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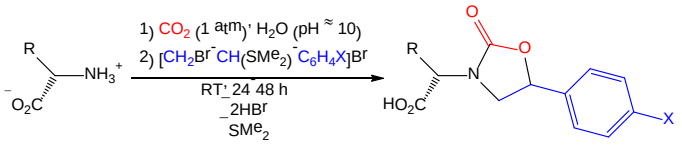
Trapping Carbamates of α-Amino Acids: One-Pot and Catalyst-Free Synthesis of 5-Aryl-2-Oxazolidinonyl Derivatives

ABSTRACT. CARBONATION OF NATURAL Α-AMINO ACIDS IN WATER AND SUBSEQUENT CYCLIZATION WITH(2-bromo-1-arylethyl)dimethylsulfonium bromidesLED TOA FAMILY OF 2-oxazolidinonyl derivatives in ca. 40-80% yields.DEPROTONATION OF SOME OF THE PRODUCTS AFFORDED THE CORRESPONDING WATER-SOLUBLECARBOXYLATES, IN 60-95% YIELDS. ANALOGOUS CONJUGATION OF THE 2-OXAZOLIDINONE SKELETON WITH AMINO ACIDS WAS PREVIOUSLY REALIZED BY COMPLICATED ROUTES, WHEREBY THE AMINO ACID CORE IS BUILT STEPWISE.

2-Oxazolidinones constitute a valuable family of five-membered cyclic carbamates,which exhibitinteresting biological properties and are employed as important key intermediates in organic synthesis.[i] Several strategies involving CO_2-fixation have been extensively explored with the aim of developingenvironmentally benignsynthetic routes to 2-oxazolidinones. In particular, unsaturated amines,[ii]halo-amines,[iii]aziridines[ia,iv] and amino-alcohols[v] have been investigated for their direct coupling with carbon dioxide, and also different three-component reaction systems are successful.[vi]In general, a catalyst is needed to promote the CO_2activation, and in addition high temperature and/or pressurized conditions might be required to achieve satisfying conversions. On the other hand,α-amino acids are ubiquitous natural compounds with several appealing properties, e.g. their water solubility, relativenon-toxicity, structural diversity provided by the side chain, and the presence of a chiral centre.Therefore, their use as precursors of valued-added chemicals has witnessed a highly growing interest.[vii]In particular, "tailor-made" α-amino acids have been regarded as essential components of modern medicinal chemistry, and indeed a significant fraction of small molecular drugs contain amino-acidic residues.[viii] However, despite the reactivity of α-amino acids has been the subject of a longtime investigation, there is still space for the extremely worthydiscovery of new reaction types.[ix]It is well established that amino acids (*aa*NH_2) in aqueous solutions reversibly and easily add carbon dioxide to generate the corresponding ammonium carbamates, Equation 1.[x]This reactivity is involved in various biological phenomena and,besides,has been extensively exploited for the development of CO_2-sequestration/storagetechnologies.[xi]

$$2\ aaNH_2 + CO_2 \acute{Y}\ [aaNH_3][aaNHCO_2] \qquad (1)$$

Amino acid carbamateshave been utilizedfor synthetic purposes, and in particular their incorporation as a robust function in the molecular structure of biologically active compounds is a promising approach.[xii]Herein, we report the use of a range of natural α-amino acids, including various moleculesbearing a hetero-function in the side chain, for the preparation of oxazolidinonyl derivatives through an unprecedented three-component reaction with carbon dioxide and a convenient C_2-synthon. Carbonation of the α-amino acids was conductedin water at ambient temperature and atmospheric pressureof CO_2, using the simple and safe balloon technique;potassium carbonate was used as a base to fix the pH within the optimal range of 9.9-10.5, in accordance with the literature.[x,xiii] Then,the addition of (2-bromo-1-arylethyl)dimethylsulfonium bromide salts resulted in the regiospecificcyclization to give 5-aryl-2-oxazolidinones (Scheme 1). Note that suchversatile sulfonium reagents[xiv] are easily accessible in a multigram scale.[xv]Products **1-4** were extracted from the aqueous phase with ethyl acetate, and finally isolated as solid/oily materials in moderate to good yields upon removal of the solvent under vacuum, without needing any purification step. In general, the amino acid was used in approximately 3:1 molar ratio with respect to the sulfonium salt. The use of a larger excess (ca. 10 equivalents) allowed to significantly increase the yields of**1-Pha, 1-Val**and**1-Try**(up to 73%); compounds**2-Try** and **3-Try** were directly obtained by this method in 55-59% yields. The residual aqueous phase containing the larger excess of L-phenylalanine was recycled twice by further additionof the sulfonium salt, affording additional amounts of the product**1-PhA** (see ESI for details).



R	*X*	
H	H	**1-Gly**
Me	H	**1-Ala**
CH_2CHMe_2	H	**1-Leu**
CH_2CH_2SMe	H	**1-Met**
CH_2Ph	H	**1-Pha**
$CH(Me)CH_2Me$	H	**1-Iso**
$CHMe_2$	H	**1-Val**
CH(OH)Me	H	**1-Thr**
$CH_2(C_8H_5N)$	H	**1-Try**
H	Me	**2-Gly**
Me	Me	**2-Ala**
CH_2CHMe_2	Me	**2-Leu**
CH_2CH_2SMe	Me	**2-Met**
$CH_2(C_8H_5N)$	Me	**2-Try**
H	Cl	**3-Gly**
Me	Cl	**3-Ala**
CH_2CHMe_2	Cl	**3-Leu**
CH_2CH_2SMe	Cl	**3-Met**
$CH_2(C_8H_5N)$	Cl	**3-Try**

H	F	**4-Gly**
CH_3	F	**4-Ala**
CH_2CHMe_2	F	**4-Leu**
CH_2CH_2SMe	F	**4-Met**

Scheme 1. Synthesis of oxazolidinonyl derivatives of naturalα-amino acids.

Compounds**1-4**are insoluble in water, and well soluble in acetone and methanol. They were characterized by analytical and spectroscopic methods.The IR spectra (in the solid state) display one intense absorption at ca. 1740 cm^{-1}, ascribable to the carbamato function, and another one in the range 1683-1705 cm^{-1}, related to the carboxylic acid group. In general, the NMR spectra consist of two sets of resonances in ca. 1:1 ratio, except for the glycine derivatives existing as single species (**1-Gly**, **2-Gly**, **3-Gly**, **4-Gly**). The two sets are related to the diastereomeric forms *SR* and *SS*, corresponding to the two different spatial orientations of the aryl unit bonded to the quaternary ring carbon. Salient NMR features (acetone-d_6 solutions) are represented by the resonances of the carbons belonging to the five-membered ring, occurringaround 76 ppm (CH), 50 ppm (CH_2) and 159 ppm (C=O), i.e. close to the values available in the literature for other 5-aryl-2-oxazolidinones. The ^{13}C NMR signal accounting for the carboxylic acid was detected in the range 169.4-173.0 ppm.
The molecular structures of **1-Gly**, **2-Leu**, **3-Gly**, **3-Ala** and **3-Leu** were confirmed by X-ray diffraction studies. A view of the structure of **3-Ala** is given in Figure 1, and relevant bonding parameters are listed in the caption. The remaining structures and related bonding parameters (including H-bonds) are shown in the ESI. Coherently with the NMR features, a 1:1 mixture of the two *R* and *S* configurations on C(1) is present within the unit cells. The C(4) centre of **2-Leu**, **3-Ala** and **3-Leu** displays the *S* configuration as in the parent amino acid.

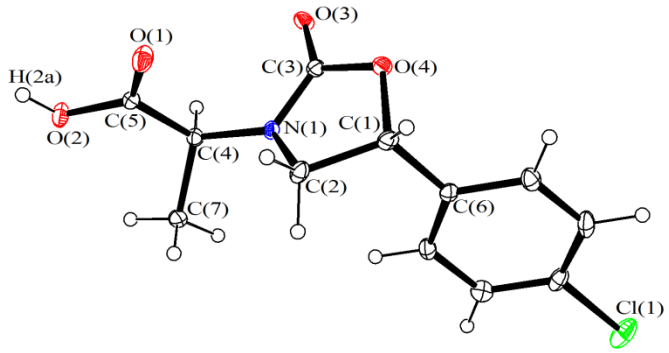
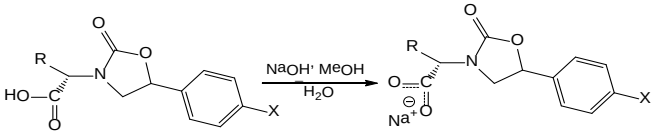


Figure 1. ORTEP drawing of **3-Ala**, with key atoms labelled. Displacement ellipsoids are at 30% probability level. Selected bond lengths (Å) and angles (deg): C(1)-C(2) 1.538(3), N(1)-C(2) 1.456(2), N(1)-C(3) 1.343(2), C(3)-O(3) 1.216(2), C(3)-O(4) 1.347(2), C(1)-O(4) 1.468(2), C(4)-N(1) 1.452(2), C(4)-C(5) 1.519(2), C(5)-O(1) 1.198(2), C(5)-O(2) 1.327(2), O(1)-C(5)-O(2) 124.58(17), O(1)-C(5)-C(4) 124.43(16), O(2)-C(5)-C(4) 110.97(15), C(5)-C(4)-N(1) 110.30(14), C(4)-N(1)-C(3) 121.14(14), C(4)-N(1)-C(2) 124.38(14), C(3)-N(1)-C(2) 111.06(15), N(1)-C(3)-O(4) 120.93(16), C(3)-O(4)-C(1) 109.00(13), N(1)-C(2)-C(1) 100.79(13), C(2)-C(1)-O(4) 103.13(13).

Compounds **1-4**constitute a substantially novel class of five-membered cyclic carbamates, generated through the incorporation in the cycle of the original amine function belonging to pre-existing natural α-amino acids.To the best of our knowledge, only the simplest member of the series reported in Scheme 1, i.e. **1-Gly**, was previously prepared, using a three-step procedurefrom 2-amino-1-phenylethanol.[xvi] In general, the N-glycination of the 2-oxazolidinone skeleton has been achieved through thestepwise modification of the latter, and thus not employingthe amino acid as a convenient building block.[xvii]The same concept was applied to the construction of alanine, {(CO_2H)CH(Me)N},[xviii] and methionine, {(CO_2H)CH(CH_2CH_2SMe)N},[xix] fragments on either 4-phenyl-2-oxazolidinone or 4,5-diphenyl-2-oxazolidinone rings: in these cases, even more elaborated multi-step protocolsare required, making use of varioushazardous chemicals including toxic metal based ones.
In order to obtain water soluble derivatives, the deprotonation of a series of compounds belonging to the series **1-4**was performed in methanol solution with one equivalent of sodium hydroxide. The respective sodium carboxylateswere obtained as hygroscopic microcrystalline solids in good to excellent yields (Scheme 2). They are well soluble in water and methanol and not soluble in acetone, except **Na-1-Try** and **Na-3-Try** which are slightly soluble in acetone.



R	*X*	
Me	H	**Na-1-Ala**
CH_2CH_2SMe	H	**Na-1-Met**
CH_2Ph	H	**Na-1-Pha**
$CH(Me)CH_2Me$	H	**Na-1-Iso**
$CH_2(C_8H_5N)$	H	**Na-1-Try**
H	Me	**Na-2-Gly**
$CH_2(C_8H_5N)$	Cl	**Na-3-Try**
CH_2CH_2SMe	F	**Na-4-Met**

Scheme 2. Synthesis of sodium carboxylates of oxazolidinonyl derivatives.

The conversion of the carboxylic acid function into carboxylate is evident based on the IR (solid state) and NMR spectra (CD_3OD). In particular, the IR band due to the carboxylate is foundat1591-1618 cm^{-1}, while the related ^{13}C NMRresonance is significantly downfield shifted, compared to the corresponding signal in the parent carboxylic acids (e.g. at 177.1 and 177.0 ppm for **Na-1Met**, 173.5 ppm for **1-Met**). Compounds **1-Pha** and **1-Met** were quantitatively recovered from their ionic counterparts **Na-1-Pha** and **Na-1-Met** upon HCl addition in water solution and subsequent extraction with ethyl acetate.

Conclusions

The straightforwardconjugation of two molecular structures of large interest in organic chemistry, i.e. the 2-oxazolidinone ring on the one hand and naturally occurringα-amino acids on the other hand, has been achieved through the construction of the five-membered cycle on the original amino group. The synthetic strategy is simple, general to afford aryl-substituted derivatives, and with a good degree of sustainability, in that it is based on the catalyst-free one-pot reaction in water between easily available precursors. The latter includecarbon dioxide, which is activated atatmospheric pressure. The efficient extraction of the products from the aqueous reaction medium renders further purification procedures unnecessary, and, as demonstrated in one model case, allows the recycle of the employed excess of amino acid. The subsequent deprotonation reaction enables water solubility, thus taking full advantage of the inclusion of the natural fragment. Remarkably, few analogous compounds were previously obtained by means of elaborated and non-green synthetic routes, based on theopposite approach as that described here, i.e. the stepwise growing of the amino acid like fragmentusually on a pre-existing oxazolidinone ring.

Conflicts of interest

There are no conflicts to declare.

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