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SYNTHESES OF 1-BENZYL-1,4-DIHYDRONICOTINAMIDES CONTAINING DIPEPTIDES AND THEIR USE IN ASYMMETRIC REDUCTION OF ETHYL BENZOYLFORMATE

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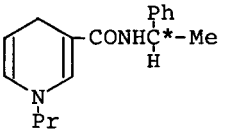
It is known that stereospecific reduction of a pyruvate to D- or L-lactate by NADH is catalyzed by lactate dehydrogenase. The stereoselective nonenzymatic reductions of esters of pyruvic acid and benzoylformic acid by 1,4-dihydronicotinamide derivatives in the presence of metal ions have been reported. For instance, the reduction of ethyl benzoylformate with N-α-methylbenzyl-1-propyl 1,4-dihydronicotinamide (1) as a chiral model for NADH at room temperature proceeded quantitatively to give ethyl(R)-(-)-mandelate with an optical purity of 19%[1]. Further, it has been reported that the reductions of menthyl esters of α-ketoacids with Hantsch esters are performed to afford corresponding menthyl mandelates with 70-80% optical yield[2]. Recently, Ohno et.al have reported that methyl mandelate with 97% optical yield is obtained in the reduction of methyl benzoylformate with diastereoisomers of N-(R)-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (2)[3]. This found is dramatically the highest value so far reported in the asymmetric reduction of α-keto esters.



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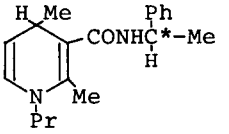

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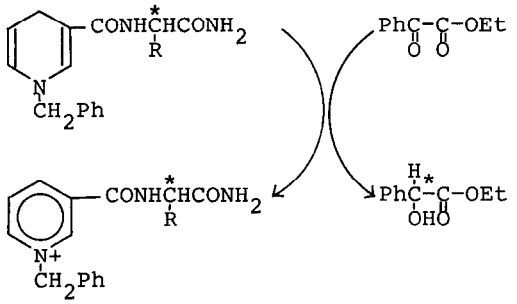
We have previously reported that the reduction of ethyl benzoylformate by 1-benzyl-1,4-dihydronicotinamide (3-6) containing amide structure of α-amino acids such as glycine, L-alanine, L-leucine and L-phenylalanine is performed to obtain ethyl mandelate quantitatively with high optical yield[4]. R-configuration was predominantly obtained in the case of 4 (optical purity; 47%) and 5 (optical purity; 26%), on the other hand, in the case of 6 (optical purity; 5%) S-configuration was given.

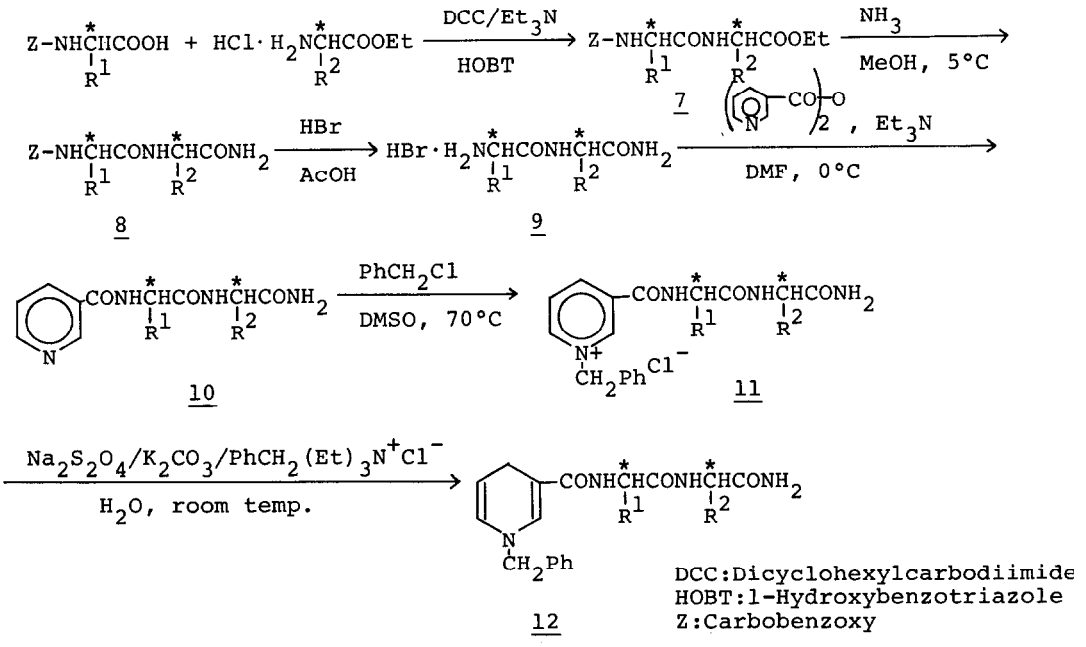


3;R=H, 4;R=CH_3
5;R=$CH_2CH(Me)_2$, 6;R=CH_2Ph

In this paper, we describe the syntheses of 1-benzyl-1,4-dihydronicotinamides (12) containing dipeptides such as L-alanyl-L-alanine, glycyl-L-alanine and L-alanyl-glycine, and their use in asymmetric reduction of ethyl benzoylformate as a model to examine the effect of peptide chain.

Syntheses of 12 were carried out by the method shown in scheme 1.

Scheme 1. Preparation of 1-Benzyl-1,4-dihydronicotinamides (12) containing Dipeptides



DCC:Dicyclohexylcarbodiimide
HOBT:1-Hydroxybenzotriazole
Z:Carbobenzoxy

7 was obtained by general DCC method in the presence of 1-hydroxybenzotriazole (HOBT) to prevent racemization. Treating 7 with a saturated methanolic solution of ammonia gas at 5°C, 8 was afforded in 80-90%. 10 was given by the reaction of nicotinic anhydride and 9 removed the protecting group (Z) with hydrobromic acid from 8, in the presence of triethylamine at 0°C. The results are shown in Table 1.

Pyridinium salt (11) was obtained, as a hygroscopic white powder, by the reaction of 10 and benzyl chloride at 70°C in dimethylsulfoxide (DMSO), as indicated in Table 2. Dihydro compounds (12) were given by the reduction of 11 with sodium dithionite-potassium carbonate in the presence of benzyltriethylammonium chloride[5], as shown in Table 3.

Table 1. Preparation of 10

Compounds	R^1	R^2	Yield (%)	mp (°C)	$[\alpha]_D^{23}$ 1)
8a	CH_3	CH_3	64	267-270	+40.2
8b	H	CH_3	52	207-209	+1.0
8c	CH_3	H	79	201-203	+28.5

1) in DMSO, c=1

The structures of 10, 11 and 12 were identified by IR, NMR and elemental analyses.

Table 2. Syntheses of 11

Compounds	R^1	R^2	Yield[1] (%)	$[\alpha]_D^{23}$ 2)	λmax 3) (nm)
11a	CH_3	CH_3	87	-28.2	265
11b	H	CH_3	98	-23.6	264
11c	CH_3	H	83	-2.2	264

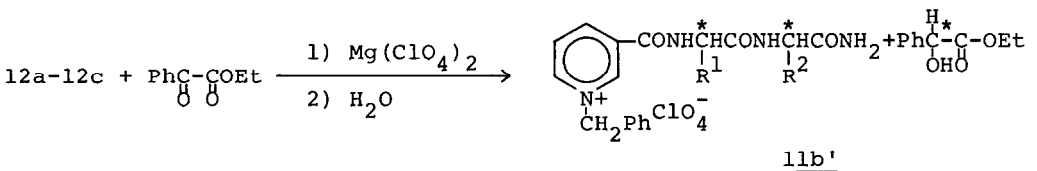
1) Benzylation step, 2) in H_2O, c=1, 3) in H_2O

Table 3. Preparation of 1,4-Dihydronicotinamides (12)

Compounds	R^1	R^2	Yield (%)	mp (°C)	$[\alpha]_D^{23}$ 1)	λmax 2) (nm)
12a	CH_3	CH_3	96	120-123	+39.2	356
12b	H	CH_3	48	183-187	-10.2	355
12c	CH_3	H	50	154-157	+15.0	356

1) in MeOH, c=1, 2) in EtOH

The reduction of ethyl benzoylformate with 12a-12c was attemped. The typical example is as follows. A mixture of 2.9 mmole each of ethyl benzoylformate, 12b and magnesium perchlorate in 100 ml of acetonitrile was allowed to react for 10 days at a room temperature. After removing acetonitrile, 30 ml of water was added. The solution was extracted three times with ether. Ether was removed in vacuo and the residue was column-chromatographed on silica gel and eluted with benzene. Ethyl mandelate was obtained and perchlorate salt (11b') was recoverd from the aqueous solution in 85-90% yield.



11b'

The configuration and optical purity of obtained ethyl mandelate are shown in Table 4.

Table 4. Asymmetric reduction of ethyl benzoylformate by use of 12a-12c

1,4-Dihydronicotinamides	R^1	R^2	Reaction Time (day)	Product (Ethyl mandelate) Yield (%)	$[\alpha]_D^{23}$ [1]	configuration	optical purity (%) [2]
12a	CH_3	CH_3	10	54	-46.8	R	45
12b	H	CH_3	10	100	+36.4	S	35
12c	CH_3	H	10	64	-26.4	R	25

1) 99.5% EtOH, c=1 2) pure ethyl mandelate $[\alpha]_D^{24}=-104°$ [6]

High yields based on ethyl benzoylformate and enantio-differentiating reaction with high optical yield by the reduction with model compounds 12a-12c were observed. It is also extremely interesting that R-configuration was predominantly obtained in the case of 12a and 12c, while S-configuration was given in the case of 12b.

The reaction mechanism of asymmetric reduction by NADH model in the presence of metal ions has been studied in detail[7-9]. We can not know exact mechanism in these reduction at present time, although the effect of the inter- or intramolecular hydrogen bonding by peptide linkage may be suggested.

The investigation on the reaction mechanism in these asymmetric reduction are now in progress.

References and Notes

1) Y.Ohnishi, M.Kagami, and A.Ohno, J.Amer.Chem.Soc., 97, 4766(1975).
2) K.Nishiyama, N.Baba, J.Oka, and Y.Inoue, J.Chem.Soc., Chem.Commun., 101(1976).
3) A.Ohno, M.Ikeguchi, T.Kimura, and S.Oka, J.Chem.Soc., Chem.Commun., 328(1978).
4) T.Endo, Y.Hayashi, and M.Okawara, Chem.Letters, 391(1977).
5) It has been reported that sodium 1-benzyl-1,4-dihydronicotinamide-4-sulfinate (BNA-SO_2Na) can be isolated as an intermediate in the course of the reduction of 1-benzylnicotinamide chloride (BNA^+Cl^-) with sodium dithionite to 1-benzyl-1,4-dihydronicotinamide (BNAH). J.F.Biellmann and H.J.Callot, Bull.Soc.Chem. Fr., 1154(1968)) We found that BNAH is obtained with excellent yield in the presence of a tetraalkylammonium chloride without forming BNA-SO_2Na.
6) R.Roger, J.Chem.Soc., 2168(1932).
7) R.A.Gase, G.Boxhoorn, and U.K.Pandit, Tetrahedron Letters, 2889(1976).
8) K.Watanabe, R.Kawaguchi, and H.Kato, Chem.Letters, 255(1978).
9) A.Ohno, T.Kimura, H.Yamamoto, S.G.Kim, S.Oka, and Y.Ohnishi, Bull.Chem.Soc.Jpn., 50, 1535(1977), ibid., 51 290, 294(1978).

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