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Improved procedures for the synthesis of (*S*)-2-[*N*-(*N′*-benzylprolyl)amino]benzophenone (BPB) and Ni(II) complexes of Schiff's bases derived from BPB and amino acids

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Abstract

(*S*)-*N*-Benzylproline (BP) was obtained by the reaction of (*S*)-proline and benzylchloride in high chemical yield (89%). (*S*)-2-[*N*-(*N′*-Benzylprolyl)amino]benzophenone (BPB) was synthesized in amounts greater than 100 g by the $SOCl_2$ promoted condensation of BP with 2-aminobenzophenone (yield 82%). Ni(II) complexes of Schiff's bases derived from BPB and amino acids were prepared by an improved procedure involving the use of KOH as a base and MeOH as solvent (yield 90–91%).

For the last 10 years, our group has been developing a new method of stoichiometric asymmetric synthesis of non-proteinogenic amino acids based on use of the chiral auxiliary (*S*)-2-[*N*-(*N′*-benzylprolyl)amino]benzophenone (BPB) and alkylation of Ni(II) complexes of Schiff's bases, derived from BPB and amino acids.[1] The method has some advantages, including the simplicity of operation, ambient temperatures of the reaction media, very high concentrations of the reagents, and the use of cheap bases (NaOH, KOH, MeONa, NaH). Other attractive features of the synthetic protocol are high rates of the alkylation reactions and facile recovery of the amino acids and the chiral auxiliary, which are convenient for the synthesis of enantiomerically enriched C-11 labelled amino acids with a short life period, employed for PET diagnostics.[2]

Unfortunately, the procedure for BPB synthesis reported by us earlier[3] is inconvenient for large scale applications. In this paper, we report a modified procedure for the synthesis of both BPB and Ni(II) Schiff's base complexes[1a,b] derived from BPB and amino acids. The synthetic protocol allows the preparation of the auxiliary and the complexes in bulk quantities (greater than 1 kg).

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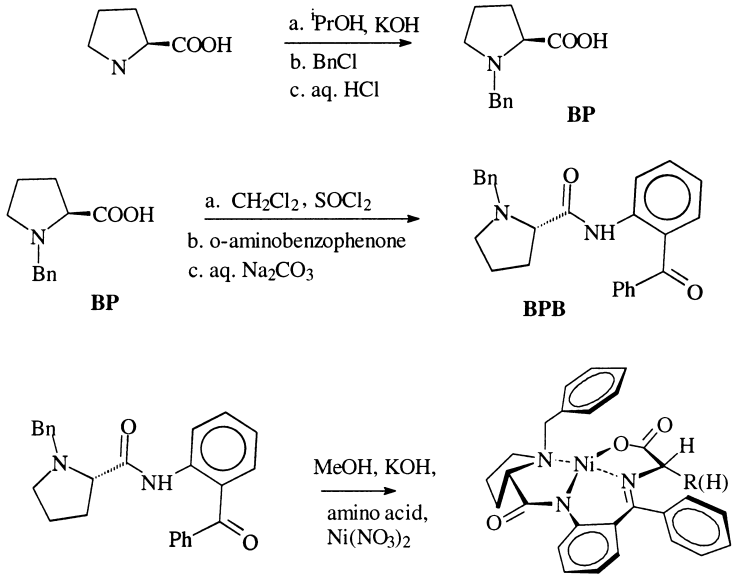
The modification of the previous synthesis included a new procedure for (*S*)-proline *N*-alkylation, which greatly improved the yields of the mono-alkylation product, *N*-benzylproline (BP), and the condensation of BP with 2-aminobenzophenone promoted by $SOCl_2$ at low temperatures (Scheme 1). Further improvement of the preparation of the Ni(II) complexes (Scheme 1) was achieved by the substitution of MeONa by KOH in the synthetic protocol. The enantiomeric purity of BPB (>99%), prepared in this way and included in the corresponding Ni-complexes, was checked by the GLC enantiomeric analysis of the amino acids (>99%) recovered from the pure diastereoisomers[1] obtained after alkylation of either gly-Ni-BPB or ala-Ni-BPB. The diastereoisomeric complexes were purified by chromatography, as described in our previous publications.[1] Their diastereoisomeric purity (before decomposition and recovery of the amino acids) was checked by NMR.



Scheme 1.

1. Experimental

The optical rotations were recorded on a Perkin–Elmer M241 polarimeter. Melting points are uncorrected. The solvents were used as purchased, without purification.

*1.1. Synthesis of (*S*)-*N*-benzylproline (BP)*

A solution of 173 g (1.17 mol) of (*S*)-proline and 254 g (4.5 mol) of KOH in 1 litre of i-PrOH was prepared with stirring at 40°C. As soon as the solution became transparent, slow addition of freshly distilled BnCl (208 g, 1.8 mol) was commenced under stirring at the same temperature. The dropwise addition took 3 h to complete, and the stirring was continued for another 6 h at the same temperature. The reaction mixture was neutralized with concentrated aqueous HCl (about 188 ml) until pH 5–6 (indicator paper), then was added to the reaction mixture $CHCl_3$ (400 ml) with stirring. The mixture was left overnight, then filtered and the precipitate was washed with $CHCl_3$. The $CHCl_3$ solutions were combined and evaporated, the residue was treated with acetone and the precipitate of crude BP filtered and additionally washed with acetone. Some BP was also recovered from the acetone washings. The

crude material was dried in air and then over P_2O_5 in vacuo to give 273 g (89%) of BP {m.p. 174–175°C, $[\alpha]_D^{20}$ −25.8 (c=1 in abs. EtOH); lit.[4]: m.p. 164°C, $[\alpha]_D^{20}$ −28.4 (c=1 in abs. EtOH)}, which was used further without any purification.

1.2. Synthesis of (S)-2-[N-(N′-benzylprolyl)amino]benzophenone (BPB)

To a solution of BP (78 g, 0.4 mol) in CH_2Cl_2 (400 ml) was added freshly distilled $SOCl_2$ (35.5 g, 0.5 mol), with stirring, at −20°C or −30°C within a period of 10 min. The stirring was continued at −10°C until the reaction mixture became almost transparent. Then a solution of 2-aminobenzophenone (50 g, 0.25 mol) in CH_2Cl_2 (200 ml) was added to the reaction mixture at −30°C with stirring. The stirring was continued at the ambient temperature for another 10 h and then a solution of Na_2CO_3 (80 g, 0.76 mol) in water (300 ml) was added to the reaction mixture with stirring at 0°C. The organic layer was separated, the aqueous layer extracted several times with CH_2Cl_2 (2×75 ml) and the organic solutions were combined and evaporated. The residue was crystallized from EtOH (150 ml). The crystalline product was filtered, the filtrate evaporated and the residue crystallized from EtOH. The combined crystalline product was dried over P_2O_5 in vacuo to give 79.4 g (81% calculated on the initial 2-aminobenzophenone) of BPB (m.p. 101–102°C, $[\alpha]_D^{20}$ −134, c=1 in MeOH, lit.[3] m.p. 101–102°C, $[\alpha]_D^{25}$ −134.5, c=0.5 in MeOH). Additional amounts of the hydrochloride of BPB were recovered from the mother liquor by the addition of concentrated aqueous HCl until pH 1 (indicator paper) and evaporation to dryness. The insoluble BPB·HCl was purified by washing the residue with acetone. The procedure could be scaled up to 1–2 kg of BPB production.

1.3. Syntheses of Gly-Ni-BPB and Ala-Ni-BPB

A solution of KOH (78.4 g, 1.4 mol) in MeOH (300 ml) was poured into a mechanically stirred mixture of BPB (76.8 g, 0.2 mol), $Ni(NO_3)_2 \cdot 6H_2O$ (116.3 g, 0.4 mol), glycine (75 g, 1 mol) or alanine (36 g, 0.4 mol) in MeOH (700 ml) under inert gas at 40–50°C. The resulting mixture was stirred at 55–65°C for 1 h in the case of Gly-Ni-BPB and 2 h in the case of Ala-Ni-BPB (a prolonged heating of the reaction mixture might result in a partial racemization of the BPB moiety) and then neutralized with AcOH (80 ml, 1.4 mol) and diluted with water to 3 litre volume. After 6 h the separated crystalline solid was filtered and washed twice with water. The complexes were sufficiently pure for further use without additional purification. In the case of the preparation of Ala-Ni-BPB, the employment of enantiomerically pure (*S*)- or racemic (*R,S*)-alanine had no influence on the final diastereomeric purity (>90%) of the isolated (*S*)-Ala-Ni-BPB. The complex could be further used for the synthesis of α-methyl-α-amino acids, as described previously.[1a]

The same procedure was shown to be valid for the syntheses, starting with BPB·HCl. In this form the chiral auxiliary was usually isolated after the alkylation procedures.[1] An additional equivalent amount of KOH should be used to neutralize the HCl evolving in the case of Ni-complex synthesis.

Gly-Ni-BPB. Average yield 91 g (91%). $[\alpha]_D^{25}$ +2006, $[\alpha]_{578}^{25}$ +2284 (c=0.1 in MeOH), lit.:[3] $[\alpha]_{578}$ +2136.

(*S*)-Ala-Ni-BPB (de >90%). Average yield 93 g (91%). $[\alpha]_D^{25}$ +2643, $[\alpha]_{578}^{25}$ +2967 (c=0.036 in MeOH).

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