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Cleavable β-Cyanoethyl Isocyanide in the Ugi Tetrazole Reaction

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Supporting Information

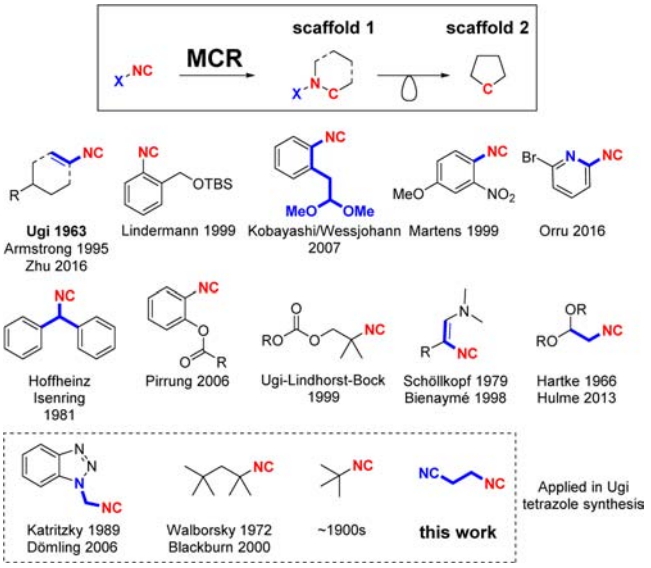
ABSTRACT: β-Cyanoethyl isocyanide is introduced as a cleavable isocyanide in the Ugi tetrazole reaction. Eleven examples are described that exhibit a broad scope and are obtained in good overall yields. The obtained 1*H*-tetrazole scaffold is an important bioisostere for carboxylic acids, and the method described here is a valuable alternative route to known procedures.

The Ugi reaction is a well-known multicomponent reaction that has a comprehensive range of starting materials.[1] Numerous reported examples revealed that aldehydes, ketones, primary or secondary amines, and isocyanides react with suitable acid components to yield a variety of scaffolds.[2−9] Moreover, it is well established that multicomponent reaction chemistry has several advantages over sequential step chemistry. They show a high degree of diversity due to the nature of the starting materials and are efficient, mild, one-pot procedures; their atom economy is remarkable since almost all atoms from the starting materials are retained in the final product.[4,5]

The 1*H*-tetrazole moiety has attracted much attention in the field of medicinal chemistry as a bioisostere of the carboxylic acid functional group. This is mainly due to a combination of a similar pK_a (4−5) and, more importantly, a 10-fold higher lipophilicty, which is potentially more beneficial when cell membrane permeability is desired.[10,11] Traditionally, there are two methods to introduce the tetrazole moiety, addition of an azide source to a nitrile or the addition of an azide source to an amide reacting through its imidoyl derivative.[12,13] However, both methods have limitations that include multistep synthesis of starting materials, expensive reagents, or a great amount of chemical waste. In this respect, the Ugi multicomponent reaction, with trimethylsilyl azide (TMS-N_3) as acid component, is a valuable alternative, provided that an efficient method for deprotection of *N*-1 is available (see Scheme 2).[3] A large set of compounds can potentially be synthesized because most of the two retained starting materials, carbonyl and amine compounds, are commercially available, eliminating the need for starting material synthesis.

The concept of convertible isocyanides was introduced as early as 1963 by Ugi with cyclohexenyl isocyanide, which can be cleaved in the Ugi reaction product using acidic conditions.[14] The concept was later extended by many others (Scheme 1).[15−28]

Scheme 1. Previously Described Convertible Isocyanides



Convertible isocyanides are highly useful in that they can be transformed into other functional groups during a multistep synthesis of complex molecules, e.g., natural products.[29] However, the majority of work performed concerns the transformation of the secondary amide formed during the Ugi and Passerini reactions into esters, thioesters, ketones, carboxylic acids, and other groups. For other isocyanide-based multicomponent reactions (IMCRs), not all of the above quoted cleavable isocyanides may be used. Previous acidic cleavage of isocyanides leading to tetrazoles include *tert*-butyl,[30] BetMIC,[31] and Walborsky's reagent (*tert*-octyl isocyanide)[31] are

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known, but we were interested in the development of a cleavable isocyanide deprotected under mild conditions due to our recent focus on the Ugi tetrazole reactions (Scheme 2).[32−36]

Scheme 2. Retrosynthetic Pathway of Our Approach

The amino acid derived isocyanides **1a**,**b** are cleaved under basic conditions (Figure 1),[35] but these cleavable isocyanides

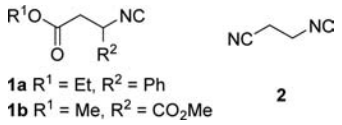


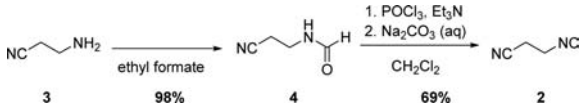
Figure 1. Isocyanides cleaved under basic conditions.

display some drawbacks. First, the deprotection takes a considerable time (overnight) with the possibility of unwanted side reactions, and second, especially the amino acid derived isocyanides require a multistep synthesis from benzaldehyde (**1a**) or aspartic acid (**1b**).

To overcome these issues, we would like to introduce the *β*-cyanoethyl protecting group which is a common phosphotriester protecting group in solid-phase oligonucleotide synthesis and cleaved under mild basic conditions.[36] The *β*-cyanoethyl protection was previously employed in the synthesis of 5-substituted-1*H*-tetrazoles,[13] and it was used by our group in two instances.[34,37] Therefore, we herein report an improved synthesis of *β*-cyanoethyl isocyanide, its use as cleavable isocyanide, and scope and limitations in the synthesis of 5-subsituted-1*H*-tetrazoles through the Ugi tetrazole multicomponent reaction.

The first step is the formylation of 3-aminopropionitrile (**3**) with ethyl formate to obtain *N*-(cyanoethyl)formamide (**4**) in excellent yield (98%). Subsequent dehydration of the formamide is performed using standard conditions ($POCl_3$/Et_3N) to yield the isocyanide **2** in 69% yield (Scheme 3).[38] This

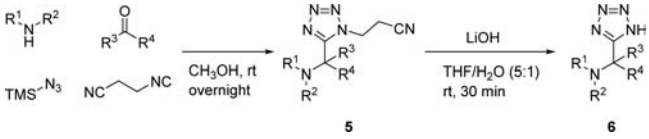
Scheme 3. Synthesis of *β*-Cyanoethyl Isocyanide

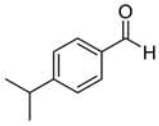
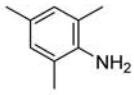
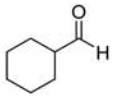
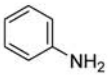
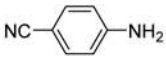
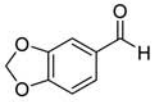
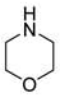
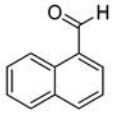
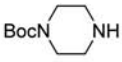
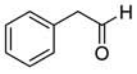
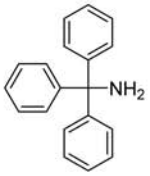
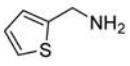
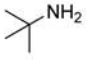
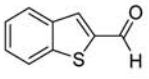
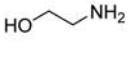
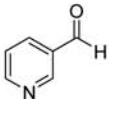


compares well to the poor 16% yield obtained with the Appel-type conditions used in the original procedure[39,40] Our high purity *β*-cyanoethyl isocyanide solidifies at room temperature, therefore, making it practical in use and, noteworthy, lacking the appalling smell of volatile isocyanides.[41] In the Supporting Information we also describe an 11 g scale synthesis of *β*-cyanoethyl isocyanide.

We then tested for the first time its reactivity in IMCR, and it reacted smoothly with cyclohexanone, aniline ,and TMS-N_3 in methanol (room temperature, overnight) to obtain the Ugi product in good yield (64%, **5c**). After this initial promising result, the scope of the reaction was investigated by reacting a diverse set of carbonyl components and amines to isolate the 1,5-disubstituted tetrazoles (**5**) in moderate to good yield (24−68%, Table 1). Aliphatic, alicyclic, and (hetero)aromatic aldehydes are accepted as carbonyl compounds and generally gave good yields; however, the Ugi products containing 1-naphthaldehyde (entry f) or benzo[*b*]thiophene-2-carboxaldehyde (entry j) gave a fair yield. Additionally, ketones such as

Table 1. Yields of the Ugi Products (5) and Deprotected 5-Substituted 1*H*-Tetrazoles (6)



entry	amine	aldehyde/ketone	yield of **5**[a]	yield of **6**[a]
a			47	84
b			35	91
c			64	73
d			66	76
e			48	69
f			36	77
g			55	93
h			68	87
i			65	83
j			24	59
k			53	81

[a]Isolated yield.

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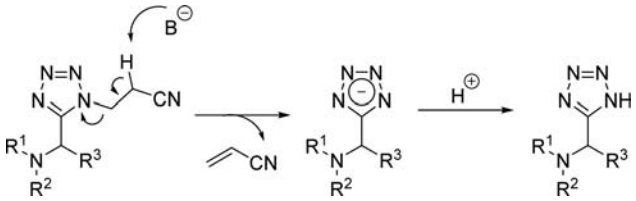
cyclohexanone (entry c) and acetone (entry (i) performed well, and the Ugi products, with a quaternary carbon center, were obtained in good yield. Primary aliphatic and (hetero)aromatic amines as well as secondary amines are suitable amine components, but sterically hindered 2,4,6-trimethylaniline (entry b) resulted in a slightly lower yield. This shows that this particular reaction has a broad scope and, moreover, exhibits a high tolerance toward functional or protecting groups including the nitrile (entry d), Boc (entry g), trityl (entry h), and alcohol (entry j).

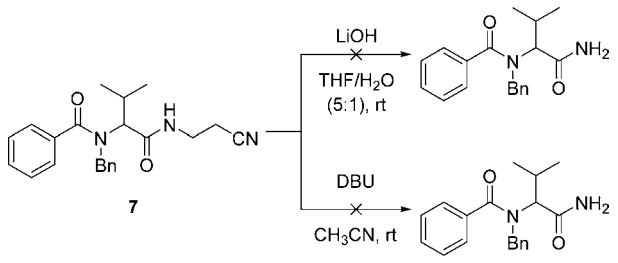
The deprotection of β-cyanoethyl protecting groups usually proceeds by using an organic base, such as DBU,[42] to abstract one of the acidic hydrogens adjacent to the nitrile. The C−H bond is broken, and the electrons flow toward the tetrazole forming the anion with expulsion of highly volatile acrylonitrile. After acidification, the 1*H*-tetrazole is obtained (Scheme 4).

Scheme 4. Mechanism for β-Cyanoethyl Deprotection



The deprotection proceeds most likely due to the stability of the intermediate tetrazole anion which is resonance stabilized. Preliminary results showed that the β-cyanoethyl isocyanide could not be cleaved from the classical Ugi product **7** and only starting material was obtained; therefore, it was not further pursued (Scheme 5).

Scheme 5. Attempted Deprotection from a Classical Ugi Product



Attempts to cleave the Ugi products under similar conditions failed, and no reaction occurred. However, we were pleased to find that deprotection with lithium hydroxide gave a clean reaction, and full conversion was obtained at room temperature within 30 min. After acidification (pH 4−5), the 1*H*-tetrazole was obtained as a solid which allowed for the convenient isolation of the products **6** in good to excellent yield (59−93%). Compounds that possess more bulky substituents tend to give excellent yields (entries **6b**, **6g**, and **6h**). Moreover, this method did not hamper the isolation of products that contain highly water-soluble groups such as morpholine (**6f**, 77%) and ethanolamine (**6k**, 81%). For compound **5c**, a single crystal was obtained, and X-ray analysis confirmed the overall structure of the protected Ugi product (Figure 2).

Finally, deprotection of the orthogonal acid-labile protecting groups from 1*H*-tetrazoles **6g** (Boc) and **6h** (trityl) was achieved under normal conditions (Scheme 6). Cleavage of the

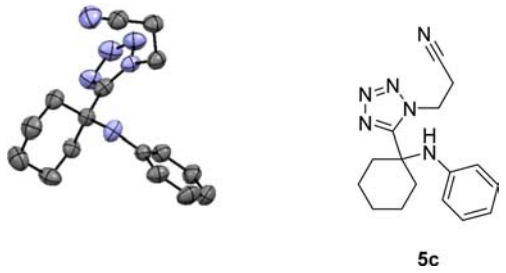
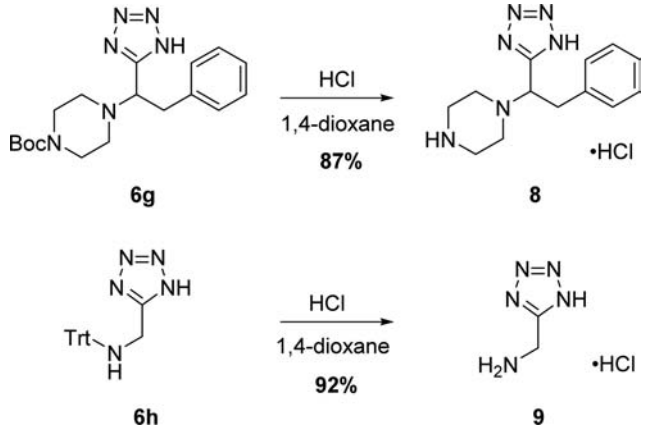


Figure 2. X-ray structure of β-cyanoethyl-protected tetrazole **5c**.

Scheme 6. Deprotection of Orthogonal Protecting Groups



Boc group led to compound **8** that contained a highly water-soluble piperazine and, potentially, allowed for further reactions on the secondary amine. After deprotection of the trityl group from **6h**, the (1*H*-tetrazol-5-yl)methanamine (**9**) was obtained, which is the α-amino tetrazole analogue of glycine.[37]

The β-cyanoethyl group is widely used during the solid-phase synthesis of polynucleotides, but rarely used otherwise, despite its mild and efficient cleavage conditions. Hence, we report here the use of the protecting group for the tetrazole moiety and its introduction in one step using β-cyanoethyl isocyanide. The herein reported β-cyanoethyl isocyanide was readily synthesized from commercially available 3-aminopropionitrile in two steps and obtained as an easy to handle solid isocyanide that reacts together with a broad range of diverse ketones, aldehydes, primary or secondary amines, and TMS-azide to yield 1,5-disubstituted tetrazoles. The 5-substituted 1*H*-tetrazoles were obtained after mild basic deprotection of the β-cyanoethyl group with short reaction times reducing unwanted side reactions and in high yields outperforming and being a vital addition to other acid or base cleavable isocyanides that are described for the Ugi tetrazole reaction. Moreover, the here presented approach may be valuable in the synthesis of biologically active compounds containing the 1*H*-tetrazole moiety. Currently, work is ongoing to investigate the further synthetic application of β-cyanoethyl isocyanide in multicomponent reaction chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01826.

X-ray crystallographic file of **5c** (CIF)

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General experimental procedures, compound characterization data, ^{1}H and ^{13}C spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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