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Synthesis of novel acetylene-containing amino acids

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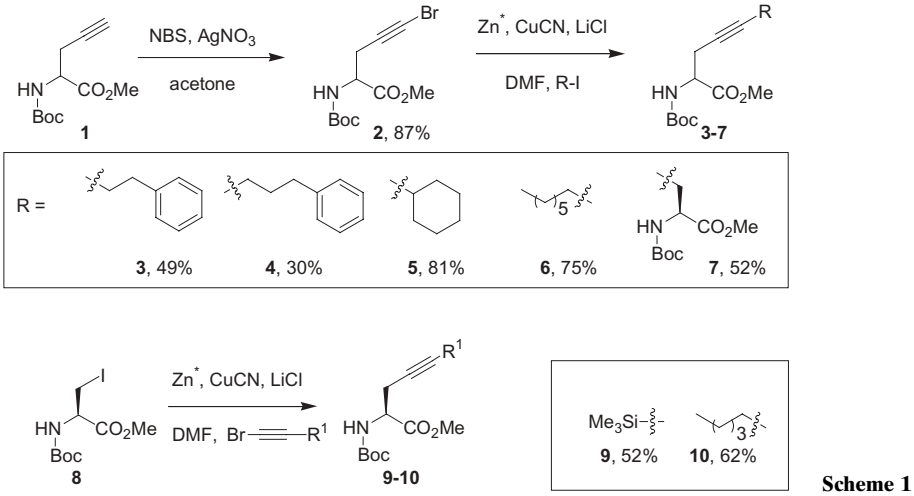
Summary. Novel synthetic procedures for the modification of non-proteinogenic acetylene-containing amino acids have been developed. The functionalization either proceeds via zinc/copper-mediated introduction of alkyl substituents, or via tungsten-catalyzed ring-closing alkyne metathesis reactions.

Keywords: Organozinc reagent – Alkyne metathesis – Non-proteinogenic amino acids – Unsaturated amino acids – Acetylenic amino acids – β-Turn mimic

Amino acids play a pivotal role in all processes in living cells. As a consequence, amino acids are very frequently used in the synthesis of (libraries of) molecules with a specific desired biological activity. Generally, when making peptide libraries, or libraries of small molecules that contain amino acid fragments, only the proteinogenic amino acids are used as the synthetic components (Jung, 1996). Recently, however, researchers more and more started to incorporate amino acids with a non-proteinogenic side chain in order to increase the diversity of the resulting compounds (Rutjes et al., 2000) Ideally, the non-proteinogenic functional group might even act as a 'handle' for further derivatization of the side chain in a combinatorial fashion (Lee et al., 1999; Wallace et al., 1998). As part of a program to develop methodology for the synthesis (Wolf et al., 2001) and applications (Wolf, 1998) of novel unsaturated amino acids, we studied the possibility to functionalize acetylene-containing amino acids – readily accessible in enantiomerically pure form via enzymatic resolution of the corresponding amino acid amides (Wolf et al., 2001) – with alkyl substituents via transition metal-mediated processes. So far, the majority of methods to functionalize acetylenic amino acids lead to enynes or aryl acetylenes (e.g. via the so-called Sonogashira reaction), but relatively few methods exist to introduce simple alkyl groups in a straightforward manner. In this contribution, we will provide two types of reactions, (i) organozinc couplings and (ii) ring-closing alkyne metathesis reactions, which both lead to novel alkyl-substitutents at the acetylene function of such amino acids.

The first route was inspired by work on organozinc chemistry from the Knochel group (Yeh and Knochel, 1989) and required an alkyl iodide on the one side and an iodo- or bromoacetylene on the other side (Scheme 1). Activated zinc inserts in the iodine-carbon bond, followed by metal exchange with copper(I), after which the resulting zinc/copper species can react with the halogenated acetylene to form a new CC-bond. Initially, we chose to start from protected propargylglycine **1**, which was brominated under mild conditions using *N*-bromosuccinimide and a catalytic amount of $AgNO_3$ (Hofmeister, 1984) to give **2**[1] in 87% yield after purification. Attempts to synthesize the corresponding more reactive iodoacetylene derivative failed due to rapid decomposition of the product. Having facile access to **2**, we subjected the bromoacetylene to a small set of iodides under the modified Knochel conditions. It appeared that the quality of the zinc powder (100 mesh, 99.998% purity)

[1] **2**, selected data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (d, J = 7.7 Hz, 1H), 4.44–4.40 (m, 1H), 3.76 (s, 3H), 2.75–2.73 (d, J = 5.0 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 155.0, 80.3, 74.6, 52.6, 51.9, 41.7, 28.3, 24.0; mp = 55°C.



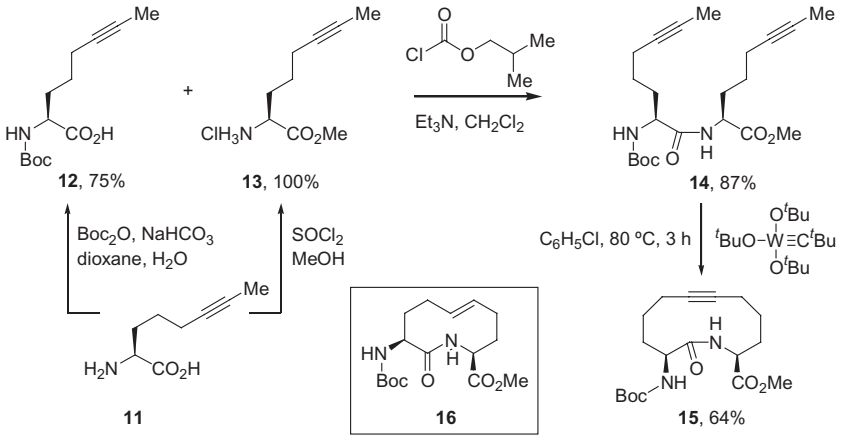
Scheme 1

and the absence of moisture in the reagents (DMF, CuCN and LiCl) were essential for a successful reaction. Thus, the novel amino acids **3–6** with different alkyl side chains were synthesized in reasonable to good yields.[2] Interestingly, it appeared also possible to couple a serine-derived iodide **8** (Jackson et al., 1998) under these conditions to give the protected diamino acid **7** in 52% yield (1:1 mixture of diastereoisomers due to the use of racemic propargylglycine **1**). The latter product, in fact, can be regarded as a conformationally restricted isostere of cystine (Aguilera, 2001) and its dicarba analogue 2,7-diaminosuberic acid (Walter et al., 1974).

Alternatively, the same serine-derived iodide **8** provided a logical entry into similar acetylenic amino acids via coupling with a number of bromoacetylenes. An advantage of the latter approach is the fact that the stereocenter stems from readily available serine, rather than from an enzymatic resolution process. Indeed, treatment of protected iodoalanine **8** with zinc and copper(I), followed by addition of the depicted iodoacetylenes resulted in the novel enantiomerically pure acetylenic amino acids **9** and **10** in reasonable yields.

Being able to functionalize the acetylenic amino acids in intermolecular reactions, we also became interested in synthesizing cyclic acetylenes. In particular, the cyclic dipeptide **15** attracted our attention as a potential target molecule, since it was demonstrated in the group of Katzenellenbogen that the corresponding olefin **16** acts a β-turn mimic (Fink et al., 1998). Therefore, our target acetylene – or the hence readily accessible corresponding (Z)-cycloolefin – might form an interesting alternative class of β-turn mimics. Although such a cyclic system could be accessible via an intramolecular version of the aforementioned zinc/copper-mediated CC-bond formation process, we decided to explore the application of ring-closing alkyne metathesis (RCAM) to reach the same goal. Considering earlier successful examples of RCAM on peptides in our group (Aguilera et al., 2001), and the fact that the cyclization precursor can be prepared from a single amino acid, rendered the metathesis approach more attractive.

[2] Typical procedure for **5**: zinc dust (116 mg, 1.408 mmol) was weighed into a 20 mL flask, which was repeatedly evacuated (with heating using a heat gun) and flushed with argon. Dry DMF (0.5 mL, distilled from CaH_2) and 1,2-dibromoethane (9.2 μL, 0.106 mmol) were added and the flask was heated at 80°C for 40 min. The reaction mixture was allowed to cool to room temperature, trimethylsilyl chloride (4 μL, 0.035 mmol) was added and the resulting mixture was stirred vigorously for a further 30 min under argon. Iodocyclohexane (69 μl, 0.528 mmol) was added and stirred at room temperature for 3 h more after which stirring was ceased to settle the zinc. CuCN (41 mg, 0.458 mmol) and LiCl (40 mg, 0.915 mmol) were heated to 150°C for 2 h and cooled to room temperature. Addition of DMF (1 mL) formed a soluble CuCN·2LiCl complex within 5 min. After cooling the Cu-complex to −15°C, the organozinc reagent was added dropwise followed by the bromoacetylene **2** (116 mg, 0.352 mmol). The mixture was allowed to stir overnight at room temperature. Water was added and the suspension was extracted using heptane, washed with brine, dried ($MgSO_4$) and concentrated. Purification using flash column chromatography (10% EtOAc in heptane) yielded **5** (100 mg, 81%) as a colorless oil. **5**: IR ν 3355, 2929, 2852, 2359, 2337, 1749, 1717, 1498, 1447, 1365, 1251, 1181, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (d, J = 7.7 Hz, 1H), 4.43–4.38 (m, 1H), 3.73 (s, 3H), 2.69–2.63 (m, 2H), 2.13 (m, 1H), 1.73–1.22 (m, 10H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 155.0, 88.1, 79.9, 73.8, 52.3, 32.7, 32.7, 28.8, 28.2, 25.8, 24.6, 23.1; HRMS (EI): calculated for $C_{17}H_{27}NO_4$ 309.1940, found 309.1937.



Scheme 2

The precursor synthesis commenced with enantiomerically pure (*S*)-2-amino-6-octynoic acid (**11**), which was either protected at the nitrogen atom with a Boc group (*viz*. **12**) or reacted at the acid function to give the corresponding methyl ester **13**. Both amino acids were then coupled via a mixed anhydride to form the dipeptide **14** in 87% yield. This RCAM precursor was now subjected to the ring-closing metathesis conditions (Fürstner et al., 2001) (10% of $(^tBuO)_3W{\equiv}C^tBu$, (Schrock, 1982) chlorobenzene, 80°C, 3h) to give the desired cycloalkane **15** in 64% yield (based on 50% conversion)[3]. This gratifying result once more clearly demonstrates the potential of ring-closing alkyne metathesis, even in combination with highly functionalized substrates such as these amino acids.

In summary, we have shown that both by using zinc/copper-mediated coupling reactions and by applying tungsten-catalyzed alkyne metathesis, functionalization of the acetylene group of non-proteinogenic amino acids with different alkyl substituents can be achieved. Further applications of both synthetic methods and the resulting products are currently under investigation.

[3] A solution of the tungsten catalyst (7mg, 10mol%) in C_6H_5Cl (2mL) was treated with a solution of **14** (49.0mg, 0.120mmol) in C_6H_5Cl (5.0mL) under an argon atmosphere and the resulting mixture was heated at 80°C for 3h. Evaporation followed by flash column chromatography (80% EtOAc in heptane) afforded **15** (21.0mg, 50%; 64% after correction for starting material) and **14** (16mg, 33%) as colorless oils. **15**: $[\alpha]_D$ =–14.6 (c = 1, CH_2Cl_2); IR ν 3313, 2931, 2865, 2249, 1744, 1667, 1520, 1366, 1170; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.7 Hz, 1H), 6.08 (d, J = 8.3 Hz, 1H), 4.78 (q, J = 6.8 Hz, 1H), 4.27 (q, J = 7.9 Hz, 1H), 3.73 (s, 3H), 2.17–2.15 (m, 4H), 2.07–1.96 (m, 2H), 1.79–1.52 (m, 4H), 1.45 (s, 9H), 0.89–0.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.8, 155.8, 80.4, 80.2, 79.3, 53.8, 52.5, 51.2, 32.8 (2×), 28.1, 24.6, 24.2, 18.3 (2×); HRMS (EI): calculated for $C_{18}H_{28}N_2O_5$ 352.1998, found 352.1984.

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