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Tandem synthesis of 1-formyl-1,2,3-triazoles

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ABSTRACT

A tandem method for preparing 4-formyl-1,2,3-triazoles via a two-step one-pot acetal cleavage/CuAAC reaction was developed. Using this method, 4-formyl-1,2,3-triazole analogs with both electron-withdrawing and electron-donating substituents were prepared in good yield and purity. Expansion of this method to a three-step tandem reaction that incorporates an additional step of azide substitution was also successful, circumventing the need for organic azide isolation. This one-pot method, noteworthy in its simplicity and mild conditions, utilizes practical, readily available reactants and relies on protic solvent to promote acid-catalyzed acetal cleavage.

Among the many attractive features of the Sharpless-Meldal copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction[1–4] is its remarkable chemical orthogonality. Not only does this allow CuAAC reactions to be employed in a diverse range of chemical environments, but it also facilitates the development of tandem reactions around this bond forming process.[5] Examples include substitution,[6–8] desilylation,[9,10] decarboxylation,[11] cross-coupling,[12] oxidation,[13] and condensation,[14] along with combinations thereof. Establishing reliable tandem CuAAC methods enables the efficient preparation of 1,2,3-triazole-containing molecules, which have shown value in diverse fields including coordination compounds,[15–17] chemosensors,[18] bioimaging agents,[17,19] and polymeric materials.[20,21]

Analogs of the 4-formyl-1,2,3-triazole motif have recently been reported to display enzyme inhibitory,[22] anti-cancer[23,24] antileishmanial[25] and anti-tuberculosis activity.[26,27] With the aldehyde group an attractive handle for synthetic diversification, such compounds have also served as synthons for preparing bioimaging,[28] anti-cancer,[23,24] and anti-tuberculosis[26,27] agents. Likewise, 4-imino-1,2,3-triazoles formed from amine condensation reactions have been shown to be useful for constructing novel coordination compounds.[29–31]

Several published methods are known for preparing 4-formyl-1,2,3-triazoles. The direct synthesis from propynal has been reported,[32] but is impractical due to this reagent's low boiling point and lack of commercial availability. A two-step method of CuAAC reaction with propargyl alcohol followed by oxidation of the hydroxymethylated triazole intermediate with reagents such as CrO_3[24] or MnO_2[30] is effective but limited to substituents that can withstand such oxidants, and is environmentally unfriendly. Advances in this approach using organic oxidants[23,33] and polymer-immobilized two-component catalysis[34] methods have recently been reported. Lastly, two-step methods using CuAAC reactions with commercially available acetal-protected propargyl aldehydes followed by deprotection of the formyl group via acid-catalyzed hydrolysis are known,[35,36] but are limited to substituents tolerant of strong acids such as HCl or TFA.

Examples of tandem click reactions involving acetal cleavage leading to aldehyde-functionalized products are lacking. The aim of this investigation was therefore to develop a reliable, mild and straightforward tandem CuAAC method to prepare 4-formyl-1,2,3-triazoles directly from practical, commercially available precursors. In addition, exploring the amenability of such conditions for expansion into three- and four-step tandem CuAAC reactions was desired. This included the evaluation of the pre-CuAAC reaction step of azide substitution, of interest because it allows the circumvention of organic azide isolation,[37] and the post-CuAAC reaction step of imine-forming condensation, of interest in coordination chemistry applications.[29–31]

During an initial study aiming to prepare 4-formyl-1,2,3-triazole compounds using a stepwise approach, common room temperature aqueous CuAAC conditions were used to click aryl azides with propargyl aldehyde diethyl acetal. As described in Table 1, it was observed that these product mixtures contained minor but significant amounts of deprotected 1-aryl-4-formyl-1,2,3-triazole products in addition to the expected diethyl acetal product analogs, as determined by ^{1}H NMR spectroscopy. This

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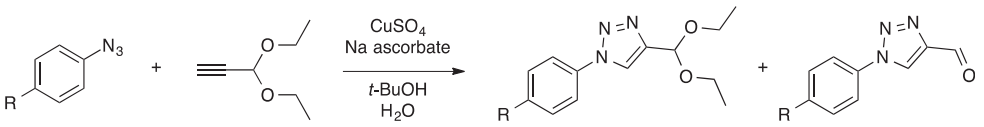
Table 1
Evaluation of temperature for two-step tandem reaction.[a]



Entry	R =	Temp.	ID	Yield **1** (%)	ID	Yield **2** (%)
1	NO_2	r. t.	**1a**	83	**2a**	15
2	CF_3	r. t.	**1b**	70	**2b**	28
3	H	r. t.	**1c**	56	**2c**	43
4	CH_3	r. t.	**1d**	67	**2d**	31
5	OCH_3	r. t.	**1e**	60	**2e**	38
6	NEt_2	r. t.	**1f**	83	**2f**	0
7	NO_2	70 °C	**1a**	0	**2a**	81
8	CF_3	70 °C	**1b**	0	**2b**	95
9	H	70 °C	**1c**	0	**2c**	88
10	CH_3	70 °C	**1d**	0	**2d**	97
11	OCH_3	70 °C	**1e**	0	**2e**	93
12	NEt_2	70 °C	**1f**	0	**2f**	95

[a] Reaction conditions: azide (1.0 mmol), alkyne (1.0 mmol), $CuSO_4$ (0.2 mmol), sodium ascorbate (0.4 mmol) in 1:1 *t*-BuOH:H_2O (10 ml) under air for 24 h.

inspired the study reported herein, aiming to determine whether aqueous CuAAC conditions could be optimized towards producing deprotected formyl analogs in what would be a two-step tandem cleavage/CuAAC reaction.

It was believed that the protic solvent environment of these conditions was adequately acidic to promote measurable acetal cleavage, albeit slowly. With the goal of enhancing the rate of deprotection relative to the initial observations, three parameters were evaluated: temperature, solvent and triazole substituent identity. As summarized in Table 1, a simple increase in the reaction temperature from room temperature to 70 °C resulted in a remarkable increase in deprotected product yields. This effect was consistent for analogs possessing representative electron-withdrawing and electron-donating substituents.

^{1}H NMR provides a straightforward method for quantitatively monitoring the progress of acetal cleavage. For the series of compounds studied, the acetal α-proton resonates between 5.6 and 5.9 ppm. After deprotection of the aldehyde functionality, this proton shifts downfield to between 10.1 and 10.4 ppm. Likewise, the triazole proton shifts downfield from 7.7–8.0 ppm to 8.3–8.5 ppm. Both ^{1}H signals appear as singlets, and integration of the peak area of these two characteristic resonances allows for determination of reaction progress. An example of the distinguishing signals between acetal and aldehyde products for the conversion of **1f** to **2f** is illustrated in Fig. S1.

Because CuAAC reactions using the $CuSO_4$/sodium ascorbate catalyst system are tolerant to a wide range of solvents, a survey of alcohol solvents was completed. As summarized in Table 2, this evaluation showed that the progress of the desired two-step tandem reaction varied considerably with alcohol solvent identity. The ideal solvent condition among those surveyed was 1:1 H_2O:*t*-BuOH. Hence, these conditions were utilized in subsequent reaction development efforts for this investigation.

An evaluation of this tandem acetal cleavage/CuAAC reaction's compatibility with an additional azide substitution step was completed (Table 3). Simple addition of sodium azide and either allyl bromide or benzyl bromide reactants to the standard aqueous CuAAC reaction conditions resulted in both allylated and benzylated triazole products. Similar to the aryl azide studies, at low temperature a mixture of major acetal products and minor formyl products were observed. At high temperature, pure formyl analogs were obtained in good yield and purity, establishing a reliable three-step tandem method for preparing 1-substituted-4-formyl-1,2,3-triazole compounds.

Crystals of **2d** and **2f** suitable for structural analysis were grown from slow evaporation of methylene chloride solutions. As shown in Fig. S2, the dihedral angle between the phenyl and triazole rings of **2d** is 0.6° and the dihedral angle between its formyl group and triazole ring is 5.5°. Fig. S3 illustrates similar structural characteristics for **2f**, where the dihedral angle between aromatic rings is 22.9° and the dihedral angle between the formyl group and triazole ring is 3.8°. The bond angles of the diethylamino nitrogen atom clearly indicate its sp^2 hybridization and conjugation with the benzene ring. Collectively, the largely coplanar neighboring π-systems of these molecules support the ability of peripheral *para*-phenyl groups to communicate electronically with the remote 4-formyltriazole units and exert substituent effects in this family of compounds.

In order to measure the extent by which *para*-phenyl substituent identity at the 1-position of the triazole is able to influence the electrophilicity of the formyl group at the 4-position, solvolysis studies were performed in CD_3OD. Degree of solvation was measured by integration of aldehyde vs. acetal ^{1}H NMR signals, along with corresponding triazole singlets. As summarized in Table S1, a trend of increasing degree of solvation was observed as electron-withdrawing strength of the 1-aryl substituent increased. This clearly demonstrates the ability of *para* phenyl substituents to influence the remote carbonyl position via electronic effects through the benzene and triazole aromatic systems.

With the goal of developing a three-step tandem reaction that includes a condensation step leading to 4-imino-1,2,3-triazole products, a survey of condensation efficiency between 4-formyl-1,2,3-triazoles and aryl amines using aqueous tandem click conditions was completed (Table 4). This initial study employed matching *para* functional groups between the triazole and aryl amine reactants, which were treated under high temperature aqueous click solvent conditions. Following isolation from the reaction solvent by extraction, the resulting mixtures were analyzed by ^{1}H NMR in order to define the spontaneity of the condensation relative to functional group identity. With the exception of the nitro-