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Short Research Article

New chiral synthons of ^{13}C- or ^{15}N-labelled α-amino acids†

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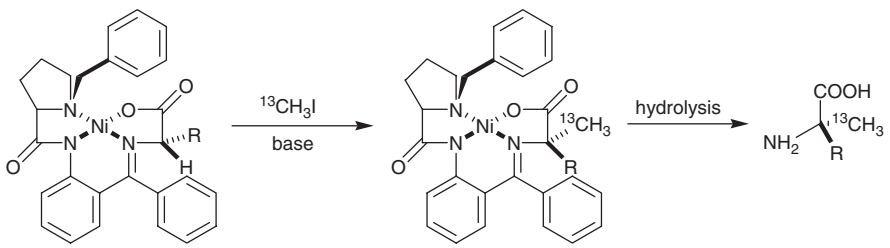
Introduction

Ni(II) complexes of Schiff bases of (*S*)-*N*-benzylproline (2-benzoylphenyl)-amide (BPB) and α-amino acids were developed as artificial analogues of pyridoxal 5′-phosphate (PLP)-dependent enzymes.[1] Their applications in the asymmetric synthesis of α-amino acids are being perfected by a number of groups worldwide.[2] Chiral synthons of α-amino acids labelled with ^{13}C or ^{15}N are useful tools in preparation of α-amino acids that are enantiomerically pure and selectively isotopically substituted for NMR and MS studies of biological systems. Based on previously described preparation of labelled nucleophilic and electrophilic glycine synthons,[3,4] different approaches to labelled α-methyl α-amino acids were evaluated. In the case of α-(^{13}C)methyl α-amino acids, two alternatives exist: (1) preparation of an alanine synthon by introduction of the α-(^{13}C)methyl group into a glycine synthon followed by an attachment of a side chain; and (2) use of α-amino acids synthons carrying a side chain and introduction of the α-(^{13}C)methyl group.

Results and discussion

The second approach was found to be more efficient for the preparative applications. (^{13}C)Methylation of sterically hindered tertiary carbon required application of up to 5-fold excess of $^{13}CH_3I$ in 1,3-dimethyl-2-imidazolidinone. KOH was used as a base. Diastereomeric excess was low: 6–20% depending on the precursor. Chemical yields of alkylations are in the range of 60–80%. Stereochemistry of the amino acid



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chiral centre of the product was D due to preferable attack of *si*-side of the intermediate carbanion. For the preparation of L-α-methyl amino acids it is necessary to build the synthon with reversed configuration (i.e. derived from D-proline instead of L-proline). α-Amino acids synthons are prepared from BPB, amino acid and nickel salt if no labelling of α-amino group, α-carbon or carboxyl carbon is required. For the synthesis of a structure carrying a label in any of the above-mentioned positions, the corresponding labelled glycine synthon could be prepared from commercially available mono-, di- or tri-labelled glycine.[3] This synthon is further monoalkylated with a suitable electrophile in order to introduce a (protected) side chain, followed by methylation by labelled or non-labelled methyl iodide. An optimization was done in order to increase yields of the complexes and decrease consumption of expensive labelled glycine.[5] Similar optimization of synthesis of a precursor for α-(^{13}C)methyltyrosine gave the ratio of BPB:amino acid:nickel nitrate = 1:1.4:1.5. This ratio allows to achieve 87% yield of the complex. The development of more diastereoselective synthons is underway.

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REFERENCES

1. Dunathan HC. *Adv Enyzmol Relat Areas Mol Biol* 1971; **35**: 79–139.
2. (a) Belokon YN. *Pure Appl Chem* 1992; **64**: 1917–1924; (b) De BB, Thomas NR. *Tetrahedron*: *Asymmetry* 1997; **8**: 2687–2691; (c) Belokon YN, Tararov VI, Maleev VI, Saveleva TF, Ryzhov MG. *Tetrahedron*: *Asymmetry* 1998; **9**: 4249–4252; (d) Cai C, Soloshonok VA, Hruby VJ. *J Org Chem* 2001; **66**: 1339–1350; (e) Belokon YN, Kochetkov KA, Ikonnikov NS, Strelkova TV, Harutyunyan SR, Saghiyan AS. *Tetrahedron*: *Asymmetry* 2001; **12**: 481–485; (f) Debache A, Collet S, Bauchat P, Danion D, Euzenat L, Hercouet A, Carboni B. *Tetrahedron*: *Asymmetry* 2001; **12**: 761–764; (g) Gu XY, Ndungu JA, Qiu W, Ying JF, Carducci MD, Wooden H, Hruby VJ. *Tetrahedron* 2004; **60**: 8233–8243; (h) Soloshonok VA, Cai C, Yamada T, Ueki H, Ohfune Y, Hruby VJ. *J Am Chem Soc* 2005; **127**: 15296–15303.
3. Jirman J, Nádvorník M, Sopková J, Popkov A. *Magn Reson Chem* 1998; **36**: 351–355.
4. Popkov A, Jirman J, Nádvorník M, Manorik PA. *Collect Czech Chem Commun* 1998; **63**: 990–994.
5. Nádvorník M, Popkov A. *Green Chem* 2002; **4**: 71–72.

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