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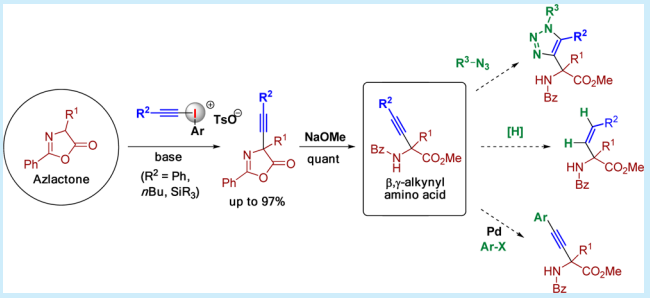
Alkynyliodonium Salt Mediated Alkynylation of Azlactones: Fast Access to C^{α}-Tetrasubstituted α-Amino Acid Derivatives

Peter Finkbeiner, Nicole M. Weckenmann, and Boris J. Nachtsheim*

Institut für Organische Chemie, Eberhard Karls Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

Supporting Information

ABSTRACT: An efficient electrophilic alkynylation of azlactones (oxazol-5(4*H*)-ones) is developed using alkynyl(phenyl)iodonium salts as the electrophilic alkyne source. After remarkably short reaction times, the desired alkyne functionalized azlactones are obtained in 60−97% yield and can be transformed easily into a variety of quaternary α-amino acid derivatives.



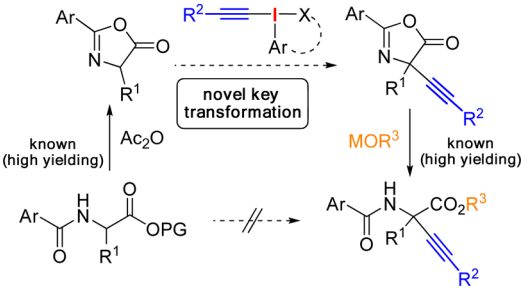
C^{α}-Tetrasubstituted α-amino acids (CTAs) are privileged building blocks for short peptides and peptidomimetics. The additional C^{α}-substituent reduces the conformational space of the peptide backbone and rigidifies its three-dimensional structure.[1] In addition, C^{α}-tetrasubstitution increases the peptides lipophilicity which has positive effects on its pharmacokinetics. In recent years, a variety of methods have been reported for the synthesis of CTAs by electrophilic additions of alkyl-, benzyl-, allyl- or propargyl electrophiles to nucleophilic cyclic or acyclic C^{α}-trisubstituted amino acid synthons.[2] Cyclic quaternary amino acids can be prepared as efficiently.[3]

However, the synthesis of quaternary β,γ-alkynyl α-amino acids is still a challenging synthetic task even though alkyne functionalized amino acids turned out to be useful reagents for the site specific functionalization of proteins.[4,5] In addition, triple bonds are easy to convert into a variety of other functional groups which renders them versatile synthons. Known methodologies for the synthesis of β,γ-alkynyl α-amino acids are based on the functionalization of α-alkynyl glycinate anions,[6] the addition of nucleophilic acetylene synthons to ketimines[7] or using β-lactams derived from chromium carben complexes.[8]

To the best of our knowledge there is only one procedure known so far for the synthesis of quaternary β,γ-alkynyl α-amino acids via an electrophilic alkyne source. In a single example, Waser and co-workers described the direct alkynylation of 2-nitro-3-phenylpropanoate using the hypervalent iodine reagent TMS-ethynyl-1,2-benziodoxol-3(1*H*)-one (TMS-EBX) as electrophilic alkyne source. Even though the method itself is very elegant, its major obstacle is the tedious conversion of the α-nitro ester into the corresponding *N*-acyl protected amino acid by a two-step sequence in which the last step is a SmI_2-mediated reduction of the corresponding hydroxylamine.[9]

In this communication we want to describe a fast and efficient access to β,γ-alkynyl α-amino acids via the direct alkynylation of azlactones. Azlactones are versatile CTA-precursors which are easy accessible from α-amino acids via cyclodehydration and, after α-functionalization, can be converted back into the open chained form as efficient through base-induced ring-opening (Scheme 1).[10−12] To the best of our knowledge there is no direct alkynylation of azlactones known so far.[13]

Scheme 1. Novel Route to β,γ-Alkynyl α-Amino Acids



As stable and easy to handle electrophilic acetylene synthons we chose to start our investigations with a variety of alkynyl(phenyl)iodonium salts **1a**−**1c** and alkynyl-1,2-benziodoxol-3-(1*H*)-ones **2a**−**2c** (Figure 1).[14−17]

In an initial experiment, the leucine-derived azlactone **3a** was treated with alkynyl(phenyl)iodonium tosylate **1a** under basic conditions. To our great delight we observed the formation of the desired C^{α}-quaternary azlactone **4** in 84% yield (Table 1 − entry 1).

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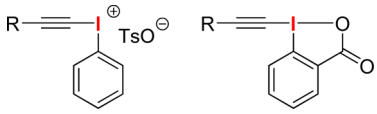
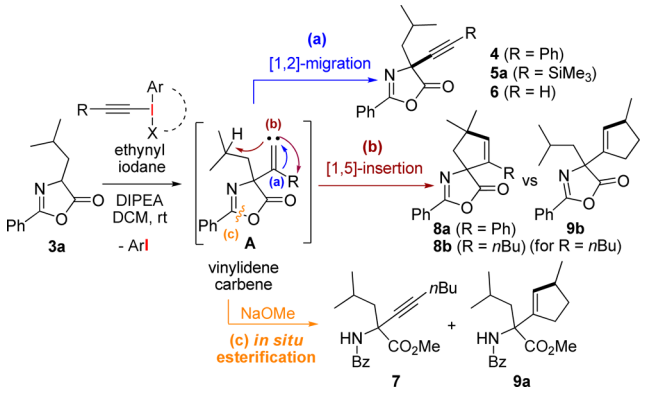


Figure 1. Structures of ethynyl(phenyl)iodonium salts (**1a**–**c**) and ethynylbenziodoxolones (**2a**–**c**).

Table 1. Reactivity of Azlactone 3a toward Different Alkynyl(aryl)iodanes and Ethynylbenziodoxolones



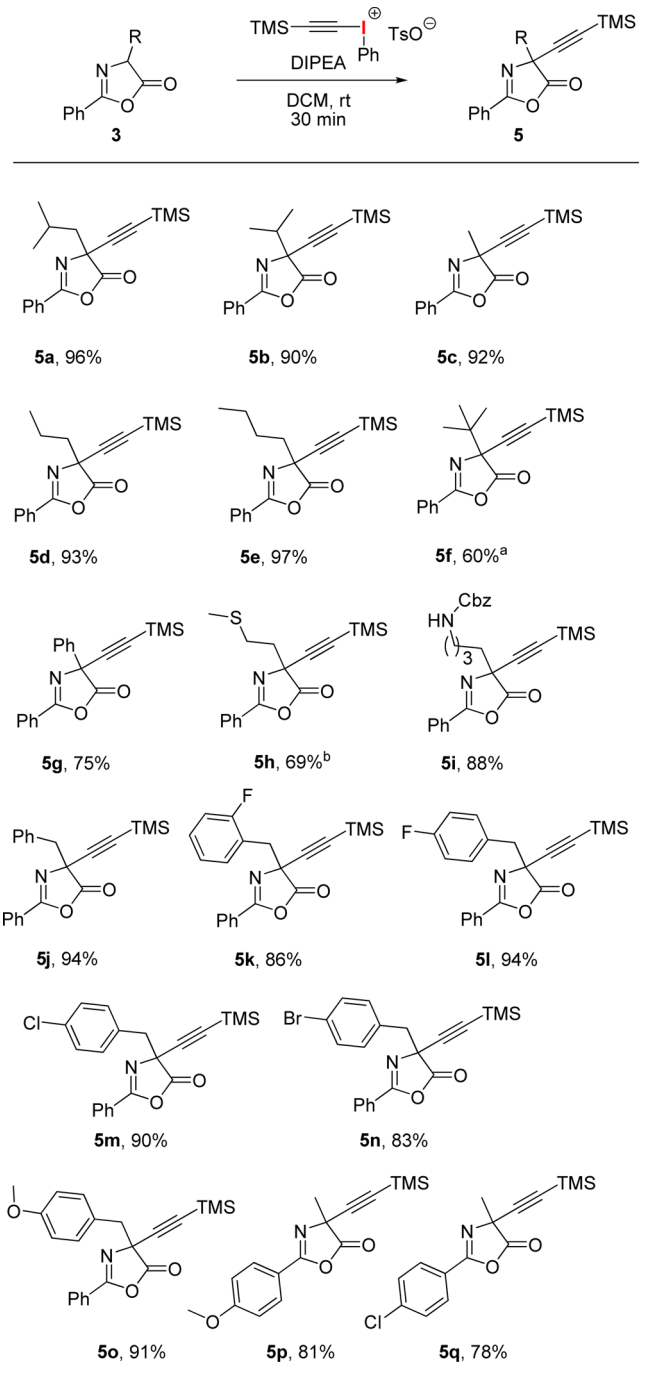
entry	ethynyliodane	R	time (h)	**4**–**7** (%)	**8** (%)	**9** (%)
1	**1a**	Ph	0.5	**4**, 84		
2	**2a**	Ph	0.5	**4**, 79	**8a**, 8	
3	**1b**	$SiMe_3$	0.5	**5a**, 96		
4	**2b**	H	2.5	**6**, 85		
5	**1c**	*n*-Bu	1	**7**, 55		**9a**, 20
6	**2c**	*n*-Bu	0.5		**8b**, 17	**9b**, 69

The corresponding benziodoxolone **2a** showed a similar reactivity, although small amounts (8%) of the spirocyclic azlactone **8a** could be isolated (Table 1 – entry 2).

Considering the generally accepted reaction mechanism for iodane-mediated alkyne transfer reactions, vinylidene carbene **A** is most likely formed as a reaction intermediate. Subsequently **A** can decompose via an [1,2]-migration to give the desired alkyne **4** (path a) or react via an [1,5]-insertion mechanism with the tertiary hydrogen of leucines alkyl side chain to give the spirocyclic cyclopentene **8** (path b).[18] For TMS-ethynyl-substituted iodane **1b** [1,2]-migration is strongly favored to give exclusively the TMS-protected alkyne **5a** in an excellent isolated yield of 96% (Table 1 – entry 3). The use of TMS-protected ethynyl-1,2-benziodoxol-3(1*H*)-one **2b** (TMS-EBX) resulted in an efficient alkynylation as well, although in situ desilylation was observed to give **6** in 85% yield (Table 1 – entry 4). Finally, 1-hexyne-containing iodanes **1c** and **2c** were investigated. Here, an interesting chemoselectivity was observed. The alkynylation of **3a** with 1-hexynyl(phenyl)-iodonium tosylate **1c** resulted in the formation of an inseparable product mixture. After in situ ring-opening with sodium methoxide (path c) the corresponding C^{α}-hexyne substituted amino acid ester **7** along with the [1,5]-insertion product of the vinylidene carbene attacking its own butyl side chain **9a** could be obtained in 55% and 20% yield respectively (Table 1 – entry 5). In contrast, the use of benziodoxolone **2c** gave exclusively two [1,5]-insertion products: [1,5]-insertion into the C^{γ}-H^{γ}-bond of the leucine side chain gave **8b** in 17% yield. However, the main product was cyclopentene-substituted azlactone **9b** (69%, Table 1 – entry 6) whose formation is similar to the formation of **9a** through an [1,5]-insertion into the aliphatic C–H bond of the butyl side chain of the vinylidene carbene **A** (R = *n*Bu).

However, since we were initially interested in the synthesis of quaternary β,γ-alkynyl α-amino acid derivatives, we further focused on the formation of compounds **4**–**6**. Here, the best results were obtained with TMS-substituted ethynyl(phenyl) iodonium salt **1b** and therefore we used this reagent for a further systematic investigation of the reactions substrate scope

Scheme 2. Substrate Scope[a,b]



[a]2.4 equiv of alkynyliodane and 3 equiv of DIPEA were reacted with **3f** for 2 d. [b]Reaction time: 2 h.

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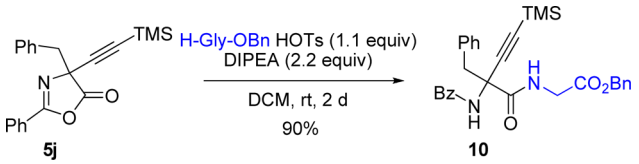
(Scheme 2). Azlactones derived from aliphatic α-amino acids such as valine (**3b**), alanine (**3c**), norvaline (**3d**) and norleucine (**3e**) all reacted smoothly to give the desired tetrasubstituted azlactones **5b**−**5e** in very high yields of 90%-97%. Sterically demanding azlactones derived from *tert*-leucine (**3f**) and α-phenylglycine (**3g**) yielded azlactones **5f** and **5g** in 60% and 75% yield respectively. Heteroatom-containing azlactones derived from methionine and lysine can also be used for our electrophilic alkynylation yielding **5h** and **5i** in 69% and 88% yield. Unfortunately, cysteine and serine derivatives could not be tested since these azlactones were synthetically not accessible from their protected amino acid precursors. Next, we investigated a variety of phenylalanine derived azlactones **3j**−**3o**. The unsubstituted derivative **3j** gave the corresponding azlactone **5j** in an excellent yield of 94%.

Halogenated phenylalanine derivatives containing 2- and 4-fluoro (**3k** and **3l**), 4-chloro (**3m**) and 4-bromo-substituents (**3n**) all reacted smoothly to yield the desired products (**5k**−**5n**) in very high yields ranging from 83% (**5n**) to 94% (**5l**). α-(4-Methoxy-benzyl)-substituted azlactone **3o** gave **5o** in 91% yield. To finalize the substrate scope we modified the 2-aryl functionality. Here we found that the introduction of a 4-methoxy or a 4-chloro-substituent does not take significant influence on the outcome of this transformation and hence the azlactones **5p** and **5q** could be obtained in 81% and 78% yield.

We initially intended to use this novel alkynylation method for the generation of quaternary β,γ-alkynyl α-amino acids and/or peptides bearing this structural motif. Therefore, a series of derivatization reactions were finally investigated. Ring-opening of the azlactone **5j** with glycine benzyl ester gave the corresponding *N*-, and *O*-protected dipeptide **10** in 90% yield (Scheme 3). Further functionalization of the triple bond has

Scheme 3. Ring-Opening of Azlactone 5j with Benzyl Glycinate



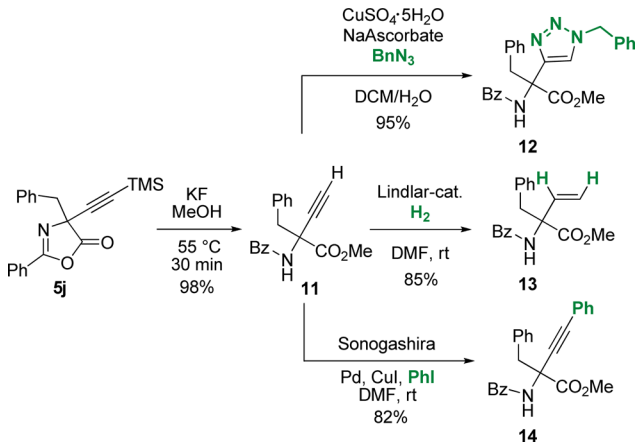
been achieved from the terminal alkyne **11** which was obtained in quantitative yield through a one pot ring-opening/deprotection cascade from **5j** (Scheme 4).

Cu-catalyzed 1,3-dipolar cycloaddition gave *N*-benzyl azide **12** in 95% yield. Reduction of **11** with Lindlar's catalyst selectively reduced the terminal alkyne to the corresponding terminal alkene **13** in 85% yield. Finally, a Sonogashira coupling of **11** with phenyl iodide provided **14** in 82% yield.

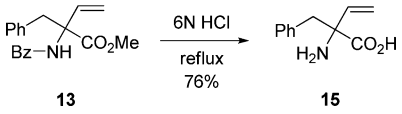
Free β,γ-unsaturated α-amino acids have attracted great attention due to their irreversible inhibitory effects on a variety of PLP-dependent enzymes such as DOPA- and ornithine-decarboxylases and transaminases.[19] We therefore tried to fully deprotect α-ethynyl amino acid **11** and α-vinyl amino acid **13** under acidic conditions. Unfortunately, standard protocols for the full deprotection of **11** under acidic conditions failed due to an undesired decarboxylative hydration of the triple bond. However, we were delighted to find that **13** could be transformed into the biologically active α-vinyl amino acid **15** by treatment with 6N HCl (Scheme 5).

In summary, we have developed the first protocol for the direct electrophilic alkynylation of azlactones. By using

Scheme 4. Derivatization of β,γ-Alkynyl Amino Acid Derivative 11



Scheme 5. Deprotection of α-Vinyl Glycine Derivative 13



alkynyl(phenyl)iodonium salts as stable and nontoxic alkyne transfer reagents highly desirable β,γ-alkynylated oxazol-5(4*H*)-ones are obtained after remarkably short reaction times and excellent yields of up to 97%. We could further demonstrate that these privileged structures can serve as versatile precursors for the synthesis of quaternary β,γ-alkynyl amino acid derivatives through a variety of subsequent synthetic transformations such as ring-openings, cycloadditions, reductions and Pd-mediated cross-couplings. An enantioselective variant of this transformation or a dynamic kinetic resolution of the racemic quaternary azlactones to obtain enantiopure quaternary α-amino acids would be highly desirable and is part of ongoing investigations in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data, including ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: boris.nachtsheim@uni-tuebingen.de.

Notes

The authors declare no competing financial interest.

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