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Efficient Synthesis of Functionalized α-Aryl α-Aminoesters via Reaction of Polyfunctional Diarylzincs with a Glycine Cation Equivalent

Frédéric Lamaty,* René Lazaro and Jean Martinez

Laboratoire des Aminoacides, Peptides et Protéines, CNRS-Universités Montpellier I & II,
Place Eugène Bataillon, 34095 Montpellier Cedex 05, France.

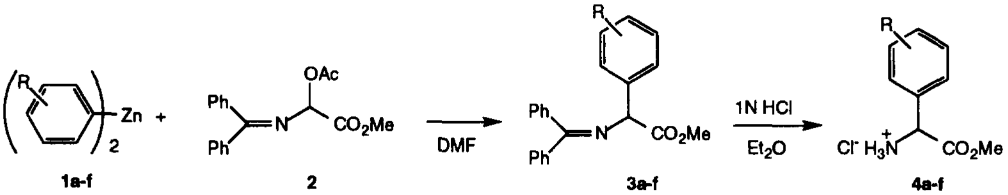
Abstract: Functionalized diarylzinc reagents, easily available from the corresponding aryl halides by a halogen-lithium exchange followed by transmetalation with $ZnCl_2$ react with a glycine cation equivalent to afford substituted α-aryl α-amino esters in good yields. © 1997 Elsevier Science Ltd.

Organozinc reagents are useful organometallic compounds for organic synthesis because of their tolerance for a wide variety of functional groups.[1] It has been shown that functionalized arylzinc compounds are easily available from the corresponding aryl halides via lithium-halogen exchange at low temperature followed by transmetalation with Zn(II) salts to provide a stable polyfunctional organozinc.[1c] Recently this potential was illustrated by the reactions of conjugate addition and cross-coupling involving functionalized arylzinc halides.[1d]

The reaction of organometallics with a glycine cation equivalent has been widely studied,[2] but to our knowledge no such a reaction involving an arylzinc reagent has been described.[3] The facile availability of diarylzinc complexes and their ability for functional group tolerance appeared to be attractive in order to synthesize aryl glycine derivatives[4] bearing a substituent on the aryl ring. α-Aryl α-amino acids are an important class of molecules because they are found in many biologically active molecules.[4,5]

In this paper, we report that functionalized diarylzincs react with an electrophilic glycine equivalent to provide after hydrolysis the corresponding α-aryl α-aminoester hydrochlorides (scheme 1).

As a first example, we have found that when the readily available[6] Schiff base **2** was stirred with 1 eq. of diphenylzinc (**1a** obtained from 2 eq. of commercially available PhLi and 1 eq. of $ZnCl_2$) during 3h at 20°C in DMF, 80% of the arylated Schiff base **3a** (R=H) was obtained after purification by column chromatography. Mild hydrolysis of **3a** with 1N HCl yielded phenylglycine methyl ester hydrochloride **4a** in 78% overall yield from **2**.



Scheme 1

It is noteworthy that a polar solvent such as DMF, commonly used in reaction of organozinc reagents, was necessary to ensure completion of the reaction.[3f] When THF was used as a solvent, no reaction was observed. This result is in sharp contrast with the reactions of arylboron or arylcopper species with the Schiff

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* frederic@ampir1.univ-montp2.fr

base **2**,[7] which are taking place in THF. Best results were obtained when 2 eq. of PhLi and 1 eq. of $ZnCl_2$ (corresponding to 1eq. of Ph_2Zn) were used for 1 eq. of **2**.

Table 1. Synthesis of α–aryl α–aminoesters

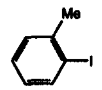
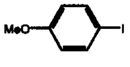
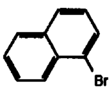
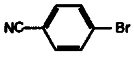
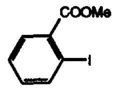
Aryl halide					
Lithium source	*t*-BuLi	*t*-BuLi	*t*-BuLi	*n*-BuLi	PhLi
Exchange temperature °C	-78	-78	-78	-78	-100
Organozinc	**1b**	**1c**	**1d**	**1e**	**1f**
Final product	**4b**	**4c**	**4d**	**4e**	**4f**
Yield (%) of **3**	80	72	73	86	65
Yield (%) of **4** (from **2**)	65	65	67	80	62

Table 1 summarizes the results[8] obtained from a variety of aryl halides. The halogen-lithium exchange (prior to transmetalation with $ZnCl_2$) was carried out at low temperature using *n*-BuLi, *t*-BuLi or PhLi as lithium sources. 2-Iodotoluene, 4-iodoanisole or 1-bromonaphtalene provided an easy access to the corresponding substituted aminoester. The examples of 4-iodobenzonitrile or 2-iodo methylbenzoate in which the benzene ring is bearing a cyano or an ester group sensitive to lithium bases illustrate the potential of this method. More careful conditions were necessary in these cases: by using low temperature and slow addition, the corresponding lithio derivatives could be generated leaving the cyano or methyl ester group unchanged. For the very sensitive methyl ester group, the best results were obtained when PhLi was used as a lithium source at a temperature of -100°C.[9] $ZnCl_2$ was added at this temperature and transmetalation provided a zinc species stable up to room temperature. THF was replaced with DMF and reaction with **2** followed by hydrolysis provided the 2-carboxyphenyl glycine dimethyl ester **4f** in 62% overall yield from **2**.

In summary, the reaction of diarylzincs with a glycine cation equivalent is an efficient method for the preparation of aryl glycine derivatives bearing a functional group.

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