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Asymmetric reductions with chiral NADH models grafted on a Merrifield resin

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Summary

A 1,4-dihydropyridine structure bearing a derivative of chiral 2-aminobutanol was used as NADH models. The so obtained reagents were grafted on a Merrifield resin. One of them allowed the obtention of an enantiomeric excess as good as that obtained with the corresponding unbound reagent.

Introduction

Increasing interest is being devoted to the use of chiral reagents in asymmetric synthesis. NADH models bearing a chiral auxiliary are promising in this field, some of them allowing the obtention of high enantiomeric excesses (1). However the work up of reactions performed with these models is generally difficult, so that an elegant alternative to this problem is the grafting of an NADH model on an insoluble support. In our laboratory we have worked in these two directions : 1) Simple models bearing the -1,4 dihydronicotinamide structure have been grafted on Merrifield resin (2) acrylic polymer (3) or silica (4). 2) Free models bearing a chiral auxiliary derived from 2 aminoalcohols have been used in the reduction of prochiral substrates (5). In the ternary complex built between the substrate the necessary involved magnesium ions and the model, the rigidity of the chiral auxiliary is enhanced by chelation of the metal by the oxygen of the amino alcohol (4).

In this report we describe the grafting of chiral models derived from 2-aminobutanol on a Merrifield resin and the results obtained with the derived reagents in asymmetric reductions.

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Experimental

Compounds 1a,b and 4a,b were prepared as previously described (5).

Merrifield resin was purchased from Merck (Art. 81878 cross-linking insured with 2 % of divinylbenzene chlorine content 4-5 %).

Quaternarization of pyridine derivatives: A mixture of 10 g of the above resin, 5 g of nicotinamide derivative : (S)-(-)-N-(pyridin-3 oyl)-2 aminobutan-1-ol: 1a or (S)-(-)-pyridin-3 oyl)-1 oxy-2 benzoylamino butan-1-ol: 1b in 100 ml of anhydrous acetonitrile was warmed at 80° for 5 days. After filtration, the resin was thoroughly washed with acetonitrile, hot water and then filtered. About 12 g of light beige grafted resin was obtained. A sample was dried at 40°/0,5 mm for analysis. Typical analysis: 2a: %C: 80.8; H: 7.1; N: 2.8; Cl: 5.0. 2b: %C: 82.5; H: 7.2; N: 1.0; Cl: 4.1.

Reduction of pyridinium salts: In a 250 ml Erlenmeyer flask a 100 ml solution of deoxygenated dimethylformamide in water (40/60) was warmed at 30°. The wet pyridinium salt 2a (or 2b) (about 10 g) was introduced, followed by a freshly prepared solution of 4 g of $Na_2CO_3,_{10}H_2O$ and 8 g of $Na_2S_2O_4$ in 100 ml of deoxygenated water. The mixture was stirred for 7 h, then filtered, washed with water, dried under vacuum for 4 days and stored under argon in a refrigerator. Grafted reagents 3a and 3b have a yellow colour. Typical analysis: 3a: %C: 81.1; H: 7.8: N: 3.4; Cl: 0. 3b: %C: 85.3; H: 7.4; N: 1.1; Cl: 3.0 (before reduction with Bu_3SnH).

The reduction of the remaining chloromethyl groups in 3b was performed by the following method (6): 7 g of resin in 150 ml of anhydrous THF were treated with 6 ml of Bu_3SnH, a trace of AIBN (Azobisisobutyronitrile) in the dark and under argon for 10 days with gentle stirring. After hydrolysis with water the resin was washed with acetone, tetrahydrofuran, ethanol, methanol, aqueous methanol and finally with ether and then dried. Typical analysis 3b: %C: 83.4; H: 7.2; N: 1.0 (no chlorine). In the infra red spectrum the absorption due to the chloromethyl group at 1270 cm^{-1} has disappeared.

The amount of dihydropyridine derivative can be estimated at 1.22 meq/g for 3a and at 0.36 meq/g for 3b.

Reduction of methylbenzoylformate with reagents bearing a chiral auxiliary.

Reduction of methylbenzoylformate with 4a and 4b was previously described (5).

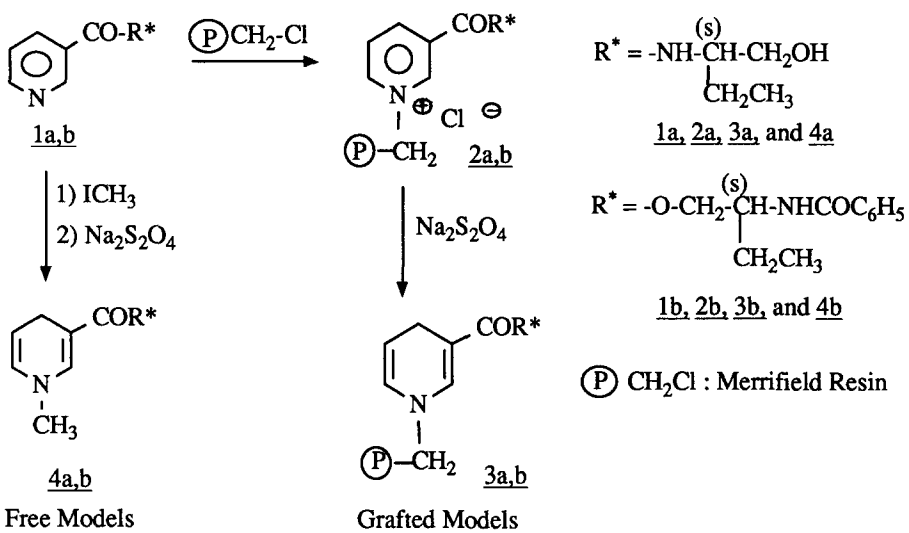
Reduction with grafted reagents 3a and 3b was performed in the following way: in a sealed tube, the grafted reagent (1.5 equivalent), methyl benzoylformate (164 mg 1.0 mmole), magnesium perchlorate (purchased from Merck, 223 mg 1.0 mmole) and a mixture of 6 ml of benzene and 6 ml of acetonitrile were introduced. The sealed tube was

warmed at 65° for 5 days.

After cooling and opening of the tube, 10 ml of water were added and the mixture was filtered. The resin was washed with acetonitrile, then with a mixture of acetonitrile/benzene (1/1). After elimination of the organic solvents, the remaining aqueous layer was extracted with dichloromethane. The organic layer was dried and the solvent evaporated to dryness. The crude methyl mandelate was purified by thin layer chromatography by using silica plates and a mixture of ether/hexane (1/2) as an eluent. Enantiomeric excesses were determined by measuring the optical rotation on a Perkin-Elmer 241 micropolarimeter or by H.P.L.C. by using a Waters apparatus and a L.K.B. enantiopac as a chiral column.

Discussion

The synthesis of unbound reagents ("free" models) and of grafted reagent bearing (S)-2-amino butanol derivatives as a chiral auxiliary is summarized in scheme 1.



Scheme 1: Synthesis of grafted and "free" NADH models.

Free models were obtained by previously described procedures.

Quaternarization of compounds 1a leading to 2a was nearly complete as proved by

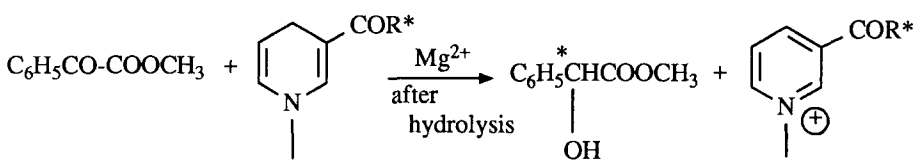
Nota: 3b was obtained after removal of the remaining chlorine with Bu_3SnH.

elementary analysis. (Starting from a Merrifield resin with a chlorine content of 5 % the theoretical nitrogen content would have been 3.3 % instead of 2.8 observed). With 1b the difference was greater (nitrogen content was only 1.0 %). The quaternarization was only partial. Even after a very long reaction time (10 days) no modification was observed. In the same conditions with nicotinamide itself, the reaction was total. By using a better swelling solvent (dimethylformamide instead of acetonitrile) no change was observed.

It can be assumed that the pore size of the polymer gel type Merrifield resin induces a steric hindrance for the access to the chloromethyl groups by large reagents such as 1a and more again 1b.

Regioselective reduction of the pyridinium salts was performed as usual with sodium dithionite leading to compounds 3a and 3b. The remaining chlorine in the chloromethyl groups in 3b was eliminated by treatment with tributytinhydride (6). This reduction could be followed by elementary analysis and by the disappearence of an absorption at 1270 cm^{-1} in the infra red spectrum.

The so obtained reagents had an amount of dihydropyridine derivative which could be evaluated at 1.22 meq/g for 3a and at 0.36 meq/g for 3b. They were used for the reduction of methyl benzoylformate (scheme 2). The results are summarized in table 1 and compared with those obtained with free models 4a and 4b.



Scheme 2: Reduction of methyl benzoylformate with chiral NADH models.

Model / Results	3a grafted	4a free	3b grafted	4b free
Chemical Yield	56%	60 %	18%	89 %
enantiomeric excess	56%	49%	6,3%	52%
configuration of major enantiomer	R	R	S	S

$R^* = -NH\text{-}\underset{\displaystyle CH_2CH_3}{\underset{|}{CH}}\text{-}CH_2OH$ for 3a and 4b

$R^* = O\text{-}CH_2\text{-}\underset{\displaystyle CH_2CH_3}{\underset{|}{CH}}\text{-}NHCOC_6H_5$ for 3b and 4b

Table 1

With model 3b the poor chemical yield and e.e. compared to 4b are certainly a consequence of the steric hindrance of the bulky chiral auxiliary. This phenomenom disturbs building up of the ternary complex model/Mg^{2+}/substrate.

The behaviour is quite different with 3a, where the chemical yield and moreover the e.e. are very similar to those observed with the free model 4a. This result is very interesting because it is generally observed that a grafted chiral NADH model is less efficient than the corresponding "free" reagent in asymmetric synthesis (7). Some chiral NADH models were previously covalently bounded to polystyrenic supports. Chemical yields were poor and the optical yields were low compared to those from homogeneous systems (e.e. falls from 47 down to a few percents.)

Among the reasons involved are : 1) the hydrophobic non polar environment of the polymer hinders the formation of the ternary complex between the substrate, magnesium ion and the model. (this complex plays a fundamental role in the enantioselectivity of the hydrogen transfer) 2) the active site is sterically hindered by the polymeric matrix and the role of the chiral auxiliary is less important than in the case of "free" reagents.

With reagent 3a, the chiral auxiliary does not cause too much steric hindrance so in the neighbourhood it remains possible to construct the ternary complex. Moreover the presence of the hydroxyl group enhances the complexation of the dihydropyridine structure with Mg^{2+}. As a consequence the enantioselectivity of the hydrogen transfer can remain as efficient as with the free model.

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