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SHORT COMMUNICATION

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Iron-Catalyzed Three-Component Synthesis of α-Amino Acid Derivatives

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Keywords: Iron / Homogeneous catalysis / Multicomponent reactions / Amino acids

An efficient, iron-catalyzed, three-component synthesis of arylglycines starting from readily available amides, glyoxalates, and arenes or heteroarenes has been developed. This method provides a versatile, atom-economic, and cost-effective route to arylglycines with water as the only byproduct. With carbamates as the amide component, various synthetically useful *N*-protected arylglycine derivatives could be prepared.

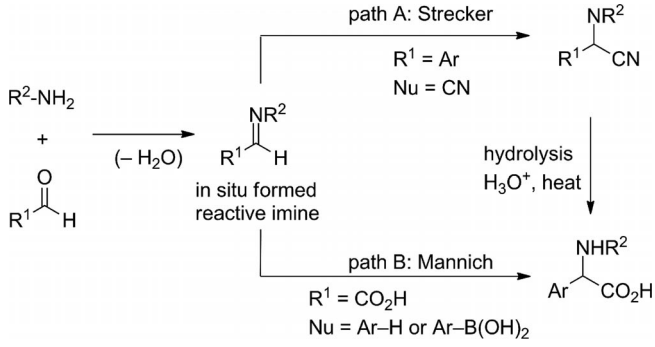
Introduction

α-Amino acids are of outstanding importance in chemistry and biology.[1] They are used in the production of drugs, nutritional supplements, fertilizers, and biodegradable plastics. As a backbone of all proteins, α-amino acids are involved in almost every biological process.[2] With the discovery of protein-based drugs[3] and the recent developments in protein engineering,[4] non-proteinogenic amino acids are becoming increasingly important. Among these non-proteinogenic amino acids, arylglycine derivatives are of particular significance. They are important building blocks for various drugs, such as β-lactam antibiotics[3a] and cardiovascular agents,[3b] and the arylglycine moiety is found in several natural products, such as vancomycin.[3c]

As a result of their importance, various methods for the synthesis of arylglycines have been developed.[5,6] Of these methods, multicomponent reactions based on the in situ formation of reactive imine derivatives, such as the Strecker reaction[7] or Mannich-type reactions,[8–10] provide the most reliable and rapid access to a wide variety of arylglycines (Scheme 1).

Nevertheless, these methods have some decisive drawbacks. The Strecker reaction uses highly toxic cyanide sources, and strongly acidic conditions are required for the hydrolysis of the α-amino nitrile (Scheme 1, path A), whereas the Petasis–(Borono–Mannich) reaction,[9] a very powerful method, uses prefunctionalized and often expensive boronic acid derivatives (Scheme 1, path B).

The direct amino- or amidoalkylation[10] of unfunctionalized arenes represents a more atom-economic[11] approach (Scheme 1, path B). With water as the only byproduct, these reactions also meet the requirements of modern, sustainable organic synthesis.[12] However, these reactions are in general limited to very reactive (hetero)arenes,[6e] and often stoichiometric amounts of strong Lewis or Brønstedt acids have to be employed.[13] Therefore, the scope of these reactions is rather limited, and considerable amounts of waste can be generated in these processes.



Scheme 1. Different synthetic routes to arylglycines.

Results and Discussion

We envisioned that the development of a general, catalytic version of such amino- or amidoalkylations of arenes should be only a matter of choosing a suitable catalyst. Early on we focused on the in situ generation of acylimines from the corresponding amides and aldehydes.[14] Owing to the high electrophilicity of these imine derivatives,[10] a higher reactivity towards less electron-rich arenes and therefore a broader reaction scope could be envisioned. To identify an appropriate catalyst, we selected the reaction between benzamide (**1a**), ethyl glyoxalate (**2a**), and *m*-xylene (**3a**) as a moderately reactive arene.[15] Preliminary studies showed that several Lewis acids could catalyze this reaction with various degrees of efficiency. One of the most efficient catalysts was $FeCl_3$. Only 5 mol-% $FeCl_3$ afforded the desired

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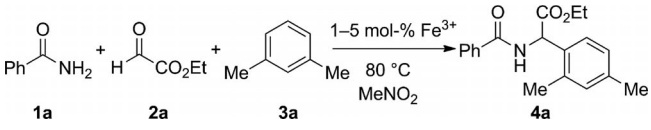
arylglycine derivative **4a** in 86% yield (Table 1, Entry 1). From an economic as well as an ecological perspective, commercially available and cheap iron salts would be ideal catalysts for this transformation.[16,17] Therefore, we tested the catalytic activity of several iron salts. Although $FeCl_3 \cdot 6H_2O$ showed comparable catalytic activity (Entries 2 and 3), $Fe(ClO_4)_3$[18] in general gave higher yields with lower catalyst loadings (Entries 4 and 5). The corresponding Fe^{2+} salts catalyzed the reaction with similar efficiency (Entry 6).[19,20] To rule out a possible "hidden" catalysis by Brønstedt acids,[21a] we conducted the reaction in the presence of the proton scavenger 2,6-di-*tert*-butylpyridine (dbpy)[21b] and observed no significant decrease in catalytic activity (Entry 7). Therefore, we assume an Fe^{3+} species to be the active catalyst.

Table 1. Optimization of the reaction parameters for the synthesis of arylglycine **4a**.



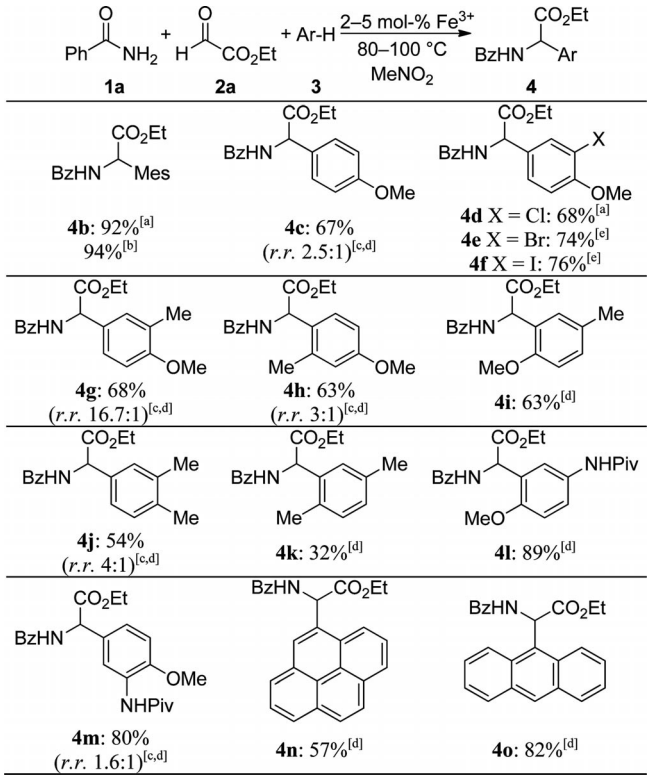
1a 2a 3a 4a

Entry	Catalyst	Yield[a] [%]
1	$FeCl_3$ (5 mol-%)	86
2	$FeCl_3 \cdot 6H_2O$ (5 mol-%)	84
3	$FeCl_3 \cdot 6H_2O$ (2 mol-%)	84
4	$Fe(ClO_4)_3 \cdot xH_2O$ (5 mol-%)	91
5	$Fe(ClO_4)_3 \cdot xH_2O$ (1 mol-%)	91
6	$Fe(ClO_4)_2 \cdot xH_2O$ (2 mol-%)	82
7	$Fe(ClO_4)_3 \cdot xH_2O$ (5 mol-%) + dbpy (10 mol-%)	86

[a] Yields are given for the isolated product. The product was obtained as a 20:1 mixture of regioisomers. Only the major regioisomer is shown.

With the optimized conditions in hand, we investigated the scope of the reaction with various arenes. In most cases the best results were achieved with 5 mol-% $Fe(ClO_4)_3$, but in individual cases similar results could be obtained with lower catalyst loadings or with $FeCl_3 \cdot 6H_2O$ (Table 2). The reactions of benzamide (**1a**) and ethyl glyoxalate (**2a**) with different electron-rich arenes, such as mesitylene or anisole and its derivatives, furnished the arylglycine derivatives **4b**–**4i** in good to excellent yields. In general, the regioselectivity of the reaction is good to excellent; often, only one regioisomer could be detected. In a few cases, for example, with anisole **4c**, the regioselectivity was lower. Unfortunately, the reaction was limited to at least moderately active arenes, such as *o*- or *p*-xylene (products **4j** and **4k**).[15] Toluene or benzene did not react under our reaction conditions.[22] However, this disadvantage proved to be a major advantage for the practicability of our method. Commercially available, technical ethyl glyoxalate, a solution of the polymer form in toluene, could be used directly without prior purification.[23,24] Interestingly, pivaloyl-protected anilines reacted chemoselectively and furnished the arylglycines **4l** and **4m** in 89 and 80% yields, respectively. Fluorescent-labeled proteins have become a powerful bioanalytical tool and are widely applied in life sciences.[25] With fluorescent polycyclic aromatic compounds, such as pyrene or anthracene, the corresponding glycine derivatives **4n** and **4o**, useful building blocks for such labeled proteins, could be synthesized in a very efficient manner.

Table 2. Study of the substrate scope of the reaction with various arenes. Reagents and conditions: **1a** (1.0 equiv.), **2a** (1.2 equiv.), and **3** (3 equiv.) in $MeNO_2$ at 80–100 °C for 24 h. Yields are given for isolated products. *r.r.* = ratio of regioisomers; Bz = benzoyl; Mes = mesityl (2,4,6-trimethylphenyl); Piv = pivaloyl.



[a] 5 mol-% $FeCl_3 \cdot 6H_2O$. [b] 2 mol-% $FeCl_3 \cdot 6H_2O$. [c] Obtained as a mixture of regioisomers; only the major regioisomer shown. [d] 5 mol-% $Fe(ClO_4)_3 \cdot xH_2O$. [e] 2 mol-% $Fe(ClO_4)_3 \cdot xH_2O$.

As shown in Table 3, primary aryl- and alkylamides were suitable substrates for the three-component reaction (**5a**–**f**)[26] and even acid-sensitive functionalities, such as an acrylamide, were well tolerated (**5f**). Performing the reaction with carbamates as the amide component allowed the efficient preparation of various *N*-protected arylglycines (**5g**–**k**), such as **5g** bearing a photolabile protecting group[27] or the Fmoc derivative **5k**.

With heteroaromatics as the nucleophilic component, lower reaction temperatures were necessary to avoid the direct addition of the heteroarene to ethyl glyoxalate.[28] Several electron-rich heterocycles, for example, thiophenes, benzofuran, *N*-tosylpyrrole, or *N*-tosylindole, gave the corresponding glycines **7a**–**7h** in yields of 50–83% (Table 4).[29] However, in general, better yields were obtained with carbamates, such as urethane, as the amide component.

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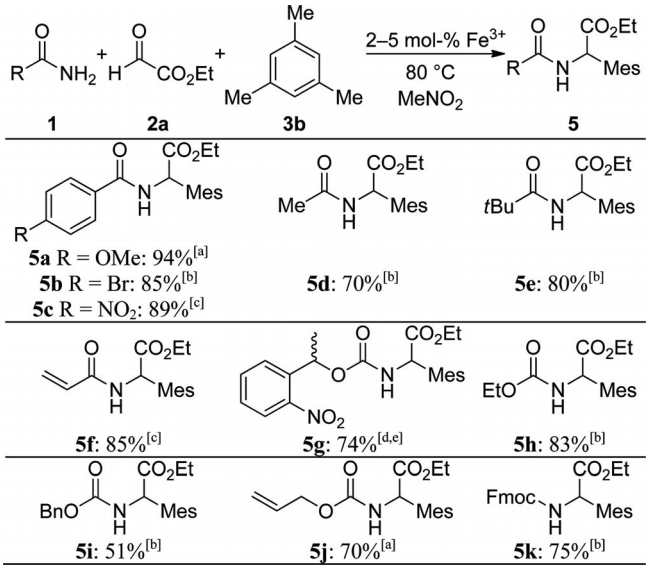
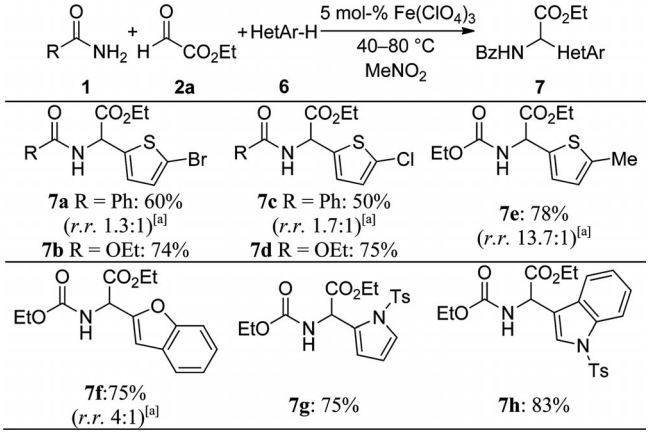
Table 3. Study of the substrate scope of the reaction with a variety of amides and carbamates. Reagents and conditions: **1** (1.0 equiv.), **2a** (1.2 equiv.), and **3b** (3 equiv.) in $MeNO_2$ at 80 °C for 24 h. Yields are given for isolated products. Mes = mesityl (2,4,6-trimethylphenyl); Fmoc = [(9*H*-fluoren-9-yl)methoxy]carbonyl.



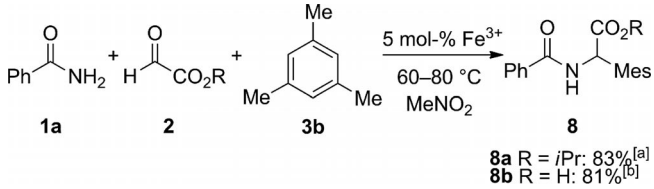
[a] 5 mol-% $FeCl_3·6H_2O$. [b] 2 mol-% $FeCl_3·6H_2O$. [c] 2 mol-% $Fe(ClO_4)_3·xH_2O$. [d] 5 mol-% $Fe(ClO_4)_3·xH_2O$. [e] Obtained as a 1:1 mixture of diastereomers.

Table 4. Study of the substrate scope of the reaction with different heterocycles. Reagents and conditions: **1** (1.0 equiv.), **2a** (1.2 equiv.), **6** (3 equiv.), and $Fe(ClO_4)_3·xH_2O$ (5 mol-%) in $MeNO_2$ at 40–80 °C for 24–48 h. Yields are given for isolated products. *r.r.* = ratio of regioisomers; Ts = tosyl.

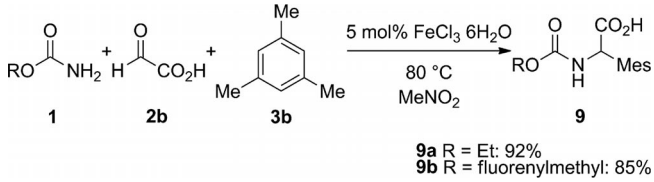


[a] Obtained as a mixture of regioisomers; only the major regioisomer is shown.

The reaction of mesitylene and benzamide with isopropyl 2-oxoacetate provided product **8a** in 83% yield (Scheme 2). This method proved to be very robust and insensitive towards air or moisture. Indeed, the reaction of mesitylene and benzamide with an aqueous solution of glyoxylic acid directly furnished the free acid **8b**. These free acids, bearing different *N*-protecting groups, would be ideal starting materials for peptide synthesis. Therefore, we investigated the reaction of glyoxylic acid with different carbamates (Scheme 3). The reaction with urethane gave the *N*-protected glycine **9a** in 92% yield, whereas the reaction with 9-fluorenylmethyl carbamate provided the Fmoc-protected arylglycine **9b**, an ideal starting material for solid-phase peptide synthesis, in 85% yield.



Scheme 2. Study of the substrate scope of the reaction with glyoxylic acid derivatives. Reagents and conditions: **1a** (1.0 equiv.), **2** (1.2 equiv.), and **3b** (3 equiv.) in $MeNO_2$ at 60–80 °C for 24 h. Yields are given for isolated products. [a] 5 mol-% $Fe(ClO_4)_3·xH_2O$. [b] 5 mol-% $FeCl_3·6H_2O$. Mes = mesityl (2,4,6-trimethylphenyl).



Scheme 3. Three-component synthesis of *N*-protected arylglycines. Reagents and conditions: **1a** (1.0 equiv.), **2b** (1.2 equiv.), **3b** (3 equiv.), and $FeCl_3·6H_2O$ (5 mol-%) in $MeNO_2$ at 80 °C for 24 h. Yields are given for isolated products. Mes = mesityl (2,4,6-trimethylphenyl).

Concerning the mechanism of this reaction, we assume the in situ formation of a reactive acylimine species followed by an electrophilic aromatic substitution. However, further studies are necessary to clarify the exact mechanism.

Conclusions

By employing cheap iron(III) salts, we have developed an efficient and versatile three-component synthesis of arylglycines starting from readily available amides, glyoxalates, and arenes or heteroarenes. This new method has a very broad scope and, because it is not necessary to exclude air or moisture, very simple to perform. By using carbamates as the amide component, various synthetically very useful *N*-protected arylglycine derivatives could be prepared. With water as the only byproduct, this method provides a sustainable route to arylglycines. Further applications as well as the development of an enantioselective variant of this method are currently being investigated in our laboratory.

Experimental Section

General Procedure for Reactions with Ethyl Glyoxalate: A 10 mL screw-cap vial was charged with the amide (1.0 equiv.), iron salt (1–5 mol-%), and $MeNO_2$ (4 mL/mmol amide). Ethyl glyoxylate (1.2 equiv.) and the aromatic compound (3.0 equiv.) were added under vigorous stirring. The reaction mixture was heated to 40–

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100 °C and stirred at this temperature for 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short plug of Celite and silica gel. The plug was rinsed with additional EtOAc. The combined filtrates were concentrated under reduced pressure. Purification of the crude residue by column chromatography (cyclohexane/EtOAc) afforded the analytically pure product.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, analytical, and spectroscopic data (^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR spectra) for all new compounds.

Acknowledgments

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[15] For an excellent overview of the nucleophilicity of arenes as well as the reactivity of various other molecules, we recommend the database of Prof. H. Mayr (LMU Munich): http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/.

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[18] For details of the exact water content of $Fe(ClO_4)_3$, see the Supporting Information.

[19] We cannot rule out the oxidation of Fe^{2+} to Fe^{3+}. Indeed, a rapid color change from green to yellow indicates the formation of Fe^{3+} species under our reaction conditions.

[20] No reaction takes place in the absence of an iron catalyst. During this study we focused on the cheapest commercially available Fe^{+3} salts, $FeCl_3$, $FeCl_3{\cdot}6H_2O$ (<0.02 €/g) and $Fe(ClO_4)_3{\cdot}xH_2O$ (0.23 €/g). Further studies with noncommercially available or more expensive Fe^{+3} salts will be reported in due course [compare $Fe(OTf)_3$: 38 €/g]. Prices obtained from Alfa Aesar on 08/02/2013.

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[22] The reaction with phenol gives the glycine derivative in <10% yield as a result of competitive oxidative coupling reactions.

[23] All the reactions shown were performed with the technical, unpurified polymer form of ethyl glyoxylate.

[24] Monomeric ethyl glyoxalate can be obtained by pyrolysis and purification by vacuum distillation. The monomeric form is

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very reactive and either polymerizes rapidly or reacts with water to form the hydrate. Therefore, monomeric ethyl glyoxalate has to be prepared just prior to use and handled under anhydrous conditions, see: T. Urushima, Y. Yasui, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 2966–2969, and references cited therein.
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[29] Reactions with indoles not bearing electron-withdrawing *N*-protecting groups or other very reactive heteroarenes led to the exclusive formation of bis(heteroaryl)methanes.

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