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One-Pot Synthesis of Macrocycles by a Tandem Three-Component Reaction and Intramolecular [3+2] Cycloaddition

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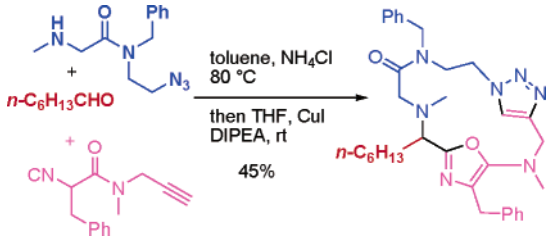
ABSTRACT



By combining three appropriately designed simple substrates, a programmed sequence involving an α-isocyano acetamide-based three-component reaction followed by a copper-catalyzed intramolecular [3+2] cycloaddition of alkyne and azide took place to afford complex macrocycles in moderate to good yields. One macrocycle and two heterocycles were produced with concurrent formation of five chemical bonds in this operationally simple process.

Macrocycles often display remarkable biological activities and many of them are used as drugs.[1] Several factors are responsible for this attractive behavior. For example, macrocycles, unlike their linear counterparts, possess a smaller number of accessible energetic conformations. This effect reduces the entropic penalty related to the binding to the target increasing the biological activity.[2] Nevertheless, they still show enough mobility to use different conformations during the pharmacokinetic and pharmacodynamic phases. This is particularly useful as true rigid analogues might show an increased biological activity in vitro with respect to their linear counterpart, but turn out to be poorly active in vivo on account of pharmacokinetic problems.[3] Macrocycles might, therefore, pass over this problem by the fact that they constitute a compromise between conformational preorganization and flexibility. A classic pathway leading to macrocycles consists of a stepwise construction of a linear substrate followed by a ring closure.[4] While this approach has been extensively employed in target-oriented synthesis of single compounds, its limitation in diversity-oriented synthesis of macrocyclic libraries is self-evident.[5] An alternative and highly efficient strategy involving a sequence of a multicomponent reaction−post functionalization has attracted much attention over the past decade [6,7] and indeed several types of complex macrocycles are now readily accessible in only a few steps by applying this strategy.[8] On the other hand, a

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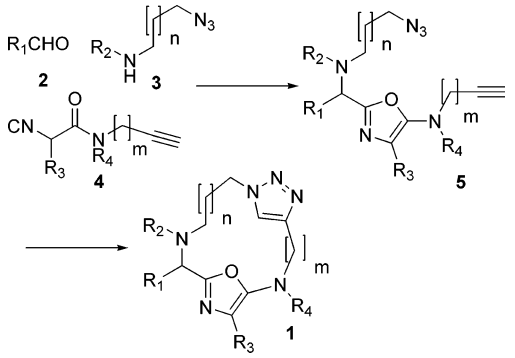
one-step multicomponent synthesis of macrocycles from readily accessible starting materials remains elusive and only a very few examples exist in the literature.[9] In connection with our ongoing project, we were interested in developing a one-pot synthesis of macrocycle **1** from appropriately functionalized isocyanoacetamides,[10] aldehydes, and amines. The underlying principle is shown in Scheme 1.

Scheme 1. One-Pot Synthesis of Macrocycles by a Three-Component Reaction/[3+2] Cycloaddition



The reaction between an aldehyde (**2**), an ω-azido amine (**3**), and an isocyanoacetamide (**4**) would give 5-aminooxazole (**5**).[11] We hypothesized that the rigidifying effect of the oxazole should render **5** more susceptible to the intramolecular [3+2] cycloaddition of tethered alkyne and azide to afford macrocycle **1** directly under appropriate conditions. The realization of this transformation is the subject of the present Letter.

With use of heptanal (**2a**), 4-azido-*N*-benzyl-1-butanamine (**3a**), and 2-isocyano-*N*-methyl-3-phenyl-*N*-(prop-2-ynyl)propanamide (**4a**) as test substrates, initial experiments indicated that copper(I) salts were unable to catalyze the entire reaction sequence shown in Scheme 1. Since ammonium chloride was capable of promoting the formation of **5a** in excellent yield, efforts were concentrated on the subsequent intramolecular [3+2] azide−alkyne cycloaddition of analyticly pure oxazole **5a** ($R_1 = n$-C_6H_{13}, $R_2 =$ Bn, $R_3 =$ Bn, $m = 1$, $n = 2$, Scheme 1). After extensive screening of reaction parameters varying the copper sources, solvents, bases, and temperatures, it was found that intramolecular alkyne/azide cycloaddition took place smoothly in tetrahydrofuran at room temperature in the presence of freshly purified copper iodide[12] and an excess of diisopropylamine to produce **1a** ($R_1 = n$-C_6H_{13}, $R_2 =$ Bn, $R_3 =$ Bn, $m = 1$, $n = 2$, Scheme 1) in over 90% yield.[13] With this result, the synthesis of **1a** from **2a**, **3a**, and **4a**, without isolation of 5-aminooxazole **5a**, was realized as follows: heating a toluene solution of **2a**, **3a**, and **4a** in the presence of ammonium chloride (1.5 equiv) at 80 °C for 4 h was followed, after removal of inorganic salt by filtration,[14] by addition of CuI (2.0 equiv), diisopropylamine (20 equiv), and tetrahydrofuran ($c = 0.001$ M). After being stirred at room temperature for 15 h, the desired macrocycle (**1a**) was isolated in 76% yield after column chromatography. It is worth noting that this procedure did not give the dimerization product during the ring closure step as reported for analogue ring closures.

The scope of this novel tandem three-component reaction/[3+2]cycloaddition reaction was next examined. Five aldehydes, four amines (Figure 1), and three isocyanoacetamides

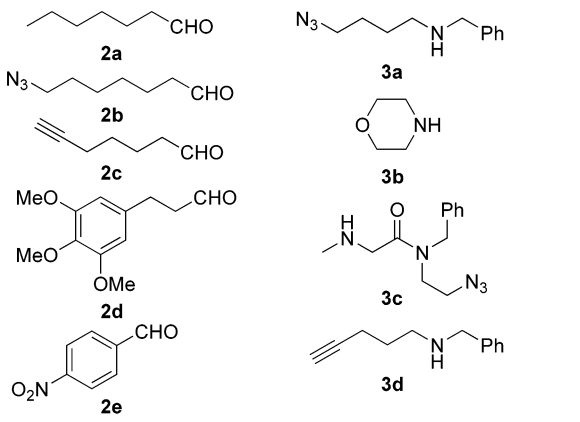


Figure 1. Aldehyde and amine building blocks.

were used. Isocyanoacetamides were synthesized in a straightforward manner starting from the corresponding formylamine derivatives which were subsequently coupled with the desired secondary amine under classical EDCI/DMAP protocol. Final dehydration with phosphorus oxychloride in

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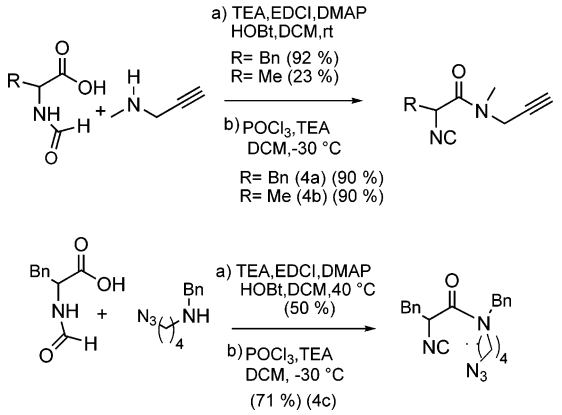
(14) Filtration of ammonium chloride is important as without filtration we registered a drop of yield (45% vs 76%).

the presence of an excess of triethylamine[15] afforded the isocyanoacetamides in excellent yields. (Scheme 2).

Scheme 2. Synthesis of Isocyanoacetamides Building Blocks



The macrocycles **1a**−**j** synthesized are listed in Figure 2. As is seen, the reaction turned out to be quite general and 14-, 15-, and 16-membered rings were readily accessible. Since 5-aminooxazole is a surrogate of dipeptide[16] and triazole is considered as a bioisostere of an amide,[17] compounds **1e**−**g**, resulting from the reaction of azido amine **3c** and appropriate reaction partners, could be regarded as cyclopeptide mimics. While the diversity can be easily introduced by varying the R_1 to R_4 residues, further structural ramification can be made by simply reversing the tethering position of alkyne and azide (**1h** vs **1i**). Even more significantly, when azide and alkyne units were tethered to aldehyde and isocyanide, respectively, macrocycles having an *exo*-tertiary amine function (**1i**, **1j**) instead of *endo*-tertiary amine (**1a**−**h**) were produced. Although the overall yield was moderate, it has to be stressed that one macrocycle and two heterocyles were produced in this experimentally simple process with the creation of five chemical bonds.

Consequently, the yield per chemical bond produced remains excellent. While the "click" [3+2] cycloaddition reaction has been extensively used for the preparation of triazole as well as bicyclic ring systems, examples dealing with the concurrent formation of a macrocycle are still rare.[18]

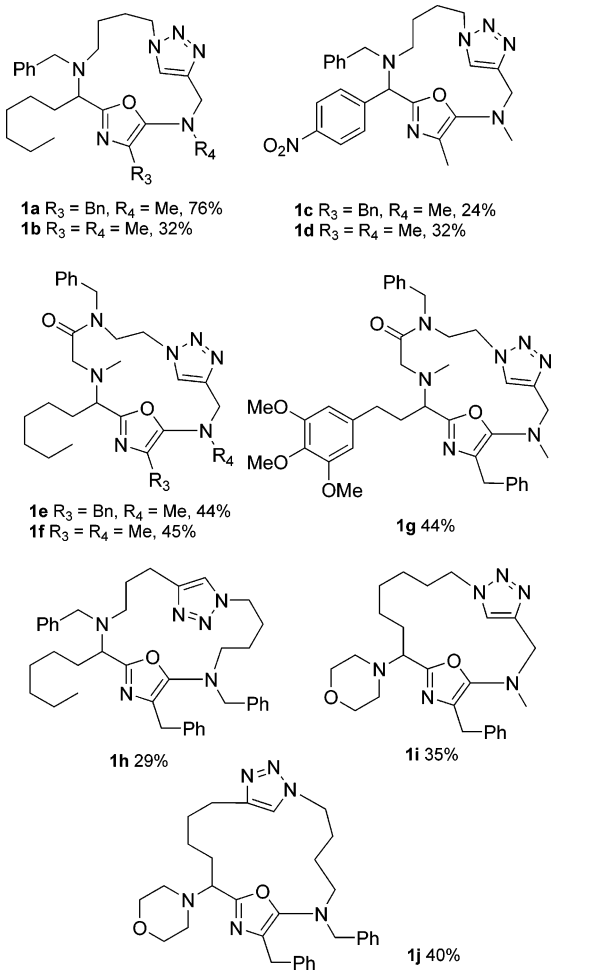


Figure 2. 14-, 15-, and 16-membered macrocycles.

The efficiency of this multicomponent domino process for the construction of macrocycle **1** is thus truly remarkable. To explore the possible conformational preorganization effect of oxazole,[19] dipeptides **6** and **7** (Figure 3) were synthesized by a Ugi four-component reaction.[20] Indeed, no reaction occurred when **6** and **7** were submitted to the established cycloaddition conditions, indicating the pivotal role of oxazole in the production of macrocycles **1a** to **1j**.

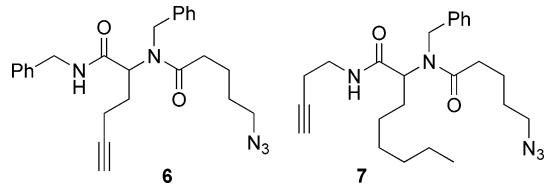


Figure 3. Dipeptides obtained via Ugi reaction.

In conclusion, we documented a very straightforward synthesis of complex macrocycles from readily accessible

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starting materials by a tandem three-component reaction/intramolecular [3+2] cycloaddition of alkyne and azide. Work is in progress to expand the number of macrocycle scaffolds synthesizable with this procedure as well as to evaluate potential biological properties of these compounds.

(19) For a review on conformation-directed macrocyclization, see: Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, *10*, 1949−1964.

(20) Two-step synthesis of a fused bicyclic ring system by a Ugi-4CR followed by intramolecular click chemistry has been developed; see: Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439−8442.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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