

Reaction of a Serine-derived Organozinc Reagent with Chloroformates and Ethyl Oxalyl Chloride Under Palladium Catalysis. Preparation of Protected (2*S*, 6*S*)-4-Oxo-2,6-diaminopimelic Acid and (2*S*)-4-Oxoglutamic Acid

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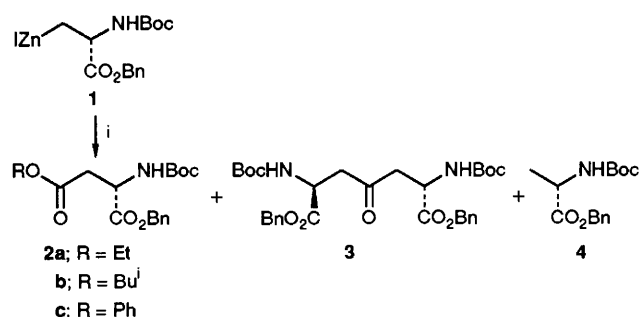
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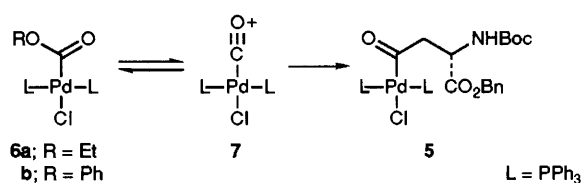
Organozinc reagent **1** reacts with phenyl chloroformate under palladium catalysis to give the protected 4-oxo-2,6-diaminopimelic acid derivative **3**, derived by formal displacement of both chloride and phenoxide; the symmetrical ketone **3**, together with protected 4-oxoglutamic acid **10**, are formed when ethyl oxalyl chloride is used as substrate.

The palladium-catalysed coupling of acid chlorides with organozinc halides is an extremely useful method for the synthesis of ketones.¹ Although stoichiometric oxidative addition of both ethyl chloroformate² and methyl oxalyl chloride³ to bis(triphenylphosphine) palladium have been reported, there appear to be only two reports of the use of this reaction for catalytic cross coupling with organometallic reagents.⁴ In connection with our recently reported method for the synthesis of 4-oxo-2-amino acid derivatives by coupling of the organozinc reagent **1** with acid chlorides under palladium catalysis,⁵ we have investigated the reaction of zinc reagent **1** with chloroformates and also with ethyl oxalyl chloride, with a view to the preparation of aspartic acid, and 4-oxoglutamic acid derivatives.

Treatment of the organozinc reagent **1** with ethyl chloroformate in the presence of bis(triphenylphosphine)palladium dichloride under sonication gave not only the expected aspartate derivative **2a** (10%), but also the 4-oxo-2,6-diaminopimelic acid derivative **3** (25%).⁶ The mass balance was made up by protected alanine **4** (Scheme 1). Reaction of the organozinc reagent **1** with isobutyl chloroformate also resulted in the formation of the symmetrical ketone **3**, together with the aspartate derivative **2b** in similar yields. Precedent for the formation of **3** was provided by the reaction of isobutyl chloroformate with *p*-tolyltributylstannane under palladium catalysis at high temperatures to give di-*p*-tolyl ketone.^{4b} Use of phenyl chloroformate (5 equiv.), however, led to the isolation of **3** (45%) with none of the aspartate derivative **2c**.



Scheme 1 Reagents and conditions: i, RO_2CCl (1.3 equiv.), $(\text{PPh}_3)_2\text{PdCl}_2$ (5 mol%), benzene : dimethylacetamide (15 : 1), sonication, 1 h



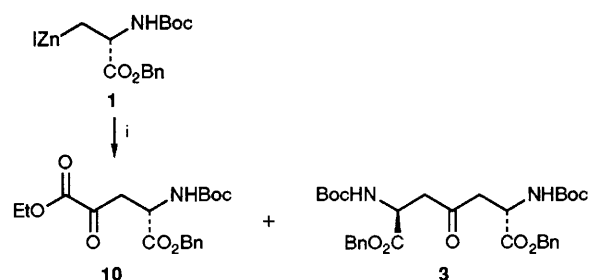
Scheme 2

Table 1 Reaction of zinc reagent **1** with ethyl oxalyl chloride under palladium catalysis

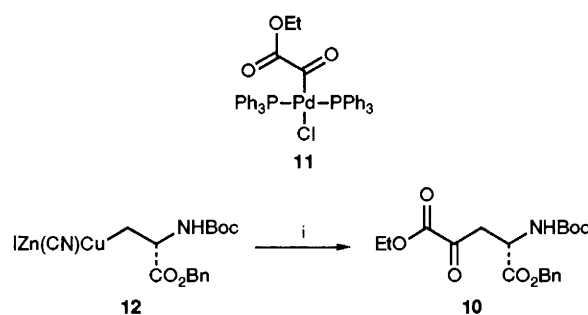
Entry	Reaction conditions	Yield(%) of 4-oxoglutamate 10	Yield ^b (%) of diaminopimelate 3
1	Sonication, 30–35°C, 1 h	24 ^a	24
2	Stirring, 20°C, 2 h	43	21
3	Stirring, 2–4°C, 2 h	34	0
4	Sonication, 30–35°C, 1 h 4 equiv. PPh_3 , w.r.t. Pd catalyst	24	0

^a A trace amount of the aspartate derivative **2a** (2%) was also isolated. ^b In all cases, the mass balance consisted principally of alanine **4**.

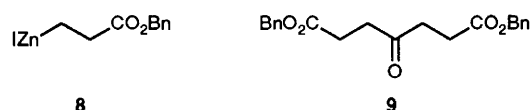
Since transmetalation is generally regarded as the rate-determining step in palladium-catalysed cross-coupling reactions,⁷ it appears reasonable that the acylpalladium complex **5** is an intermediate in the pathway leading to **3**. Complex **5** could in principle be formed by nucleophilic attack on the initial oxidative addition product **6a**, although it appears more likely that this complex can undergo loss of ethoxide⁸ (or in the case of **6b**, phenoxide) to generate a cationic carbonyl complex **7**, which then suffers nucleophilic attack by the zinc reagent **1** (Scheme 2). It is, therefore, likely in the case of **6a** that transmetalation by the zinc reagent **1** can compete with loss of ethoxide, thereby leading to the formation of the aspartate derivative **2a**, whereas loss of phenoxide from **6b** is presumably faster. Support for the proposal that attack of the zinc reagent **1** on a cationic palladium complex **7** can occur is provided by our observation that treatment of the zinc reagent **1** with carbon monoxide (101.325 kPa) under sonication (30–35°C, 2 h) in the presence of catalytic $(\text{PPh}_3)_2\text{PdCl}_2$ gave **3** in low yield (21%). This latter process has been proposed as a mechanism for the formation of $(\text{PPh}_3)_2\text{Pd}$ from $(\text{PPh}_3)_2\text{PdCl}_2$ and diethylzinc under a CO atmosphere.⁹ An alternative mechanism for the formation of **3** requires decomposition of the chloroformate to give phosgene,^{4b} followed by palladium-catalysed coupling with the zinc reagent **1**. This pathway might also involve the palladium complex **7** as an intermediate.



Scheme 3 Reagents and conditions: i, EtOCOCOC (1.3 equiv.), $(\text{PPh}_3)_2\text{PdCl}_2$ (5 mol%), benzene : dimethylacetamide (15 : 1), see Table 1 for details of conditions



Scheme 4 Reagents and conditions: i, EtOCOCOC (1.3 equiv.), benzene : dimethylacetamide : tetrahydrofuran (15 : 1 : 10), 0°C, 3 h



In order to establish that the formation of symmetrical ketones was not confined to the organozinc reagent **1**, we investigated the reaction of the organozinc reagent **8** with phenyl chloroformate under the same conditions as employed for reagent **1**, and isolated the corresponding symmetrical ketone **9** (41%).¹⁰ Treatment of phenylzinc chloride with phenyl chloroformate in tetrahydrofuran under sonication in the presence of $(\text{PPh}_3)_2\text{PdCl}_2$ (5 mol%) gave benzophenone (38%), which established that ketone formation can also occur in this solvent.

In view of the formation of the dimer **3**, we decided to investigate the reaction of zinc reagent **1** with ethyl oxalyl chloride. Treatment of the organozinc reagent **1** with ethyl oxalyl chloride in the presence of $(\text{PPh}_3)_2\text{PdCl}_2$ under sonication conditions (30–35°C) allowed the isolation not only of the expected 4-oxoglutamic acid derivative **10** (24%), but also protected 4-oxo-2,6-diaminopimelic acid **3** (24%), together with a trace (2%) of the aspartate derivative **2a** (entry 1, Table 1) (Scheme 3).¹¹ Carrying out the reaction without sonication (entry 2), at a lower temperature (entry 3) or in the presence of an excess of PPh_3 (entry 4) all result in reduced production of **3**. These results suggest that decarbonylation of an intermediate ethyl oxalyl palladium species **11** is a necessary step in the formation of **3**. In view of the moderate yields of the palladium-catalysed processes, ethyl oxalyl chloride was treated with the zinc/copper reagent **12**¹² to give protected 4-oxoglutamic acid **10** (61%),¹³ with no trace of other coupled products (Scheme 4).

Efforts to improve the yields of this symmetrical ketone synthesis, which is tolerant of reactive functional groups, and further experiments to understand the mechanism of the reactions involving ethyl oxalyl chloride are underway.

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