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One-Pot Procedure for Diazo Transfer and Azide−Alkyne Cycloaddition: Triazole Linkages from Amines

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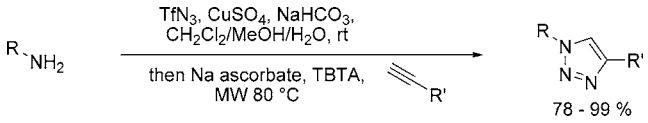
ABSTRACT



A one-pot reaction for Cu(II)-catalyzed diazo transfer and Cu(I)-catalyzed azide−alkyne 1,3-dipolar cycloaddition (sometimes called click reaction) is reported. 1,4-Disubstituted 1,2,3-triazoles are obtained in excellent yields from a variety of readily available amines without the need for isolation of the azide intermediates. The reaction has a broad scope and is especially practical for the synthesis of multivalent structures because compounds substituted with multiple azides are potentially unstable.

The Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and alkynes[1,2] has found widespread application, e.g., in combinatorial drug research[3] and material science.[4] Due to its outstanding chemoselectivity and mild conditions, the reaction has been especially used in bioconjugate chemistry.[5,6]

In this field, the construction of multivalent structures is often required because multivalency in ligand−receptor interactions is an important principle used by nature to increase weak interactions to biologically relevant levels.[7]

A common strategy to assemble multivalent ligands is the covalent attachment of the epitope to a scaffold. Several approaches using the azide−alkyne cycloaddition for this purpose have been reported.[8−10]

Although organic azides are stable against most reaction conditions, compounds of low molecular weight or those containing several azides (like multivalent scaffolds) tend to be explosive and are difficult to handle.[11] Thus, some procedures to generate the azide in situ followed by azide−alkyne cycloaddition have been reported.[10,12] In these cases,

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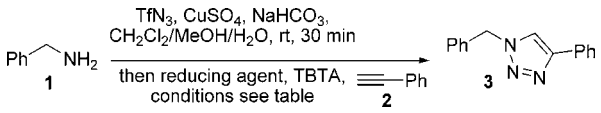
Table 1. Evaluation of the Reaction Conditions for a Sequential One-Pot Procedure



entry	amine (equiv)	conditions[a]	TBTA (mol %)	T (°C)	reaction time	yield (%)
1	1.5	A	5	rt	39 h	traces
2	1.5	B	5	rt	39 h	traces
3	1.5	A		80 MW	8 h	92[b]
4	1.5	A	5	80 MW	30 min	quant
5	1.0	A	5	80 MW	30 min	94
6	1.0	B		80 MW	20 min	89

[a] Conditions: (A) 2 mol % of $CuSO_4$, then 10 mol % of Na ascorbate; (B) 10 mol % of $CuSO_4$, then 30 mol % of Cu powder. [b] After 4 h, an additional 2 mol % of $CuSO_4$ and 10 mol % of Na ascorbate were added.

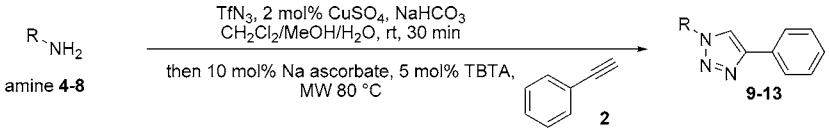
the substitution of halides with sodium azide is used. While circumventing the isolation of the azide intermediate, this approach has the disadvantage that nucleophilic replacement of halides only proceeds easily in the case of activated halides, e.g., in benzylic or anomeric positions.

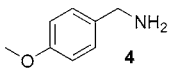
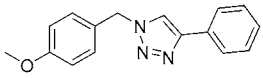
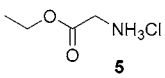
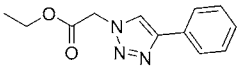
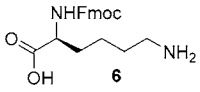
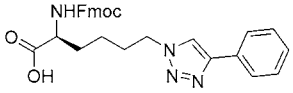
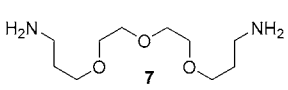
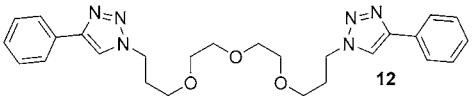
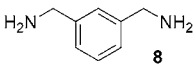
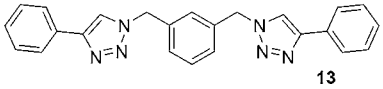
Another efficient and convenient method for generating organic azides is the Cu(II)-catalyzed diazo transfer to amines using trifluoromethanesulfonyl azide.[13,14] The reaction is not restricted to special amines, and a great variety of them is commercially available. Hence, amines are adapted functionalities for the generation of multivalent structures.

Herein, we report convenient one-pot procedures for generating triazole-linked (multivalent) structures starting from amines and avoiding the isolation of the azide intermediates. The essential element of these procedures is to generate the Cu(I) species required for the azide−alkyne cycloaddition by adding a reducing agent after complete or during Cu(II)-catalyzed diazo transfer.

The reaction conditions for a sequential one-pot procedure were optimized using a simple test system starting from benzylamine **1** (Table 1). First, the diazo transfer was performed by analogy with literature-known conditions at ambient temperature[14,15] but with sodium bicarbonate as base. After complete conversion to benzylazide, phenylacetylene **2** (1 equiv) and the reducing agent were added directly without any workup procedure. Two different reagents were tested: (A) sodium ascorbate[2] and (B) Cu powder, which was used together with 10 mol % $CuSO_4$ to obtain the Cu(I) species by comproportionation.[5,16] Heating to 80 °C by microwave irradiation was required in both cases to obtain high yields within reasonable reaction times. Whereas in the case of sodium ascorbate as reducing agent reaction times of less than 1 h could be achieved only by addition of the Cu(I)-stabilizing ligand tris(benzyltriazolylmethyl)amine (TBTA)[17] (cf. entries 3 and 4), the Cu/$CuSO_4$ system gave

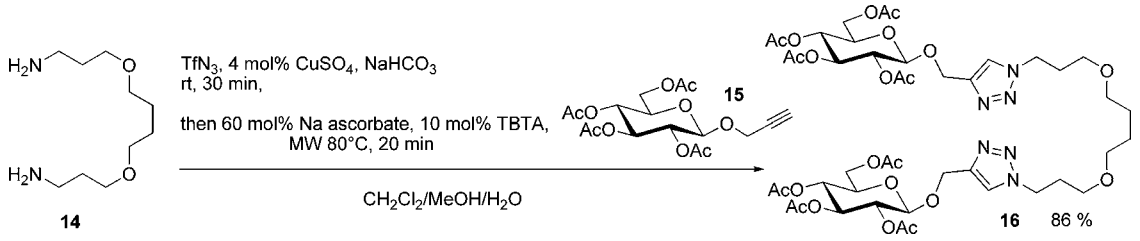
Table 2. One-Pot Synthesis of 1,2,3-Triazoles from Amines[a]



entry	amine	product	MW-irradiation time	yield
1	 **4**	 **9**	30 min	78 %[b]
2	 **5**	 **10**	10 min	81 %[c]
3	 **6**	 **11**	20 min	94 %[d]
4	 **7**	 **12**	20 min	99 %
5	 **8**	 **13**	10 min	88 %

[a] Amounts of reagent are given per amino group. [b] The reaction was performed at 120 °C. [c] 2 equiv of $NaHCO_3$ was used. [d] 30 mol % of Na ascorbate was used.

Scheme 1. Synthesis of a Divalent Glycoconjugate Using the One-Pot Procedure



comparable reaction rates and yields without this additive (entry 6). Using an excess of amine **1** (1.5 equiv relative to **2**) gave slightly higher yields but was not essential (cf. entries 4 and 5).

While both variants proceeded well, we decided to use sodium ascorbate as reducing agent for further studies because the Cu/$CuSO_4$ system seemed to be less reliable regarding the formation of side products. To prove the general adaptability, different amines **4**−**8** were applied in the described one-pot procedure (Table 2). In all cases, the triazole products **9**−**13** were isolated in very good yields.

The fact that Fmoc-protected lysine **6** could be converted to **11** without problems illustrates the potential use of the procedure for the functionalization of peptides. The use of diamines **7** and **8** resulted in high yields of bis-triazoles **12** and **13**, showing the capability for generating multivalent structures.

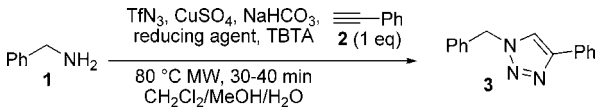
Multivalency plays an important role in carbohydrate−lectin interactions which are responsible for many biological recognition and signal transduction processes.[7,18] Therefore, much attention has been paid to the synthesis of multivalent neoglycoconjugates as ligands for lectins.[8,10,19]

To show the convenience of our approach for the synthesis of multivalent glycoconjugates, we prepared divalent glucoconjugate **16** (Scheme 1). Starting from diamine **14** and propargyl glucoside **15**, the reaction proceeded cleanly, obtaining **16** in a yield of 86%. A detailed study using this approach for the synthesis of multivalent glycoconjugates is ongoing and will be reported in due course.

We next investigated the possibility to perform diazo transfer and cycloaddition as a one-step one-pot reaction. In orienting experiments we could show that neither the alkyne interferes with the diazo transfer nor a considerable reaction of triflyl azide and alkyne takes place in the presence of 2 mol % of $CuSO_4$, 10 mol % of sodium ascorbate, and 5 mol % of TBTA. This is remarkable since copper-catalyzed reactions between sulfonyl azides and alkynes have been reported.[20] Therefore, we added all components of our test system simultaneously, and the desired triazole **3** was formed in yields slightly lower than those of the sequential one-pot procedure (Table 3). Both reducing agents could be applied; however, in this case the Cu/Cu(II) system turned out to be more reliable.

It has been reported that ionic azides react with dichloromethane to form explosive diazidomethane.[21] Therefore, an alternative procedure for the preparation of triflyl azide and its use in diazo transfer reactions has been published recently, in which dichloromethane is replaced with toluene.[22] In order to test whether these conditions are also compatible with our one-pot procedure, we reacted **1** and **2** in different ternary solvent mixtures. With the system toluene/2-propanol/water we found conditions that gave product **3** of our test reaction in a yield of 77% (Scheme 2). Although this yield

Table 3. One-Step, One-Pot Reaction



entry	amine (equiv)	$CuSO_4$ (mol %)	reducing agent	TBTA (mol %)	yield (%)
1	1.5	2	10 mol % of Na ascorbate	5	93
2	1.0	10	30 mol % of Cu powder		82

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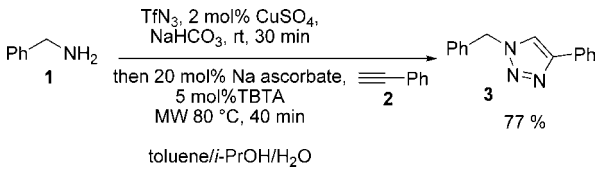
Scheme 2. Sequential One-Pot Procedure in Toluene, Isopropyl Alcohol, and Water



is lower compared to that given in Table 1, entry 5, this procedure represents a safe alternative suitable for reactions on a larger scale.[23]

In conclusion, efficient one-step and sequential one-pot procedures for diazo transfer and azide−alkyne cycloaddition have been developed giving access to triazoles commencing with amines being commercially available in a great variety. The one-pot reaction has a broad scope and is especially practical for the synthesis of multivalent structures because the isolation of intermediate azides is prevented. While the one-step procedure is convenient, the sequential variant, however, has the advantage that it can be more easily followed by TLC and gives higher reaction yields.

Acknowledgment. We thank Prof. W. Pfleiderer, Universität Konstanz, for valuable discussions regarding the $Cu/CuSO_4$ reducing system and Biotage AB for providing a microwave synthesizer.

Supporting Information Available: Experimental procedures and full characterization of compounds **11**−**13** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) It has to be noted that even if diazidomethane is formed, it would be converted to stable triazole derivatives in the subsequent azide−alkyne cycloadditions. However, we could never identify side products resulting from such a reaction.