Carbonylative Coupling of an Amino Acid-derived Organozinc Reagent with Functionalized Aryl Iodides: Synthesis of Kynurenine

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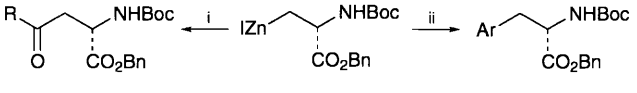
The utility of the palladium(0) catalysed reaction of the serine-derived organozinc reagent **6** with functionalized aryl iodides, under a carbon monoxide atmosphere, to give protected 4-aryl-4-oxo α-amino acids **8** is illustrated by a short synthesis of L-kynurenine.

We have, for some time, been interested in exploring the reactivity of serine-derived organometallic reagents in order to develop effective and direct methods for the synthesis of non-proteinogenic amino acids in enantiomerically pure form. For example, the organozinc reagent **1**, simply prepared by treatment of protected iodoalanine with activated zinc, reacts under palladium catalysis with acid chlorides to give 4-oxo α-amino acids **2**, and also with aryl iodides to give 3-aryl α-amino acids **3** (Scheme 1).[1] Each of these reactions tolerates the presence of a variety of other functional groups in the electrophile.

The synthesis of L-kynurenine **4**,[2] an intermediate in the metabolism of L-tryptophan to nicotinic acid ribonucleotide *via* the kynurenine pathway, presented us with a challenge since the most direct approach requires the coupling of an anthranilic acid chloride **5** with a suitable serine-derived zinc reagent such as **6**[3] (Scheme 2). However many nitrogen protecting groups are incompatible with acid chlorides, enhance the acidity of protons on nitrogen, or are sufficiently bulky that they severely retard reaction rates. An indirect approach involving attempted coupling of *ortho*-nitrobenzoyl chloride with zinc reagent **6** was unsuccessful.

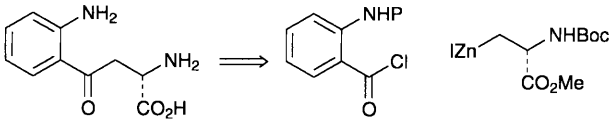
Given these problems, our attention then turned to an alternative strategy, involving the palladium-catalysed carbonylative cross coupling of organozinc reagents with aromatic iodides as a route to unsymmetrical ketones. The viability of this type of process has been well established using a wide variety of organometallic reagents,[4] although the use of zinc reagents has only received a small amount of attention.[5]

In the event, reaction of iodobenzene **7a** with zinc reagent **6** in THF under an atmosphere of carbon monoxide (1 atmosphere, balloon) in the presence of (*tetrakis*)triphenylphosphine palladium(0) [$Pd(Ph_3P)_4$] at room temperature gave the protected 4-phenyl-4-oxo α-amino acid **8a** (60%) (Scheme 3),



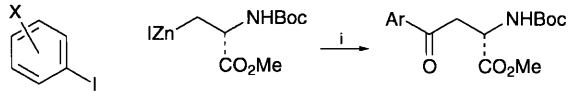
2 **1** **3**

Scheme 1 *Reagents*: i, RCOCl, Pd^0; ii, ArI, Pd^0



4 **5** **6**

Scheme 2



7 **6** **8**

Scheme 3 *Reagents and conditions*: i, CO (1 atmosphere), $Pd(PPh_3)_4$ (5 mol%), THF, room temp. 30 h

identical to material prepared by direct coupling of zinc reagent **6** with benzoyl chloride according to our previously reported method.[6] No protected phenylalanine was isolated from this reaction, implying that direct reaction of iodobenzene and the zinc reagent **6** did not compete under the reaction conditions. The use of $Pd(Ph_3P)_4$ was crucial for success, since other palladium catalysts appeared to be significantly less effective.

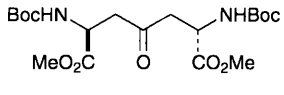
Given the effectiveness of this reaction, and especially taking note of the mild reaction conditions, we have explored the scope and limitations of the process using a variety of functionalized aryl iodides **7** as substrates. Our results are outlined in Table 1. Most strikingly, the presence of an unprotected amino group in both *ortho* and *para* positions results in satisfactory yields of the desired products **8j** and **8l**, respectively.

The reaction is sensitive to the electronic effects of the substituents on the aromatic ring, but does give satisfactory results in all cases except when the substituents are strongly electron-withdrawing or are sited in the *meta* position. In cases in which low yields of the desired 4-aryl-4-oxo α-amino acids **2** were isolated, significant amounts of protected 4-oxo-2,6-diaminopimelic acid **9** were isolated. We have already established that ketone **9** is the major product from palladium catalysed reaction of zinc reagent **1** with phenyl chloroformate,[7]

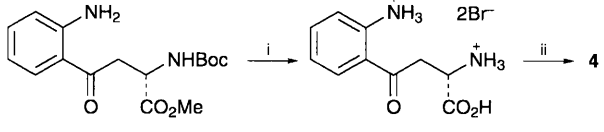
Table 1 Preparation of protected 4-aryl-4-oxo α-amino acids **8**

Aryl Iodide		Product	Ar	Yield (%)[a]
Iodobenzene	**7a**	**8a**	C_6H_5	60
1-Naphthyl Iodide	**b**	**b**	1-$C_{10}H_8$	54
4-Iodotoluene	**c**	**c**	4-MeC_6H_4	59
2-Iodoanisole	**d**	**d**	2-$MeOC_6H_4$	50
3-Iodoanisole	**e**	**e**	3-$MeOC_6H_4$	40
4-Iodoanisole	**f**	**f**	4-$MeOC_6H_4$	58
2-Iodonitrobenzene	**g**	**g**	2-$O_2NC_6H_4$	13[b]
3-Iodonitrobenzene	**h**	**h**	3-$O_2NC_6H_4$	27[b]
4-Iodonitrobenzene	**i**	**i**	4-$O_2NC_6H_4$	0[b]
2-Iodoaniline	**j**	**j**	2-$H_2NC_6H_4$	52
3-Iodoaniline	**k**	**k**	3-$H_2NC_6H_4$	17[b]
4-Iodoaniline	**l**	**l**	4-$H_2NC_6H_4$	56

[a] All yields are based on (*R*) methyl 2-(*tert*-butoxycarbonylamino)-3-iodopropanoate. [b] The major product in each of these reactions was the symmetrical ketone **9**.



9



8j **10**

Scheme 4 *Reagents and conditions*: i, HBr (30% in AcOH), room temp. 20 min; ii, propylene oxide, Pr^iOH

and that it is also formed on treatment of zinc reagent **1** with catalytic amounts of $Pd(Ph_3P)_2Cl_2$ under an atmosphere of CO in the absence of added electrophile.

Removal of the protecting groups from the adduct **8j** was achieved by treatment with 30% HBr–HOAc to give the corresponding bis(hydrobromide) salt **10**, which was then converted to the free amino acid **4** using propylene oxide (90% overall yield from **8j**) (Scheme 4).† This chemistry represents a short synthesis of kynurenine **4** from commercially available materials, and it is sufficiently flexible to enable the preparation of analogues.

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Footnote

† These conditions are derived from those reported by Salituro and McDonald for an analogous deprotection (see ref. 2).

References

1 R. F. W. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes, *J. Org. Chem.*, 1992, **57**, 3397.
2 For a recent synthesis, and references to earlier work, see: F. G. Salituro and I. A. McDonald, *J. Org. Chem.*, 1988, **53**, 6138.
3 We have chosen to employ zinc reagent **6**, rather than zinc reagent **1**, since the necessary precursor to **6**, (*R*)-methyl 2-(*tert*-butoxycarbonylamino)-3-iodopropanoate, is significantly easier to prepare than the corresponding precursor to zinc reagent **1**. See: M. J. Dunn, R. F. W. Jackson, J. Pietruszka and D. Turner, *J. Org. Chem.*, 1995, **60**, 2210 for the preparation of **6**, and J. A. Bajgrowicz, A. El Hallaoui, R. Jacquier, C. Pigiere and P. Viallefont, *Tetrahedron*, 1985, **41**, 1833, for the preparation of the required precursor.
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