Efficient synthesis of β- and γ-amino acid derivatives using new functionalised zinc reagents: enhanced stability and reactivity of β-amido zinc reagents in dimethylformamide

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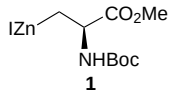
The new zinc reagents 3 and 4 are not sufficiently stable to be prepared efficiently in THF, but they can be prepared in DMF under mild and convenient conditions; subsequent palladium- catalysed coupling with aromatic iodides gives protected β- and γ-amino acids 11 and 12 in generally good yields.

There has been increasing interest in the development of new synthetic routes to β-amino acids, due to their importance as components of natural products and modified peptides.[1] The asymmetric synthesis of β-amino acids has most often relied on use of the chiral pool. For example, homologation of α-amino acids,[2] ring-opening of aziridine carboxylates[3] and modification of aspartic acid[4–6] and asparagine[7] have each been explored. γ-Amino acids have also been prepared using similar strategies, for example by modification of glutamic acid[4] and by homologation of α-amino acids.[8] A direct asymmetric synthesis of aryl β- and γ-amino acids has also been recently reported.[9]

In view of our development of other amino acid-derived zinc reagents, such as the nucleophilic alanine equivalent **1** prepared from protected iodoalanine **2**,[10] we have explored the potential of the related reagents **3** and **4** for the synthesis of enantiomerically pure β- and γ-amino acids. The necessary iodide precursors for the two reagents, **9** and **10**, were prepared from the protected aspartic and glutamic acid derivatives **5** and **6** by standard methods.†



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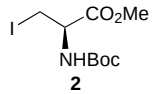

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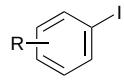
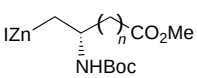
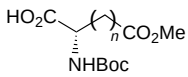


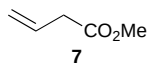
8a R = H
b R = 2,3-(C=C)$_2$
c R = 4-Me
d R = 2-MeO
e R = 4-MeO
f R = 2-NH$_2$
g R = 4-Br
h R = 2-F
i R = 4-F
j R = 2-NO$_2$
k R = 3-NO$_2$
l R = 4-NO$_2$



3 *n* = 1
4 *n* = 2



5 *n* = 1
6 *n* = 2



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Our initial efforts to prepare the zinc reagents **3** and **4**, by using zinc dust activated using the Knochel procedure in THF as solvent,[11] were disappointing. For example, formation and coupling of the zinc reagent **3** with *p*-iodonitrobenzene **8l**, under the conditions previously developed for the zinc reagent **1**, gave the β-homophenylalanine derivative **11l** in disappointing yield (25%). Similar results were obtained using the zinc reagent **4**.

^{1}H NMR spectroscopy of the zinc reagent **3** prepared in [$^2H_8$]THF indicated clearly that the main problem was β-elimination of the urethane group to give the alkene **7**. Examination of the ^{13}C NMR spectrum of the reagent **3** in [$^2H_8$]THF indicated that there was significant coordination of the urethane carbonyl group to zinc (implied by the downfield shift of the urethane carbon atom upon formation of the zinc reagent), whilst coordination of the ester carbonyl was much less pronounced (Table 1). We suggest that this lack of ester coordination results in a relatively facile β-elimination of the urethane group (promoted by the internal Lewis acid), since the conformation required for elimination can be easily attained. This stands in sharp contrast to the ^{13}C NMR spectrum of the serine-derived reagent **1** in [$^2H_8$]THF, which indicates that both ester and urethane carbonyl groups are coordinated to zinc, which in turn, we believe, is responsible for the significantly greater stability of this reagent than the reagent **3** in THF. In contrast to the situation in [$^2H_8$]THF, the ^{13}C NMR spectrum of **3** in [$^2H_7$]DMF showed no significant changes in the shifts of the two carbonyl carbon atoms on conversion of iodide **9** into zinc reagent **3**, which we interpret as indicating that there is no coordination of either carbonyl group to zinc in this solvent. It is interesting to note that in [$^2H_7$]DMF, the serine-derived zinc reagent **1** preserves ester coordination (Table 1), indicating that intramolecular co-ordination of an ester group which results in a 5-membered ring is especially favourable. We therefore explored the preparation of the zinc reagent **3** in dipolar aprotic solvents, and were pleased that all solvents employed (DMF, DMA, NMP and DMSO) were effective.[12] In all the solvents, preparation of the zinc reagent **3** and its subsequent coupling with iodobenzene, to give **11a**,‡ occurred at room temperature in good yield. Given the convenience of using DMF,[13] subsequent reactions were all carried out with this solvent, and are summarised in Table 2 and Scheme 1. The only disappoint-

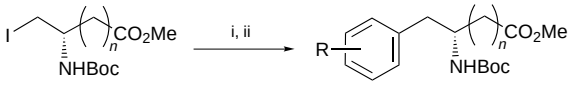
Table 1 ^{13}C NMR chemical shifts (δ) of zinc reagents **1** and **3**

	THF		DMF	
	Ester	Carbamate	Ester	Carbamate
2	171.93	157.20	169.57	155.10
1	177.28	159.91	175.35	154.24
9	172.68	157.04	170.50	154.88
3	174.14	160.79	171.38	154.34

Table 2 Preparation of β-amino acids

Aryl iodide	Product	Ar	Yield (%)[a]
8a Iodobenzene	**11a**	Ph	73
8b 1-Iodonaphthalene	**11b**	1-Naphthyl	61
8c 4-Iodotoluene	**11c**	4-MeC_6H_4	73
8d 2-Iodoanisole	**11d**	2-MeOC_6H_4	56
8e 4-Iodoanisole	**11e**	4-MeOC_6H_4	68
8f 2-Iodoaniline	**11f**	2-$H_2NC_6H_4$	33
8g 4-Bromoiodobenzene	**11g**	4-BrC_6H_4	58
8h 2-Fluoroiodobenzene	**11h**	2-FC_6H_4	46
8i 4-Fluoroiodobenzene	**11i**	4-FC_6H_4	65
8j 2-Iodonitrobenzene	**11j**	2-$O_2NC_6H_4$	20
8k 3-Iodonitrobenzene	**11k**	3-$O_2NC_6H_4$	47
8l 4-Iodonitrobenzene	**11l**	4-$O_2NC_6H_4$	89

[a] All yields are based on iodide **9**.



9 $n = 1$ **11** $n = 1$
10 $n = 2$ **12** $n = 2$

Scheme 1 *Reagents and conditions:* i, Zn* (prepared from Zn dust using 1,2-dibromoethane, followed by Me_3SiCl, in DMF), 15 min, room temp.; ii, **8** (1.33 equiv.), $Pd_2(dba)_3$ (2.5 mol%), P(*o*-$MeC_6H_4)_3$ (10 mol%), room temp., 3 h

Table 3 Preparation of γ-amino acids

Aryl iodide	Product	Ar	Yield (%)[a]
8a Iodobenzene	**12a**	Ph	68
8c 4-Iodotoluene	**12c**	4-MeC_6H_4	68
8d 2-Iosoanisole	**12d**	2-$MeOC_6H_4$	69
8e 4-Iodoanisole	**12e**	4-$MeOC_6H_4$	68
8f 2-Iodoaniline	**12f**	2-$H_2NC_6H_4$	56
8h 2-Fluoroiodobenzene	**12h**	2-FC_6H_4	34
8l 4-Iodonitrobenzene	**12l**	4-$O_2NC_6H_4$	80

[a] All yields are based on iodide **10**.

ing yields occur with the use of *ortho* substituents, which appear to be caused by steric problems, rather than by electronic ones. The reasonable result obtained with 2-fluoroiodobenzene is in sharp contrast to our previous complete failure to promote coupling with this substrate.[10]

In an analogous way, the iodide **10** can be converted into the zinc reagent **4**, which then undergoes coupling with a range of aromatic iodides in good yield to give a series of γ-amino acids **12**. These results are summarised in Table 3.

These results indicate that it is possible to prepare both β- and γ-amino acids using organozinc chemistry at room temperature in a straightforward manner. Further applications of zinc reagents **3** and **4**, and of related zinc/copper reagents, to the synthesis of other classes of β- and γ-amino acid derivatives will be reported in a future full paper.

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Footnotes and References

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† The aspartic and glutamic acid derivatives **5** and **6** were converted into the corresponding *N*-hydroxysuccinimide esters (*N*-hydroxysuccinimide, *N*,*N*′-dicyclohexylcarbodiimide) (ref. 14), reduced to the alcohols ($NaBH_4$, H_2O–THF), and then converted into the iodides **9** and **10**, respectively (PPh_3, I_2 imidazole, CH_2Cl_2) (ref. 15).

‡ The enantiomeric purity of **11a** was determined by comparison of its specific rotation, [$[\alpha]_D$ +20.8 (*c* 1.28, MeOH)] with the literature value [+19.9 (*c* 1.29, MeOH] (ref. 16). As an additional check, the ee of this compound was determined as >98% (by comparison with a racemic sample) by capillary electrophoresis using α-cyclodextrin as chiral selector.

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