A New Direct Method for the Synthesis of Enantiomerically Pure Protected α-Amino Acids

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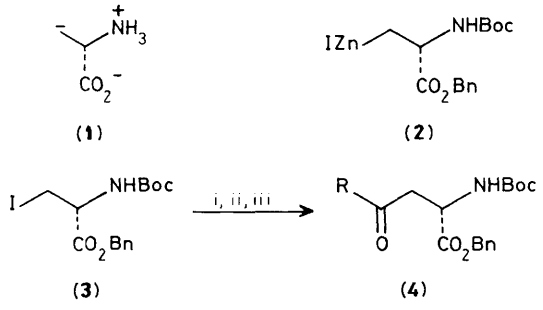
The organozinc reagent (**2**), prepared from the protected β-iodo alanine derivative (**3**) using ultrasonic activation, is efficiently acylated using acid chlorides in the presence of $(Ph_3P)_2PdCl_2$ to give high yields of enantiomerically pure protected γ-keto α-amino acids (**4**).

New methods for the synthesis of enantiomerically pure α-amino acids have been widely explored.[1] In particular, major progress has been made in the use of both nucleophilic and electrophilic glycine equivalents.[2] The use of electrophilic[3—6] and nucleophilic[7,8] alanine equivalents has, by contrast, received much less attention.† We now report that the organozinc reagent (**2**), prepared from L-serine, is a synthetic equivalent for the nucleophilic alanine synthon (**1**), coupling efficiently with acid chlorides to give enantiomerically pure protected L-γ-keto α-amino acid derivatives (**4**).[9] The availability of D-serine allows the synthesis of protected D-α-amino acids with equal facility.

Much recent progress has been made in the use of functionalised zinc reagents in organic synthesis.[10] In particular, treatment of ethyl 3-iodopropionate with zinc–copper couple in benzene–dimethylacetamide produces a homoenolate equivalent which couples under palladium catalysis with acid chlorides,[11] and aryl and vinyl iodides (and the corresponding triflates).[12] We have now applied this procedure to the β-iodo alanine derivative (**3**), which can be easily prepared in four steps from L-serine.‡

Addition of a solution of the protected β-iodo alanine derivative (**3**) to a suspension of zinc–copper couple in benzene–dimethylacetamide, followed by sonication§ for 30 minutes, during which time the temperature of the bath rose to 35 °C, resulted in disappearance of (**3**) as monitored by thin layer chromatography. Addition of catalytic bis(triphenylphosphine)palladium dichloride and then the acid chloride, and further sonication to 40 °C for 30 minutes followed by work-up and flash chromatography gave high yields (Table 1) of the protected γ-keto α-amino acids (**4a—f**)[13,14] (Scheme 1). Treatment of the β-iodo alanine derivative (**5**), derived from D-serine, with benzoyl chloride under the same conditions gave the corresponding protected D-amino acid (**6a**), (62%).

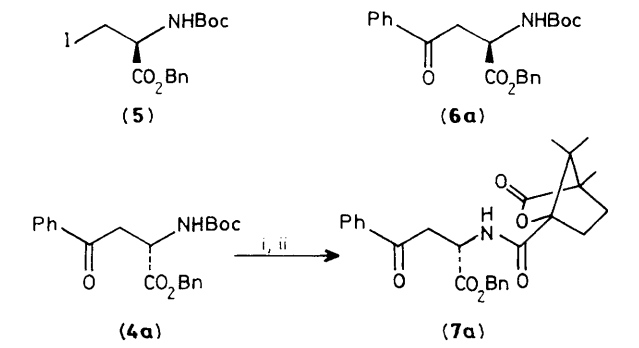
The optical purity of each of the protected α-amino acids (**4a—f**) was determined by one of two alternative methods.



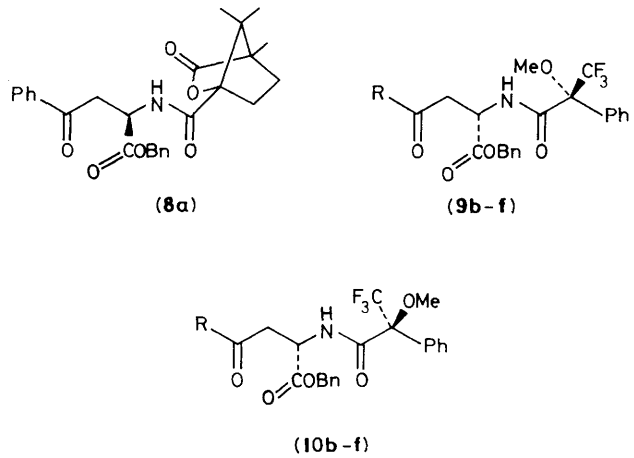
Scheme 1. *Reagents and conditions:* i, Zn/Cu couple (1.7 equiv.), benzene/dimethylacetamide (15 : 1), sonication 20 °C to 35 °C, 30 min; ii, $(Ph_3P)_2PdCl_2$ (5 mol. %); iii, RCOCl (1 equiv.), sonication 35 °C to 40 °C, 30 min.

Table 1. Preparation of γ-keto α-amino acid derivatives (**4**).

Substrate	Product	R	Yield/%
PhCOCl	(**4a**)	Ph	70
2-Furoyl Chloride	(**4b**)	2-Furyl	90
MeCOCl	(**4c**)	Me	80
EtCOCl	(**4d**)	Et	83
Pr^iCH_2COCl	(**4e**)	Pr^iCH_2	76
Bu^tCH_2COCl	(**4f**)	Bu^tCH_2	84



Scheme 2. *Reagents and conditions:* i, trifluoroacetic acid, 20 °C, 15 min; ii, (1S)-(−)-camphanic chloride (1 equiv.), dimethylaminopyridine (1 equiv.), CH_2Cl_2, 20 °C, 16 h.



† *Note added in proof:* another approach to synthon (**1**) has just appeared: J. E. Baldwin, M. G. Mahoney, and M. North, *J. Chem. Soc., Perkin Trans. 1*, 1989, 833.

‡ β-Iodo alanine derivative (**3**) was prepared by an analogous procedure to that described for the corresponding *N*-methoxycarbonyl derivative.[8]

§ Sonication was performed using a Hillsonic FM 100 ultrasound cleaning bath.

Conversion of compound (**4a**) to the free amine, followed by treatment with (1*S*)-(−) camphanic chloride gave the camphanamide (**7a**) (Scheme 2). The diastereoisomeric camphanamide (**8a**) was prepared from the protected D-amino acid (**6a**). Examination of the camphanamide derivatives (**7a**) and (**8a**) by proton n.m.r. spectroscopy indicated no diastereoisomeric contamination. The enantiomeric purities of the remaining examples (**4b—f**) were determined by conversion to the (*R*) and (*S*) Mosher amide[15] derivatives (**9b—f**) and (**10b—f**), respectively in an analogous manner. Here, both proton and fluorine n.m.r. spectroscopy indicated no detectable diastereoisomeric contamination. We can therefore conclude that, within the limits of n.m.r. spectral analysis, the amino acid derivatives (**4**) are optically pure, indicating that no racemisation had occurred during their preparation.

We are currently exploring the scope of the organozinc reagent (**2**) for the synthesis of other classes of optically active α-amino acid.

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