1-Substituted (*S*)-3-(*p*-Tolyl)sulphinyl-1,4-dihydropyridines: Novel NADH Model Compounds

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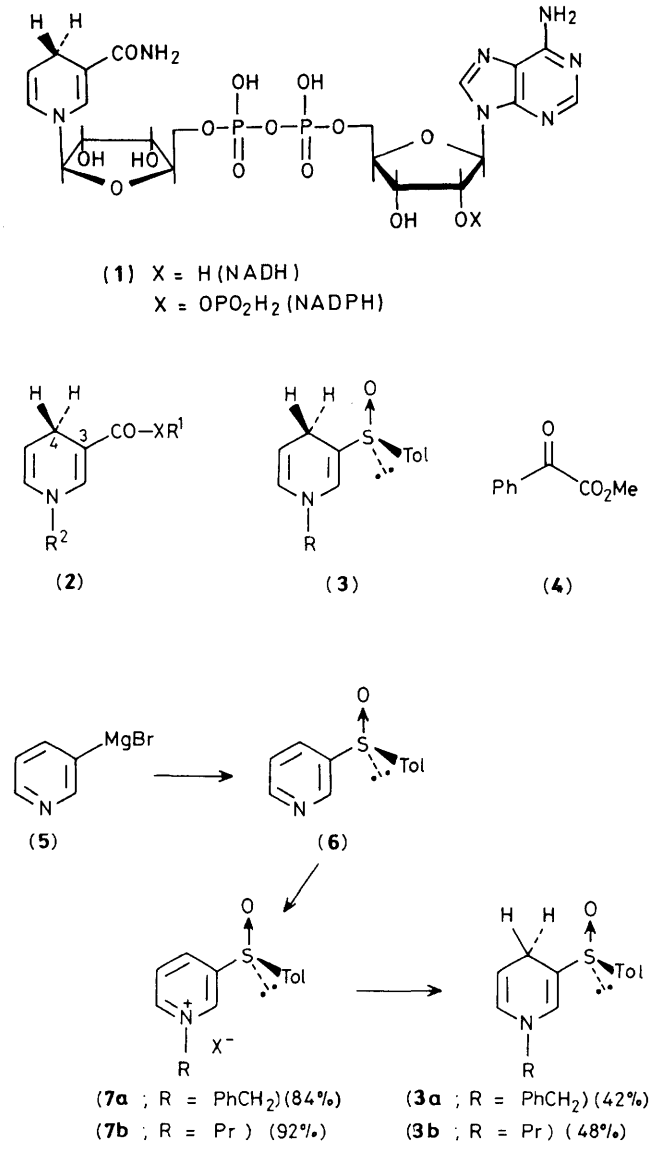
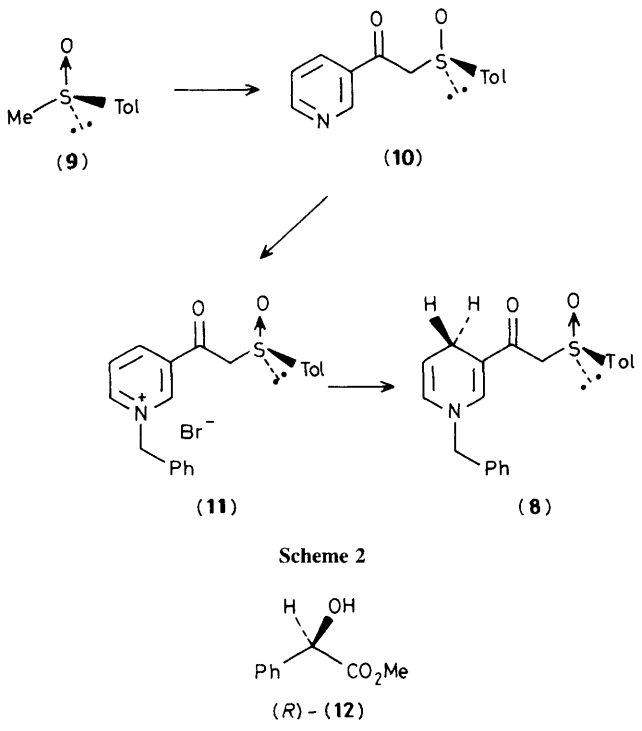
Preparation of novel NADH model compounds, (*S*)-3-(*p*-tolyl)sulphinyl-1,4-dihydropyridines and their use in the asymmetric reduction of methyl benzoylformate are described.

In the field of asymmetric synthesis, the attention of many organic chemists has been focused on modelling of enzymes or coenzymes,[1] *e.g.* NAD(P)H (**1**), a very important electron donor in many biological systems.[2] Since Ohno and co-workers reported the first example of asymmetric reduction by a model compound of NADH in 1975,[3] numerous asymmetric reductions by such compounds have been reported.[4] Almost all of these model compounds consisted of 3-carbonylated (*e.g.* amide or ester) 1,4-dihydropyridines (**2**) with a chiral group far from the C(4) reaction centre, very often resulting in products of relative low optical purity.[5] The carbonyl function plays an important role in stabilization of the labile dihydro-



Scheme 1. Tol = *p*-tolyl.



Scheme 2

Table 1. Asymmetric reduction of (**4**) with (**3**).[a]

Reagent	Metal salt	Time /days	Chemical yield[b]/%	Optical yield[c]/%
(**3a**)	$Mg(OCl_4)_2$	7	68.3	91.7
(**3a**)	$Mg(OCl_4)_2$	14	76.8	93.9
(**3a**)	$Zn(OCl_4)_2 \cdot 6H_2O$	7	28.1	95.4
(**3a**)	$Zn(OCl_4)_2 \cdot 6H_2O$	14	42.8	96.0
(**3b**)	$Mg(OCl_4)_2$	7	66.5	96.4
(**3b**)	$Mg(OCl_4)_2$	14	74.9	96.5
(**3b**)	$Zn(OCl_4)_2 \cdot 6H_2O$	7	26.7	93.1
(**3b**)	$Zn(OCl_4)_2 \cdot 6H_2O$	14	46.6	97.1

[a] *General procedure*: To a suspension of the metal salt (0.3 mmol) and dihydropyridine (**3**) (0.3 mmol) in absolute acetonitrile (6 ml) was added methyl benzoylformate (**4**) (0.3 mmol) in absolute acetonitrile (3 ml) and the mixture was stirred under argon in the dark at 30 °C for 1—2 weeks. After dilution with water, the reaction mixture was extracted with dichloromethane. The extract was washed with brine, dried (Na_2SO_4), and concentrated to leave a crude product, which was purified by preparative t.l.c. (SiO_2) to give methyl mandelate (**12**). [b] Isolated yield. [c] Based on the optical rotation of pure methyl (*R*)-mandelate, $[\alpha]_D^{20}$ −144.0 (*c* 1.0, MeOH).

pyridine moiety but precludes direct introduction of chirality at C(3). Therefore, for efficient asymmetric induction it is desirable that a functional group with both appropriate electron-withdrawing and significant chiral character is directly introduced at C(3). We have proposed a chiral sulphinyl group,[6,7] because its electron-withdrawing ability is similar to that of an amide or ester. Herein we describe the synthesis of the novel NADH model compounds, 1-substituted (*S*)-3-(*p*-tolyl)sulphinyl-1,4-dihydropyridines (**3**) and their use in effective asymmetric reduction of methyl benzoylformate (**4**).

3-Pyridylmagnesium bromide[8] (**5**) was treated with (−)-menthyl (*S*)-(*p*-tolyl)sulphinate, $[\alpha]_D^{25}$ −200° (*c* 1.00, acetone),[9] in ether–tetrahydrofuran(THF) at −78 °C to give the sulphoxide (**6**), m.p. 53—54 °C, $[\alpha]_D^{26}$ +79.8° (*c* 0.57, $CHCl_3$), in 53% yield. The optical purity of the product (**6**) shown to be nearly 100%† by ^1H n.m.r. analysis using the chiral shift reagent Eu(tfc)$_3$.‡[10] Reaction of (**6**) with benzyl bromide and propyl iodide afforded the corresponding quaternary salts (**7**), which were reduced with sodium dithionite under the known conditions[11] to give the chiral dihydropyridines (**3**) (Scheme 1). The dihydropyridine (**8**) with a sulphinylated keto function at C(3) was also prepared as follows (Scheme 2). The anion of (*R*)-methyl *p*-tolyl sulphoxide (**9**)[9,12] was treated with methyl nicotinate to give the keto sulphoxide (**10**), m.p. 102—102.5 °C, $[\alpha]_D^{25}$ +239.0° (*c* 0.53, $CHCl_3$), in 72% yield. Although reduction of the corresponding quarternary salt (**11**) with sodium dithionite resulted in the exclusive formation of the desulphinated

† The use of 3-pyridyl-lithium instead of 3-pyridylmagnesium bromide produced a partial racemisation of (**6**).

‡ Eu(tfc)$_3$ = tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).

product, treatment with sodium cyanoborohydride[13] in dichloromethane–water gave the desired product (**8**), m.p. 110—111 °C, $[\alpha]_D^{25}$ +247.9° (*c* 1.06, $CHCl_3$), in 41% yield.

The reactions of the novel NADH model compounds (**3**) and (**8**) with an activated ketone, methyl benzoylformate (**4**) were studied. The 3-(*p*-tolyl)sulphinyl derivatives (**3a**) and (**3b**) successfully reduced the ketone, but the carbonylated compound (**8**) was chemically very stable and did not react with the substrate. These results suggest that the sulphinyl group is suitable for stabilisation of the dihydropyridine moiety without diminishing the moderate electron donor ability of the model compound.

Results of the asymmetric reduction of (**4**) by (**3**) are summarised in Table 1. In all runs methyl (*R*)-mandelate (**12**) was obtained in above 90% enantiomeric excess. The stereoselectivity was somewhat higher in reactions catalysed by Zn^{II} perchlorate, while the chemical yields were higher in those catalysed by the Mg^{II} salt. Although the exact transition state for the asymmetric reduction is not known, the high optical yields could be due to the closeness of the reaction centre and the chiral sulphur atom bearing three different kinds of substituents (the lone pair electrons, the oxygen atom, and the aryl group).

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