

Development of Novel Procedures for the Synthesis of 1,2,3-Triazoles

Thesis

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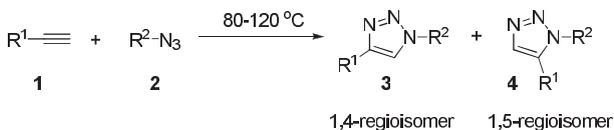
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1. Introduction, aims

Copper(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC reaction)

Triazole synthesis based on the reaction between azides and alkynes is known since the early 1960s (Huisgen 1,3-dipolar cycloaddition).¹

The uncatalyzed transformation of terminal alkynes requires high temperature (80-120 °C) and usually affords the product as an approximately 1:1 mixture of 1,4- and 1,5-regioisomers. High regioselectivity can be achieved only in instances, where the alkyne bears either a bulky or strong electron withdrawing substituent.



Scheme 1.: Huisgen 1,3-dipolar cycloaddition for the transformation of terminal alkynes

A breakthrough was achieved in this field of chemistry in the early 2000s. Sharpless and Meldal reported in their independent works that in the presence of copper(I) ions the reaction proceeds even at room temperature.^{2,3} Under catalytic conditions the formation of the 1,4-regioisomer is favored and the reaction is characterized by excellent regioselectivity.

Synthesis of 1-monosubstituted 1,2,3-triazoles

Owing to their biological activity not only has the demand raised for disubstituted derivatives but also for 1-monosubstituted triazoles (**5**). The synthesis of these compounds could seemingly be achieved easily by the reaction of acetylene gas and the corresponding azides (**2**). However, the use of acetylene gas is problematic under ordinary laboratory

¹ Huisgen, R. in *1,3-Dipolar Cycloadditional Chemistry*; Padwa, A., Ed.; Wiley: New York, **1984**.

² Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

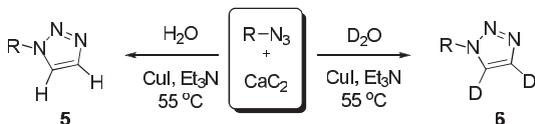
³ Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

conditions. Therefore, these compounds are often synthesized through 4-trimethylsilyl-1,2,3-triazoles, using ethynyltrimethylsilane as source of the acetylene moiety.

Jiang et al.⁴ were the first to report the direct use of calcium carbide as acetylene source. The method they reported proved effective solely for the transformation of aryl azides.

Based on these findings we aimed at developing a method that allows the efficient synthesis of 1-monosubstituted triazole derivatives using acetylene generated *in situ* from calcium carbide.

The use of calcium carbide as acetylene source offers the possibility for the synthesis of deuterated triazoles when deuterium-oxide is used for the generation of acetylene.



Scheme 2.: Application of in situ generated acetylene in the synthesis of triazoles

Palladium catalyzed cross coupling reactions

In the last decades a number of transition metal catalyzed cross coupling reactions have been developed for the formation of carbon-carbon and carbon-heteroatom single bonds.

Among these reactions palladium catalyzed cross coupling reactions are of outstanding significance. The importance of these reactions is well illustrated by the fact that Nobel prize in chemistry was awarded for this field of chemistry in 2010.⁵

Sonogashira-Hagihara reaction

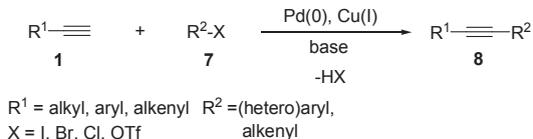
This thesis provides only a brief description of the Sonogashira-Hagihara reaction that is directly related to our research.

The Sonogashira-Hagihara reaction that is based on the co-catalysis of palladium and copper is a very efficient tool for coupling reactions between *sp* and *sp*² hybridized carbon centers.⁶

⁴ Jiang, Y.; Kuang, C.; Yang, Q. *Synlett* **2009**, 3163.

⁵ Halford, B.; *Chemical and Engineering News* **2010**, 88, 7.

The reaction can be considered as a catalytic variant of the Stephens-Castro reaction that leads to the formation of carbon-carbon single bonds in the reaction between copper(I) acetylides and aryl halides. Palladium catalysis enables milder reaction conditions. The *in situ* generation of the copper(I) acetylide overcomes the hardships of isolation and treatment of the copper(I) compound.



Scheme 3.: General reaction scheme of the Sonogashira reaction

Sonogashira reaction in multistep syntheses

Diarylacetylenes are often synthesized by reaction sequences based on repeated Sonogashira couplings. This method is justified by the fact that starting aryl halides are available in a much wider variety and at a lower price than aryl acetylenes. Although the use of acetylene gas would offer a cost efficient method for the introduction of the acetylene moiety, its use in laboratory scale syntheses is cumbersome and protected acetylene derivatives are used as source of the carbon-carbon triple bond unit. A sequence based on a Sonogashira coupling-protecting group removal-Sonogashira coupling scheme furnishes diarylacetylenes. This method is well applicable for the synthesis of unsymmetrically substituted derivatives, since the protecting group hinders the formation of symmetric, disubstituted arylacetylens in the first cross coupling step. Under proper reaction conditions it is possible to perform the whole reaction sequence as a one-pot procedure.



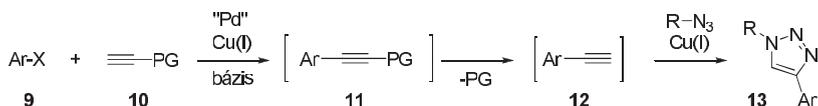
Scheme 4.: Sequential synthesis of diaryl acetylens

⁶ Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

Sequential Sonogashira – CuAAC reaction

Two widely used transformations of acetylene chemistry are the palladium catalyzed, copper(I) co-catalysed Sonogashira reaction by which aryl halides are coupled with terminal alkynes, and the copper(I) catalyzed „click” reaction (CuAAC reaction) between terminal alkynes and azides furnishing 1,2,3-triazoles.

Common points between the two transformations open up the possibility of performing these reactions as a one-pot procedure in a sequential manner to obtain 4-aryl-1,2,3-triazoles directly from aryl halides.



Scheme 5.: Proposed steps for the one-pot synthesis of 1,4 triazoles

Due to the cumbersome applicability of acetylene gas, and in order to avoid double arylation, we planned to couple the carbon-carbon triple bond moiety to the aromatic scaffold in the form of ethynyltrimethylsilane (**10a**) or 2-methyl-3-in-2-ol (**10b**). Following the cross coupling step and protecting group removal, the liberated terminal acetylene can be converted to 1,4-disubstituted 1,2,3-triazoles by the reaction with organic azides.

2. Results I. Synthesis of 1-monosubstituted 1,2,3-triazoles

A method has been developed that allows the synthesis of 1-monosubstituted 1,2,3-triazoles employing various organic azides and calcium carbide as cheap and readily available acetylene source.

Many 1-monosubstituted triazoles together with their 4,5-dideutero analogues were synthesized using this method. The reactivity of benzyl azide and its *para*-substituted derivatives (halo-, nitro- derivatives), and a secondary benzyl azide derivative was examined (**14a-b**, **15a-b**, **16a-b**). Reactivity studies were extended to aliphatic azides bearing various functional groups (ciano-, chloro-, alkenyl) and to an aromatic azide as well (**17a-b**, **18a-b**, **19a-b**).

Product	Reaction time [h]	Yield[%]	Product	Reaction time [h]	Yield [%]	Deuteration [%]		
	14a	6	90		14b	6	81	91.4%
	15a	6	57		15b	6	84	90.3%; in benzylic position 92.6%
	16a	6	74		16b	6	81	89.9%
	17a	40	92		17b	40	86	92.9%
	18a	6	81		18b	6	91	91.9%
	19a	16	64		19b	16	42	92.7%

^a Reaction conditions: 0.44 mmol azide, 0.022 mmol (5 mol%) CuI, 0.22-0.23 g (technical grade, ≥ 2.6 mmol) calcium carbide, 170 μ l H₂O or D₂O, 335 μ l Et₃N.

^b Deuterium content could not be determined due to overlaps in the ¹H-NMR spectrum.

Table 1.: Representative compounds synthesized in the course of the research

Observations regarding deuterium incorporation

In the course of our investigations we made two interesting observations about deuterium incorporation.

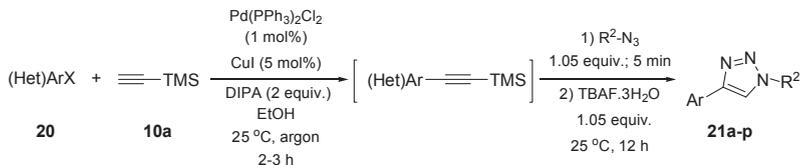
¹H-NMR spectra showed significant intensity differences between peaks corresponding to protium in the 4th and 5th position of the triazole ring. Isotopic effect may provide a rational explanation for this observation.

The protium content of our samples was higher than one would have expected on the basis of the protium content of the D₂O used in the reactions. (The nominal deuterium content

of the deuterium oxide sample was above 99%). A possible explanation for this phenomenon is that protium traces in the reaction mixture are accumulated in the triazole product due to isotopic effects. To prove this theory the reaction of benzyl azide was repeated using a 1:1 mixture of H₂O and D₂O. Product analysis found 70% protium content in contrast to the 50% value expected in the absence of isotope effect. The inequality between the amounts of 4- and 5-monodeuterated derivatives could also be observed in this case. Detailed analysis found the following product composition: 5:1:3:1 (4H,5H: 4H,5D: 4D,5H: 4D:5D).

3. Results II. Synthesis of 4-aryl-1,2,3-triazoles via sequential one-pot synthesis

A one-pot procedure was developed that allows the conversion of iodobenzene, its substituted derivatives and other hetero(aromatic) iodo compounds to 4-aryl-1,2,3-triazoles. The reaction sequence that incorporates three reaction steps afforded the desired triazole derivatives in moderate to good yields. The procedure and the applied reaction conditions are illustrated in Scheme 6.



X = I, except for (Het)Ar = 2-pyridyl; X = Br

Scheme 6. General procedure for the sequential Sonogashira-CuAAC transformation

Various iodobenzene derivatives, bearing electron donating and electron withdrawing substituents (**21a-g**), heteroaromatic iodo compounds (2-iodothiophene, 3-iodopyridine) (**21h-i**) were evaluated as starting aryl halides. With the exception of *para*-nitro-iodobenzene we managed to isolate the corresponding 4-aryl-1,2,3-triazoles in good yields (**21f**).

The possibility to extend the procedure to aryl bromides was also examined. Under the developed reaction conditions ethynyltrimethylsilane does not react with bromobenzene. To exploit this finding the corresponding 4²-bromophenyl-substituted triazole was selectively synthesized starting from 1-bromo-4-iodobenzene (**21g**). 2-bromopyridine proved to be

reactive enough to take part in the cross coupling reaction and the 2'-pyridyl-substituted triazole product was isolated in moderate yield (**21j**).

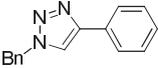
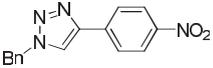
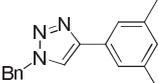
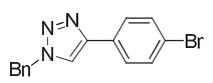
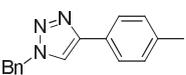
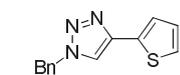
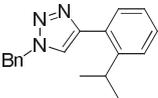
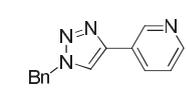
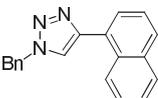
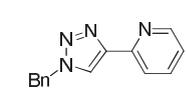
Product	Yield [%] ^a	Product	Yield [%] ^a
 21a	70	 21f	32
 21b	74	 21g	60
 21c	76	 21h	54
 21d	65	 21i	63
 21e	55	 21j^b	53

Table 2.: Examples for 1-alkyl-4-phenyl-1,2,3-triazoles synthesized in the course of the research

After having studied the scope and limitation of suitable aryl halides we turned our attention towards suitable azides. In accordance with our expectations the *in situ* generated aromatic alkyne reacted readily with aliphatic azides (eg. azidomethyl phenylsulfide, 5-azidovaleic acid ethylester and 1-azido-3-chloro-2-methylpropane) to afford the desired products in good yields (**21k-m**). Synthesis starting from bulky adamantyl azide afforded 1-adamantyl-4-phenyl triazole only in 24% yield (**21n**). The probable explanation for this is that the bulky adamantyl group slows the CuAAC reaction and the otherwise less expressed side-reaction, e.a. the homocoupling of terminal alkyne becomes dominant. The newly developed one-pot procedure was successfully used in the transformations of protected sugar and amino acid derivatives. Corresponding products (**21o-p**) were isolated in moderate yields.

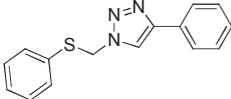
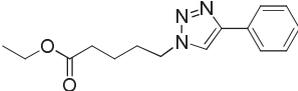
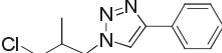
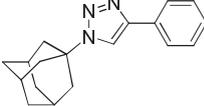
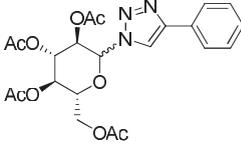
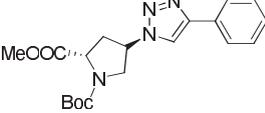
Product		Yield [%] ^a
	21k	77
	21l	58
	21m	69
	21n	24
	21o	54
	21p	61

Table 3.: Examples for 1-alkyl-4-phenyl-1,2,3-triazoles synthesized in the course of the research

It is noteworthy to mention that the developed procedure requires mild conditions and can be applied to a wide variety of substrates.

4. Publications directly related to the results of the doctoral thesis

1) Efficient Synthesis of Deuterated 1,2,3-Triazoles

Zsombor Gonda, Krisztián Lőrincz, Zoltán Novák
Tetrahedron Letters **2010**, 51, 6275-6277.

2) The Sequential Sonogashira-Click Reaction: A Versatile Route to 4-Aryl-1,2,3-Triazoles

Krisztián Lőrincz, Péter Kele, Zoltán Novák
Synthesis **2009**, 3527-3532.