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One-pot synthesis of aryl glycines and other unnatural amino acids from serine derivatives

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Abstract—A mild and highly efficient one-pot synthesis of aryl glycines from easily available serine derivatives is described. This methodology is also applied to the synthesis of other uncommon amino acids.

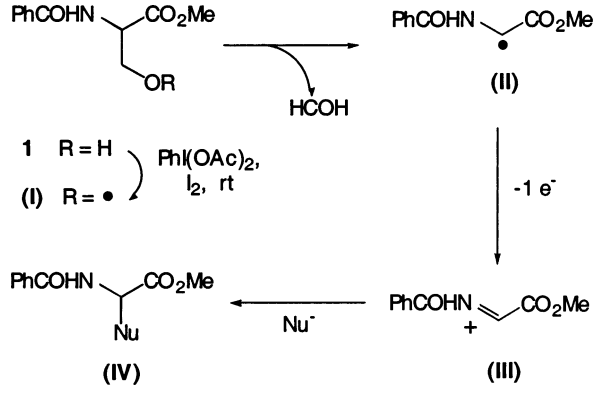
The synthesis of non-proteinogenic amino acids is of great interest, due to their importance as building blocks in the synthesis of alkaloids, peptides and other compounds with therapeutic utility.[1] For instance, by incorporating unnatural amino acids into biologically active peptides and proteins, their activity, stability, bioavailability and binding specificity may be improved.[2]

Among the non-proteinogenic amino acids, the aryl glycines constitute a particularly important class. These amino acids are components of the glycopeptide antibiotics, such as vancomycin and teicoplanin,[3] and the β-lactam antibiotics nocardicins.[4] They are also found in the marine alkaloids dihydrohamacanthins and dragmacidins, which present potent and selective cytotoxic activity.[5] Besides, it was recently discovered that some aryl glycines could selectively modulate the activity of metabotropic glutamate receptors (mGluRs),[6] and are used to develop new drugs for the treatment of various neurodegenerative diseases. This range of potent biological activities has fuelled intense research to obtain new aryl glycines.[7] Until now, the most widely used method to obtain these amino acids is the Strecker reaction,[8] which requires toxic cyanide reagents. We report here on an alternative methodology which uses non-toxic reagents and inexpensive serine esters as precursors and takes place under very mild conditions.

This method is based on the β-fragmentation of a primary alkoxyl radical (I) (Scheme 1), generated on treatment of the serine derivative **1** with (diacetoxyiodo)benzene (DIB) and iodine.[9] After the scission, the resulting radical (II) is oxidized by excess reagent to a cationic glycine equivalent (III),[10] which can be trapped by nucleophiles to afford new amino acids (IV).

When the serine derivative **1** was treated with DIB and iodine at room temperature and under sunlight irradiation for 2 h, the acetoxy derivative **2** (Scheme 2) was obtained in excellent yield (94%). This acetate results from trapping of the glycine cationic intermediate by acetate ions from the reagent (DIB). It is remarkable that some side reactions which usually compete with the β-fragmentation of primary alkoxyl radicals (such as oxidation),[9] were not observed here.

The acetate **2** is a convenient precursor of other non-proteinogenic amino acids (Table 1, method A). In fact,



Scheme 1. Synthesis of unnatural amino acids from serine derivatives.

Keywords: aryl glycines; unnatural amino acids; alkoxyl radicals; fragmentation; nucleophilic addition; *N*-acyliminium ions.

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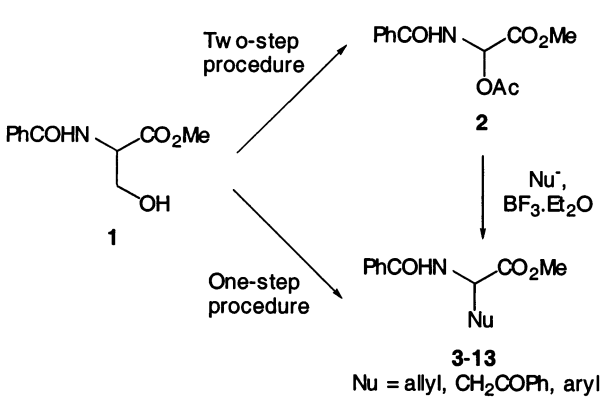
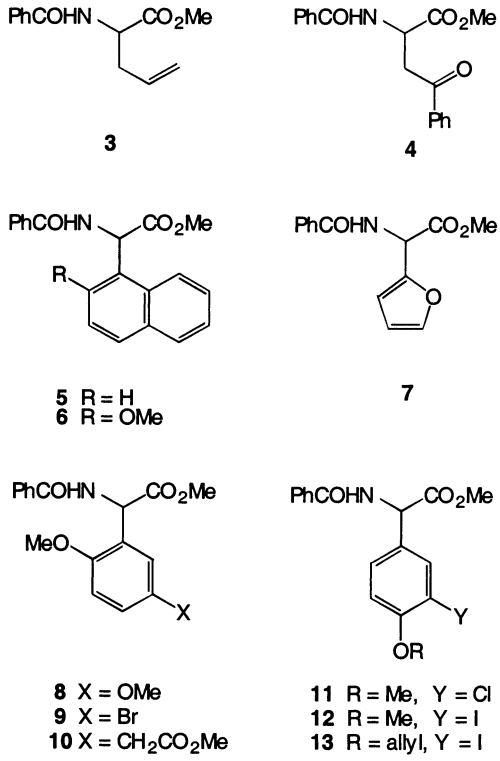


Scheme 2. One-pot versus two-step synthesis of unnatural amino acids.

when it was treated with allyltrimethylsilane and boron trifluoride etherate in dichloromethane (entry 1), the allyl derivative **3** (Scheme 3) was obtained in good yield (70%, 66% overall yield from **1**). Allyl glycines are versatile building blocks in the synthesis of more complicated amino acids and alkaloids;[11] besides, some of them show distinct antibiotic activity and could be applied as enzyme inhibitors.[12]

When the acetate **2** was treated with phenyl (trimethylsilyloxy)ethylene and $BF_3{\cdot}Et_2O$, yielding the γ-oxo-amino acid **4** (Scheme 3) in 67% yield (63% global yield from **1**). This amino acid is an analog of the homophenylalanines, which have been used in the synthesis of enzymes with angiotensin converting enzyme activity.[13] The same method could be applied to obtain other γ-oxo-α-amino acids, since some of them



Scheme 3. Aryl glycines and other non-proteinogenic amino acids.

are components of antifungal, antibiotic and anti-inflammatory drugs.[14]

The reaction of **2** with a variety of aromatic nucleophiles, such as naphthalene, methoxynaphthalene,

Table 1. Synthesis of aryl glycines and other non-proteinogenic amino acids

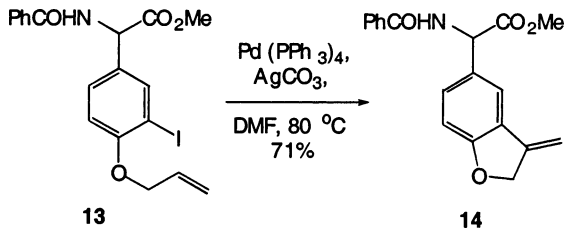
Entry	Nucleophile (equiv.)[a]	**Method A**. Products (%)[b]	**Method B**. Products (%)[c]
1	Allyltrimethylsilane (5)	**3** (66)	**3** (35), **2** (52)[d]
2	Ph-CH(OTMS)=CH_2 (5)	**4** (63)	**4** (30), **2** (55)[d]
3	Naphthalene (10)	**5** (65)	**5** (63)
4	2-Methoxynaphthalene (10)	**6** (90)	**6** (95)
5	Furan (10)	**7** (80)	**7** (79)
6	1,4-Dimethoxybenzene (10)	**8** (84)	**8** (91)
7	4-Bromoanisole (10)	**9** (71)	**9** (72)
8	Methyl (4-methoxy)phenylacetate (10)	**10** (76)	**10** (82)
9	2-Chloroanisole (10)	**11** (84)	**11** (90)
10	2-Iodoanisole (10)	**12** (86)	**12** (91)
11	2-Iodo-1-allyloxybenzene (10)	**13** (82)	**13** (86)

[a] All the nucleophiles were commercial products or were obtained therefrom by methylation or allylation. In the case of the aromatic nucleophiles, most of the unreacted reagent was recovered, being easily separated from the desired products.

[b] **Method A (two-step procedure)**: The serine derivative **1** (1 mmol) in dry dichloromethane (15 ml) was treated with DIB (2.5 mmol) and iodine (1 mmol) and stirred at room temperature and under nitrogen for 2.5 h. Then it was poured into aqueous 10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. The reaction mixture was purified by chromatography and the acetate **2** was isolated. The latter was dissolved in dry dichloromethane and cooled to 0°C. Then $BF_3{\cdot}Et_2O$ (2 equiv.) and an excess of the nucleophile (Table 1) were added. The reaction was allowed to reach rt and stirred for 4 h. Afterwards, it was poured into aq. $NaHCO_3$ and extracted with CH_2Cl_2. The yields are given for products purified by chromatography on silica gel. All new compounds were fully characterized by ^1H and ^{13}C NMR, IR, MS-HRMS and elemental analysis.

[c] **Method B (one-pot procedure)**: The serine derivative **1** (1 mmol) in dry dichloromethane (15 ml) was treated with DIB (2.5 mmol) and iodine (1 mmol) and stirred at room temperature and under nitrogen for 2.5 h. After that time, it was cooled to 0°C and $BF_3{\cdot}Et_2O$ (2 equiv.) and an excess of the nucleophile were added. The reaction was allowed to reach rt and stirred for 4 h. Then it was poured into aqueous $NaHCO_3$–10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. The yields are given for products purified by chromatography on silica gel.

[d] Different conditions and amounts of reagents were tried. When the reaction was forced to completion, complex mixtures of products were formed, and the overall yield of products **3** and **4** did not improve.



Scheme 4. Synthesis of a methylenedihydrobenzofuran glycine.

furan, anisol derivatives, etc. was also studied (Table 1, entries 3–11), yielding the aryl glycines **5**–**13** (Scheme 3) in good to excellent yields (69–96%, 65–90% overall yield from **1**).

We reasoned that this two-step sequence could be shortened to a one-pot reaction by adding the Lewis acid and the nucleophile immediately after the fragmentation step. The results of the one-pot reaction are shown in Table 1 (method B).

In the case of the allyl glycine **3** (entry 1) and the 4-oxohomophenylalanine **4** (entry 2), the one-pot reaction was clearly inferior to the two-step procedure. Different conditions and amounts of reagents were tried, with similar results. However, in the case of the aryl glycines **5**–**13** (entries 3–11), the one-pot method was comparable or superior to the two-step procedure.

Thus, using naphthalene (entry 3) and 2-methoxynaphthalene (entry 4), the desired naphthyl glycines **5** and **6** were obtained. These interesting amino acids could replace phenylglycine in peptidomimetics and modified proteins. The reaction with furan (entry 5) also proceeded in good yields to afford compound **7**. To our knowledge, this unnatural amino acid has not been previously obtained.

The use of 4-substituted-anisol nucleophiles (entries 6–8) afforded the alkoxyphenylglycines **8**–**10** in good to excellent yields. The introduction of a halogenated aromatic ring as in compound **9** is remarkable since the haloaryls can be used in sp^2–sp^2 reactions to introduce other aryl, alkynyl or alkyl groups.[15] On the other hand, the methyl acetate chain present in amino acid **10** ($X = CH_2CO_2Me$) could be used to form a link with other amino acids in macrocyclic or double-chain peptidomimetics.

The formation of 3-halo-4-alkoxyphenylglycines was also studied (entries 9–11), since 3-chloro-4-hydroxyphenylglycines are present in several products with pharmacological activity, such as the promising antibiotic ramoplanin.[16]

The introduction of the aryl groups took place with total regioselectivity, affording the desired 3-halophenylglycines **11**–**13** in excellent yields. The allyl group in derivative **13** could be easily removed,[17] releasing the 3-halo-4-hydroxyphenylglycine.

In this stage, we decided to study the formation of the hitherto unknown benzofuran glycines (Scheme 4).[15e] Thus, the allyl derivative **13** was treated with a Pd(0) catalyst, affording the methylenedihydrobenzofuran derivative **14** in 71% yield. By using other substituted allyl groups, different 3-alkyl chains could be introduced, and used to link with other amino acids in peptidomimetics.

In summary, a one-step procedure for the synthesis of aryl glycines and other non-proteinogenic amino acids has been developed, which gives good to excellent yields for the aryl glycines. In the case of the allyl glycine **4** and the γ-oxoderivative **5**, an alternative two-step procedure gave good results. The simplicity, mildness and versatility of this methodology, coupled with its low toxicity, make it ideal for the synthesis of new amino acids. The study of the biological activity of the new aryl glycines is underway and will be reported in due course.

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