4g) in 2ml of THF was next added at the same temperature and stirring continued for 2h. The resin was filtered, and washed successively with THF, CH_2Cl_2 and ether. Hydrolysis of the Schiff base was carried out at room temperature by treatment with a 1N HCl solution in THF for 12h. The resin was recovered by filtration, and was washed with H_2O and THF. The combined filtrates were adjusted to pH 12 with 5N NaOH and were then extracted with ether. The organic layer was dried and evaporated.

[17] M.Calmes, J.Daunis, A.Hanouneh, R.Jacquier, *Tetrahedron Asymm.*, 1993, 4, 2437

(*Received in UK* 9 *April* 1994)