A new approach to the synthesis of dipeptides with unnatural amino acids using organozinc chemistry

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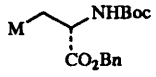
Dipeptides which incorporate an iodoalanine unit at either the N- or C-terminus can be converted into the corresponding organozinc reagents upon treatment with activated zinc. The C-terminal dipeptide organozinc reagents undergo palladium-catalysed reaction with electrophiles to give dipeptides incorporating non-proteinogenic amino acids without loss of stereochemical purity. The N-terminal organozinc reagents are less synthetically useful.

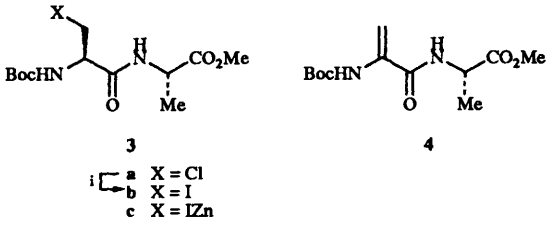
The serine-derived organozinc reagent **1** is an effective reagent for the preparation of enantiomerically pure α-amino acids,



1 M = IZn
2 M = IZn(NC)Cu

either using palladium catalysis[1] or by transmetallation to the zinc/copper reagent **2** followed by reaction with electrophiles.[2] These results establish that a carbon–zinc bond at the β-position of an amino acid is kinetically stable to a significant extent both to protonolysis by the acidic NH group and to β-elimination with loss of the carbamate anion. We now report that it is also possible to incorporate a carbon–zinc bond in the side-chain of simple dipeptides, and that reaction of these intermediates with electrophiles leads to stereoisomerically pure modified dipeptides. Previous approaches to the modification of peptides by carbon–carbon bond formation have not permitted complete control of stereochemistry, since they have almost always relied on diastereoselective processes.[3–10]

As our initial starting material we chose to prepare the dipeptide **3b**, incorporating a β-iodoalanine unit at the N-terminus. The immediate precursor to the dipeptide **3b**, the chloro derivative **3a**, was prepared by coupling *N*-Boc-β-chloroalanine with alanine methyl ester using dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in dichloromethane (90%). Treatment of the dipeptide **3a** with sodium iodide in acetone proceeded slowly at 40 °C to give the required iodide **3b**. Use of more vigorous conditions (acetone at reflux) leads to significant amounts of the dehydropeptide **4** (Scheme 1).

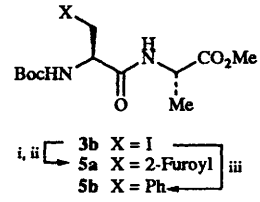


3 **4**

i: **a** X = Cl; **b** X = I; **c** X = IZn

Scheme 1 *Reagents and conditions:* i, NaI (3 equiv.), acetone, 40 °C, 15 d

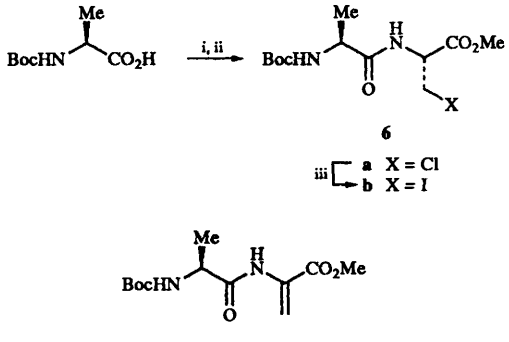
Reaction of the iodide **3b** with activated zinc,[11] followed by addition of 2-furoyl chloride and catalytic palladium(0), resulted in a low yield (12%) of the desired peptide **5a** (as a single stereoisomer), together with significant amounts of Boc-Ala-Ala-OMe. Since these results implied that the organozinc reagent **3c** was unstable towards proton-transfer, the iodide **3b** was treated with activated zinc in the presence of iodobenzene and catalytic Pd^0. In this case a small amount of Boc-Phe-Ala-OMe **5b** was isolated (10%), together with the starting iodide **3b** (50%) (Scheme 2), suggesting that the reaction of zinc with **3b** was being inhibited.



i, ii: **3b** X = I; **5a** X = 2-Furoyl; **5b** X = Ph; iii

Scheme 2 *Reagents and conditions:* i, Zn*, THF, 35 °C [prepared from zinc dust by treatment with 1,2-dibromoethane (5 mol%), and then chlorotrimethylsilane (3 mol%), in THF]; ii, 2-furoyl chloride, $[Pd_2(dba)_3]$ (2.5 mol%), PPh_3 (10 mol%); iii, Zn*, THF, PhI, $[Pd_2(dba)_3]$ (2.5 mol%), P(*o*-tol)$_3$ (10 mol%), 50 °C, 4 h

Given these rather disappointing results, we turned to the C-terminal iodide **6b**, isomeric with the iodide **3b**. The necessary precursor, the chloride **6a**, was prepared by coupling of *N*-Boc protected alanine with β-chloroalanine methyl ester (70%).[6,12] Transformation of **6a** into **6b** by treatment with sodium iodide in acetone proceeded slowly (15 days) at 35 °C (75%). As we had already observed during the preparation of **3b**, use of more vigorous conditions led to the formation of the dehydropeptide **7** (Scheme 3). Treatment of the iodide **6b** with



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iii: **a** X = Cl; **b** X = I

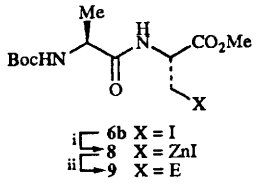
7

Scheme 3 *Reagents and conditions:* i, Bu^{i}OCOCl (1.1 equiv.), Et_3N (1.1 equiv.), THF, −15 °C, 1 h; ii, Ala(β-Cl)-OMe (1 equiv.) and Et_3N (1.1 equiv.) in DMF, −15 °C, 1.5 h, then room temp., 2 d; iii, NaI (5 equiv.), acetone, 35 °C, 15 d

Table 1 Preparation from the dipeptide **6b** of the C-terminal modified dipeptides **9a–g**

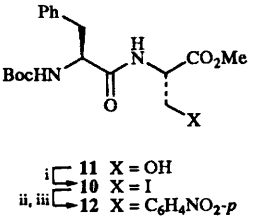
Electrophile	Catalyst	Temp. (T/°C)	Time (t/h)	Product	E	Yield (%)
PhCOCl	$[Pd_2(dba)_3]/PPh_3$	20	1	**9a**	PhCO	31
2-FurylCOCl	$[Pd_2(dba)_3]/PPh_3$	20	1	**9b**	2-FurylCO	51
4-BrC_6H_4COCl	$[Pd_2(dba)_3]/PPh_3$	20	1	**9c**	4-BrC_6H_4CO	25
PhI	$[Pd_2(dba)_3]/P(o\text{-tol})_3$	50	2	**9d**	Ph	15
4-$O_2NC_6H_4I$	$[Pd_2(dba)_3]/P(o\text{-tol})_3$	50	2	**9e**	4-$O_2NC_6H_4$	63
4-BrC_6H_4I	$[Pd_2(dba)_3]/P(o\text{-tol})_3$	65	2	**9f**	BrC_6H_4	20
1-Iodonaphthalene	$[Pd_2(dba)_3]/P(o\text{-tol})_3$	65	2	**9g**	1-Naphthyl	41

activated zinc under conditions identical with those used earlier for the formation of the zinc reagent **3c** led to efficient formation of the corresponding zinc reagent **8**, which was characterised in [$^2H_8$]THF by ^1H NMR spectroscopy, and appeared to be significantly more stable than the isomeric zinc reagent **3c**. Palladium-catalysed reaction of the zinc reagent **8** with a range of electrophiles, under unoptimised conditions, gave the corresponding dipeptides **9a–g** (Scheme 4). Our results are detailed in Table 1.



Scheme 4 *Reagents and conditions:* i, Zn*, THF, 35 °C; ii, electrophile, $[Pd_2(dba)_3]$ (2.5 mol%), phosphine ligand (10 mol%), THF

As an additional example, Boc-Phe-Ala(β-I)-OMe **10** was prepared directly (60%) from Boc-Phe-Ser-OMe **11** using $[P(OPh)_3Me]I$.[13] This transformation was complete within 0.5 h, which represents a very significant improvement over our previous method. Treatment of the iodide **10** with zinc, followed by addition of catalytic Pd^0 and 4-iodonitrobenzene, gave Boc-Phe-Phe(4-NO_2)-OMe **12** (55%) (Scheme 5).



Scheme 5 *Reagents and conditions:* i, $[P(OPh)_3Me]I$ (2 equiv.), DMF, room temp., 0.5 h; ii, Zn*, THF, 35 °C; iii, 4-$IC_6H_4NO_2$, $[Pd_2(dba)_3]$ (2.5 mol%), $P(o\text{-tol})_3$ (10 mol%), 50 °C, 12 h

Experimental

Typical experimental procedure: preparation of Boc-Ala-Phe(4-NO_2)-OMe 9e

A mixture of zinc dust (0.3 g, 4.5 mmol), 1,2-dibromoethane (0.042 g, 20 mm^3, 0.023 mmol) and dry tetrahydrofuran (0.34 cm^3) in a dry, nitrogen-purged flask was heated to 65 °C, with stirring, for 5 min with accompanying effervescence. After the flask had been cooled to room temperature, trimethylchlorosilane (6 mm^3, 0.05 mmol) was added to it and the contents were sonicated for 30 min.[2] After this, the reaction mixture was warmed to 35 °C, and a solution of Boc-Ala-Ala(β-I)-OMe (0.3 g, 0.75 mmol) in dry tetrahydrofuran (0.75 cm^3) was added to it *via* a syringe. It was then stirred at 35 °C for 30 min until no starting material remained [TLC analysis, light petroleum (bp 40–60 °C)–ethyl acetate (2:1)]. After the reaction mixture had been cooled to room temperature and diluted with dry tetrahydrofuran (5 cm^3) and the excess of zinc had settled, the supernatant was carefully removed from the residue *via* a syringe into a dry, nitrogen-purged flask. The solution of zinc reagent was warmed to 50 °C, and tris(dibenzylideneacetone)dipalladium(0) (0.018 g, 0.02 mmol), tri-*o*-tolylphosphine (0.024 g, 0.08 mmol) and 4-iodonitrobenzene (0.249 g, 1.0 mmol) were added to it sequentially. After being stirred for 2 h the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (50 cm^3), washed with aqueous hydrochloric acid (0.1 mol dm^{-3}; 25 cm^3) and water (3 × 25 cm^3), dried ($MgSO_4$) and evaporated to give the crude product. Column chromatography of this over silica gel [light petroleum (bp 40–60 °C)–ethyl acetate, 4:1] yielded Boc-Ala-Phe(4-NO_2)-OMe **9e** (0.184 g, 0.46 mmol, 63%).

Acknowledgements

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