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A concise three-component synthesis of α-amino esters derived from phenylglycine and phenylalanine

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ABSTRACT

α-Amino esters have been synthesized using a straightforward three-component reaction among preformed or in situ-generated aromatic or benzylic organozinc reagents, primary or secondary amines and ethyl glyoxylate. The procedure, which is characterized by its simplicity, allows the concise synthesis of phenylglycine and phenylalanine derivatives.

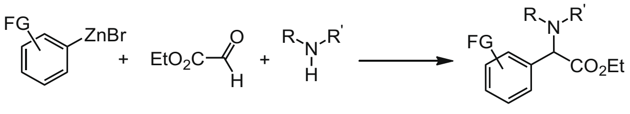
α-Amino acids constitute one of the most important families of natural products and play central roles both as building blocks of proteins and as intermediates in metabolism. They are continuously employed in the elaboration of peptides and as chiral pool in ligand design and multistep synthesis.[1] Amino acids also constitute attractive building blocks in combinatorial chemistry or drug discovery and in the past years there has been an increasing interest in various approaches that access novel non-proteinogenic α-amino acid derivatives.[2]

Although numerous methods allow the efficient preparation of α-amino acid derivatives, only a limited set of examples employing multicomponent procedures have been disclosed to date. For instance, the Petasis three-component reaction[3] among boronic acids, amines and glyoxylic acid has been efficiently employed for the diastereoselective synthesis of pyrrolidine-derived arylglycines[4] or the one-pot sequential Petasis-type α-amino ester formation and palladium-catalyzed cyclization process.[5] However, despite the fact that this method affords a very convenient access to a variety of α-amino acid derivatives, the procedure is featured by rather important reaction times and the impossibility to operate with some electron-deficient arylboronic acids. Furthermore, to the best of our knowledge, there is no mention of the use of functionalized benzylzinc reagents in one-step multicomponent procedures leading to α-amino esters derived from phenylalanine.[6]

Our group has recently developed a multicomponent procedure allowing the efficient formation of a range of α-substituted amines such as diarylmethylamines, 1,2-diarylethylamines or benzylamines starting from preformed or in situ-generated organozinc reagents, amines and aldehydes.[7] Herein, we report preliminary results regarding the use of ethyl glyoxylate as the aldehyde derivative in the procedure to provide an instant access to a variety of α-amino esters.

As a starting point of the study, we imagined to apply the experimental conditions employed in our previous works regarding the multicomponent coupling of arylzinc reagents, aromatic aldehydes and secondary amines to the synthesis of α-amino esters. In this purpose, it was simply envisaged to replace aromatic aldehydes by a non acidic glyoxylic acid equivalent under the form of ethyl glyoxylate.[8] The fate of the expected three-component coupling is depicted in Scheme 1.

Thus, arylzinc reagents (>2 equiv) were preformed in acetonitrile from aryl bromides using zinc dust and cobalt catalysis,[9] and allowed to react with secondary amines (1 equiv) and ethyl glyoxylate (1.3 equiv) at room temperature. Results were generally unsatisfactory with only moderate conversion of the substrates into the expected α-amino esters after a 4 h period. However, a real improvement was obtained by simply heating the solution at 50 °C for several hours.[10] In a second step, we envisaged to extend the procedure to functionalized benzylzinc reagents and noticed from preliminary experiments that under standard conditions, these reagents were clearly more reactive than arylzinc compounds. Furthermore, having shown in a previous work that benzyl bromide can be easily activated in situ using zinc dust in the presence of aldehydes and amines to afford coupling products in excellent yields,[7d] we chose to simplify the process by operating under these Barbier-like conditions. Thus, functionalized benzyl bromides (2.2 equiv) were allowed to react with amines (1 equiv) and ethyl



Scheme 1.

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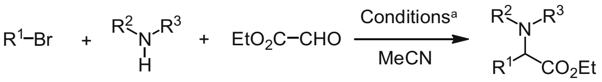
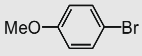
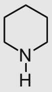
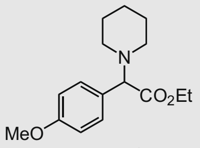
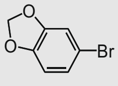
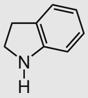
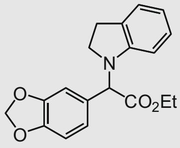
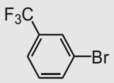
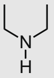
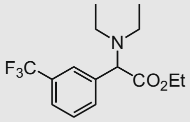
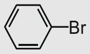
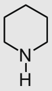
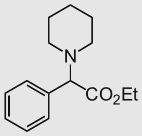
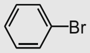
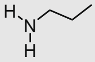
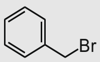
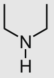
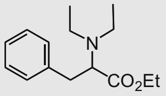
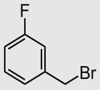
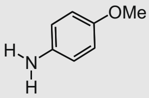
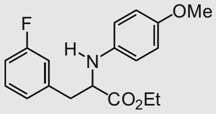
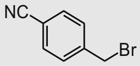
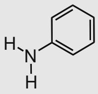
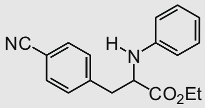
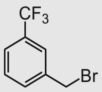
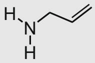
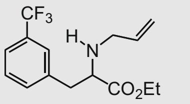
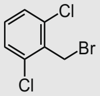
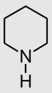
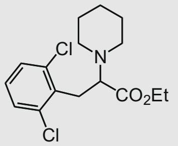
glyoxylate (1.3 equiv) in the presence of zinc dust at room temperature.[11] Results with respect to the use of both aromatic and benzylic bromides in the three-component coupling are presented in Table 1.

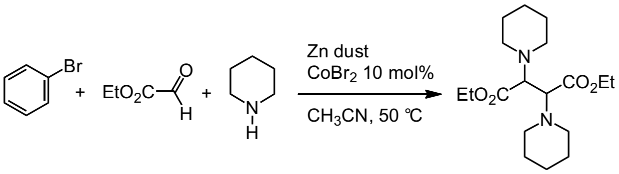
Results range from satisfactory for aryl bromides (entries 1–4) to excellent for benzyl bromides (entries 6–10). It can be noted that the nature of functionalities might be of minor importance for the efficiency of reactions since the three-component coupling

Table 1
Three-component coupling between organic bromides, amines and ethyl glyoxylate



Entry	Organic bromide	Amine	Time (h)	Product	Isolated yield (%)
1			3		66
2			4		55
3			4		50
4			4		60
5			2	–	–
6			1		93
7			1		67
8			1		77
9			1		80
10			1		87

[a] For a functionalized bromobenzene as the halide, the organozinc compound is preformed using Zn dust and $CoBr_2$ as a catalyst. The following three-component coupling is carried out at 50 °C. For a functionalized benzyl bromide as the halide, the substrate is activated in situ using Zn dust only and the reaction is conducted at ambient temperature.



Scheme 2.

performs as well with phenyl bearing both electron-withdrawing and electron-donating groups. The position of the substituent does not influence the course of the reaction and it has to be noted that even hindered benzyl bromides can undergo the coupling (entry 10). Furthermore, the possibility to operate with *p*-anisidine as the amine provides a potential instant access to phenylalanine derivatives by oxidative deprotection of the PMP group (entry 7).[12]

However, the procedure presents some limitations. A major drawback concerns the absence of coupling between primary amines, glyoxylate and aromatic organozinc reagents (entry 5). This is likely due to the formation of an imine, which is not reactive towards arylzinc reagents. This limited reactivity of non-activated imines towards nucleophiles is a well-known issue. Another limitation is the impossibility to realize three-component couplings involving aryl bromides under Barbier-like conditions. Indeed, a bis-amino ester resulting from the C-C reductive coupling of the formal iminium ion under such reductive conditions (presence of Zn dust) is the major product of the reaction (Scheme 2).

In conclusion, this work demonstrates that preformed or in situ-generated organozinc reagents can be very convenient nucleophiles in three-component couplings with ethyl glyoxylate and amines. To the best of our knowledge, this constitutes the first example of the use of organozinc reagents in such a multicomponent procedure leading to α-amino acid derivatives. The development of an enantioselective version of the reaction is ongoing and will be reported in due course.

Acknowledgement

The authors thank Dr. Jacques Royer (Université Paris Descartes) for helpful discussions.

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10. *General procedure starting from aryl bromides*: A dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (40 mL). Cobalt bromide (0.66 g, 3 mmol), zinc bromide (0.68 g, 3 mmol), phenyl bromide (0.32 mL, 3 mmol), zinc dust (6 g, 92 mmol) and trifluoromethanesulfonic acid (0.2 mL) were added to the solution under vigorous stirring (ca. ~500 rpm). After ca. 15 min, the aryl bromide (30 mmol) was added to the solution and as soon as the exothermic reaction had began (ca. 5 min), a water bath at room temperature was used to moderate the temperature of the medium. After 30 min, stirring was stopped and the surrounding solution was taken up using a syringe and transferred into another flask containing the amine (10 mmol) and ethyl glyoxylate (~50% solution in toluene, 2.6 mL, ~13 mmol) in 10 mL acetonitrile. After 5 min at room temperature, the mixture was heated at 50 °C for 3–4 h using an oil bath. The reaction was then quenched with a saturated ammonium chloride solution (150 mL) and the organic products extracted with dichloromethane (2 × 100 mL). After removal of the solvent, a chromatographic purification on neutral alumina using a pentane/dichloromethane mixture as an eluant (80/20→10/90) afforded the pure product.
11. *General procedure starting from benzyl bromides*: A dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (40 mL). Zinc dust (2 g, 30 mmol) and trifluoromethanesulfonic acid (0.2 mL) were added under vigorous stirring (ca. ~500 rpm). After 5 min, the amine (10 mmol), ethyl glyoxylate (~50% solution in toluene, 2.6 mL, ~13 mmol) and the functionalized benzyl bromide (22 mmol) were added to the solution and allowed to react for 1 h at room temperature. The reaction was quenched with a saturated ammonium chloride solution (150 mL) and the organic products extracted with dichloromethane (2 × 100 mL). After removal of the solvent, a chromatographic purification on neutral alumina using a pentane/dichloromethane mixture as an eluant (80/20→10/90) afforded the pure product. Alternatively, the pure α-amino ester could be obtained from the crude oil using an acid-base work-up, as detailled in Ref. 7b.
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