Published in final edited form as:

Tetrahedron Lett. 2017 November 22; 58(47): 4450–4454. doi:10.1016/j.tetlet.2017.10.023.

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

James T. Fletcher, Joseph A. Christensen, and Eric M. Villa

Department of Chemistry, Creighton University, 2500 California Plaza, Omaha, NE 68178, U.S.A

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.

TOC image

Keywords

Acetal; Aldehyde; Click chemistry; Tandem reaction; 1; 2; 3-Triazole

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

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Supplementary data

Supplementary data related to this article can be found at _____. Crystallographic information for the SC-XRD analysis of **2e** and **2f** can be found in the Supplementary data. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre: **2e** as CCDC 1565067 and **2f** as 1565068. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: despoit@ccdc.cam.ac.uk).

molecules, which have shown value in diverse fields including coordination compounds,^{15–17} chemosensors,¹⁸ bioimaging agents,^{17,19} and polymeric materials.^{20,21}

Analogues of the 4-formyl-1,2,3-triazole motif have recently been reported to display enzyme inhibitory,²² anti-cancer^{23,24} antileishmanial²⁵ 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 antituberculosis^{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 catalysis³⁴ 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 ^1H NMR spectroscopy. This 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.

¹H 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 ¹H 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 Figure S1.

Because CuAAC reactions using the CuSO₄/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 H₂O:*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 Figure 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°. Figure 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 sp² 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 CD₃OD. Degree of solvation was measured by integration of aldehyde vs. acetal ¹H 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 ^1H NMR in order to define the spontaneity of the condensation relative to functional group identity. With the exception of the nitro-substituted analog, each derivative was capable of forming significant quantity of imine product despite the use of an aqueous 1:1 H_2O :*t*-BuOH solvent system.

Encouraged by these results, three-step tandem reactions incorporating acetal cleavage, CuAAC and condensation were attempted by simple addition of all reagents at the onset of the reaction. Having demonstrated the individual compatibility of these reactants with each of the three steps in this sequence, it was expected that the electron-rich systems would produce the largest ratio of 4-imino-1,2,3-triazole products. Surprisingly, it was observed for these three-step tandem reactions that as the electron-donating ability of the substituents increased the amount of acetal-containing products increased (Table 5).

Considering the requirements of each step of the sequence, it was proposed that the increasingly basic nature of the electron-rich aryl amine reactants was interfering with the ability of the solvent system to generate sufficient acidity to promote acetal cleavage. While the electron-poor nitro analog showed successful deprotection but failed to condense, analogs of increasing electron density showed the disparate outcome of both stalling at the acetal cleavage stage and proceeding to successful condensation. Under the conditions studied, none of the utilized analogs were capable of establishing a balance of sufficient nucleophilicity to promote spontaneous condensation together with insufficient basicity to allow solvent-promoted acid-catalyzed acetal cleavage.

A simple solution to this issue was a time-delayed introduction of aryl amine into the reaction mixture. When added at the 20 h time point (not optimized) instead of at the reaction onset, no acetal products were observed and the ratio of formyl and imino products closely resembled that in the one-step condensation studies. While optimization of this reaction was not a focus of this study, it appears that a three-step tandem approach for preparing 4-imino-1,2,3-triazoles from commercially available reactants is indeed feasible if a time-delayed introduction of reagents were to be employed. It is noteworthy that a four-step tandem reaction also including an azide substitution step analogous to that shown in Scheme 3 was attempted, but failed due to cross-reaction between the organic bromides and aryl amine reactants.

In conclusion, a mild and effective method has been established to prepare 4-formyl-1,2,3-triazoles from commercially available reactants via a two-step tandem acetal cleavage/CuAAC transformation.[38] Using this method, 4-formyl-1,2,3-triazole analogs with both

electron-withdrawing and electron-donating substituents at the 1-position can be prepared in good yield and purity. It is proposed that the simplicity of this tandem method will be useful for efficiently preparing a wide range of 1-substituted-4-formyl- 1,2,3-triazoles. 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.

While condensation reactions converting 4-formyl-1,2,3-triazoles into 4-imino- 1,2,3-triazoles were effective even in an aqueous environment, a three-step tandem reaction incorporating an additional step of condensation leading to imine analogs was successful only when a time-delayed introduction of amine was used. This incompatibility is likely due to the acid-catalyzed nature of the acetal cleavage step. Future work will focus on more closely investigating the parameters of the imine-forming condensation reaction and using tandem methods to prepare new 4-imino-1,2,3-triazole motifs for applications in coordination chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This publication was made possible by grants from the National Institute for General Medical Science (NIGMS) (5P20GM103427), a component of the National Institutes of Health (NIH), and its contents are the sole responsibility of the authors and do not necessarily represent the official views of NIGMS or NIH. JAC acknowledges Creighton University's Baumann Family Scholarship for financial support.

References

1. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew Chemie Int Ed.* 2002; 41:2596–2599.
2. Tornøe CW, Christensen C, Meldal M. *J Org Chem.* 2002; 67:3057–3064. [PubMed: 11975567]
3. Kolb HC, Finn MG, Sharpless KB. *Angew Chemie Int Ed.* 2001; 40:2004–2021.
4. Meldal M, Tornøe CW. *Chem Rev.* 2008; 108:2952–3015. [PubMed: 18698735]
5. Hassan S, Müller TJJ. *Adv Synth Catal.* 2015; 357:617–666.
6. Fletcher JT, Keeney ME, Walz SE. *Synthesis.* 2010:3339–3345.
7. Zeini Jahromi E, Gailer J. *Dalton Trans.* 2010; 39:329–336.
8. Fletcher JT, Reilly JE. *Tetrahedron Lett.* 2011; 52(42):5512–5515. [PubMed: 22368306]
9. Fletcher JT, Bumgarner BJ, Engels ND, Skoglund DA. *Organometallics.* 2008; 27:5430–5433.
10. Fletcher JT, Walz SE, Keeney ME. *Tetrahedron Lett.* 2008; 49:7030–7032.
11. Kolarovi A, Schnürch M, Mihovilovic MD. *J Org Chem.* 2011; 76:2613–2618. [PubMed: 21391535]
12. Majumdar KC, Ganai S. *Tetrahedron Lett.* 2013; 54:6192–6195.
13. Janreddy D, Kavala V, Kuo CW, Chen WC, Ramesh C, Kotipalli T, Kuo TS, Chen ML, He CH, Yao CF. *Adv Synth Catal.* 2013; 355:2918–2927.
14. Souza FB, Pimenta DC, Stefani HA. *Tetrahedron Lett.* 2016; 57:1592–1596.
15. Mindt TL, Müller C, Stuker F, Salazar J-F, Hohn A, Mueggler T, Rudin M, Schibli R. *Bioconjug Chem.* 2009; 20:1940–1949. [PubMed: 19803478]
16. Struthers H, Mindt TL, Schibli R. *Dalton Trans.* 2010; 39:675–696. [PubMed: 20066208]
17. Mindt TL, Schweinsberg C, Brans L, Hagenbach A, Abram U, Tourwé D, Garcia-Garayoa E, Schibli R. *ChemMedChem.* 2009; 4:529–539. [PubMed: 19235821]

18. Lau YH, Rutledge PJ, Watkinson M, Todd MH. *Chem Soc Rev.* 2011; 40:2848. [PubMed: 21380414]
19. Struthers H, Spingler B, Mindt TL, Schibli R. *Chem - A Eur J.* 2008; 14:6173–6183.
20. Sumerlin BS, Vogt AP. *Macromolecules.* 2010; 43:1–13.
21. Qin A, Lam JWY, Tang BZ. *Chem Soc Rev.* 2010; 39:2522. [PubMed: 20571673]
22. Gonzaga DR, Senger M, Da Silva FDC, Ferreira VF, Silva FP. *Eur J Med Chem.* 2014; 74:461–476. [PubMed: 24487194]
23. Sambasiva Rao P, Kurumurthy C, Veeraswamy B, Santhosh Kumar G, Shanthan Rao P, Pamanji R, Venkateswara Rao J, Narsaiah B. *Bioorganic Med Chem Lett.* 2013; 23:1225–1227.
24. Sambasiva Rao P, Kurumurthy C, Veeraswamy B, Santhosh Kumar G, Poornachandra Y, Ganesh Kumar C, Vasamsetti SB, Kotamraju S, Narsaiah B. *Eur J Med Chem.* 2014; 80:184–191. [PubMed: 24780595]
25. Ferreira SB, Costa MS, Boechat N, Bezerra RJS, Genestra MS, Canto-Cavaleiro MM, Kover WB, Ferreira VF. *Eur J Med Chem.* 2007; 42:1388–1395. [PubMed: 17445951]
26. Boechat N, Ferreira VF, Ferreira SB, Ferreira MDLG, Silva FDC, Bastos MM, Costa MS, Lourenc MCS, Pinto AC, Krettli AU, Aguiar AC, Teixeira BM, Silva NV, Martins PRC, Bezerra FAFM, Camilo ALS, Silva GP, Costa CCP. *J Med Chem.* 2011; 54:5988–5999. [PubMed: 21776985]
27. Costa MS, Boechat N, Rangel ÉA, da Silva FdeC, de Souza AMT, Rodrigues CR, Castro HC, Junior IN, Lourenço MCS, Wardell SMSV, Ferreira VF. *Bioorganic Med Chem.* 2006; 14:8644–8653.
28. Pisal MM, Annadate RA, Athalye MC, Kumar D, Chavan SP, Sarkar D, Borate HB. *Bioorg Med Chem Lett.* 2017; 27:979–988. [PubMed: 28073677]
29. Hagiwara H, Minoura R, Okada S, Sunatsuki Y. *Chem Lett.* 2014; 43(6):950–952.
30. Hagiwara H, Okada S. *Chem Commun.* 2016; 52:815–818.
31. Hagiwara H, Tanaka T, Hora S. *Dalt Trans.* 2016; 45:17132–17140.
32. Sarmiento-sánchez JI, Ochoa-terán A, Rivero IA. *Arkivoc.* 2011; ix:177–188.
33. Tale RH, Gopula VB, Toradmal GK. *Tetrahedron Lett.* 2015; 56:5864–5869.
34. Diz PM, Coelho A, El Maatougui A, Azuaje J, Caamano O, Gil Á, Sotelo E. *J Org Chem.* 2013; 78:6540–6549. [PubMed: 23738944]
35. Lee I, Choe YS, Choi JY, Lee KH, Kim BT. *J Med Chem.* 2012; 55:883–892. [PubMed: 22236086]
36. Wu J, Green N, Hotchandani R, Hu Y, Condon J, Huang A, Kaila N, Li HQ, Guler S, Li W, Tam SY, Wang Q, Pelker J, Marusic S, Hsu S, Perry Hall J, Telliez JB, Cui J, Lin LL. *Bioorganic Med Chem Lett.* 2009; 19:3485–3488.
37. Brase S, Gil C, Knepper K, Zimmermann V. *Angew Chemie - Int Ed.* 2005; 44:5188–5240.
38. General procedure for cleavage/CuAAC. To a 20 mL screw-top vial was added (in order) CuSO₄ (0.032 g, 0.2 mmol), L-ascorbic acid sodium salt (0.079 g, 0.4 mmol), water (5 mL), *t*-butyl alcohol (5 mL), aryl azide reactant (1.0 mmol) and propargyl aldehyde diethyl acetal (0.158 mL, 1.1 mmol). The vial was then capped and stirred at either room temperature or 70° C for 24 hr. The reaction mixture was then extracted between CH₂Cl₂ and 5% NH₄OH (aq). The organic layer was separated, dried with MgSO₄ and gravity filtered. The solvent was removed via rotary evaporation to give the isolated product or product mixture used for NMR analysis. Further purification was accomplished by silica gel chromatography using either CH₂CH₂ or 20:1 CH₂CH₂:ethyl acetate eluent.

Highlights

- A tandem, two-step acetal cleavage/CuAAC method was developed.
- Acetal cleavage is promoted by protic solvent at moderate temperature.
- A tandem, three-step substitution/acetal cleavage/CuAAC reaction was successful.
- Tandem imine formation was successful only with a time-delayed amine addition.

Table 1Evaluation 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

^aReaction conditions: azide (1.0 mmol), alkyne (1.0 mmol), CuSO₄ (0.2 mmol), sodium ascorbate (0.4 mmol) in 1:1 *t*-BuOH:H₂O (10 ml) under air for 24 h.

Table 2Evaluation of alcohol solvents for two-step tandem reaction^a

Entry	Solvent	Yield 1d (%)	Yield 2d (%)
1	MeOH	85	9
2	EtOH	79	14
3	<i>i</i> -PrOH	69	30
4	<i>t</i> -BuOH	8	49
5	<i>t</i> -BuOH:H ₂ O	0	97

^aReaction conditions: azide (1.0 mmol), alkyne (1.0 mmol), CuSO₄ (0.2 mmol), sodium ascorbate (0.4 mmol) in solvent (10 ml) under air for 24 h.

Table 3

Evaluation of temperature for three-step tandem reaction^a

Entry	R =	Temp.	ID	Yield 1 (%)	ID	Yield 2 (%)
1	Allyl	r. t.	1g	76	2g	4
2	Benzyl	r. t.	1h	73	2h	13
3	Allyl	70° C	1g	0	2g	71
4	Benzyl	70° C	1h	0	2h	67

^a Reaction conditions: organic bromide (1.0 mmol), sodium azide (1.0 mmol), alkyne (1.0 mmol), CuSO₄ (0.2 mmol), sodium ascorbate (0.4 mmol) in 1:1 t-BuOH:H₂O (10 ml) under air for 24 h.

Table 4Evaluation of substituent identity on direct condensation^a

Entry	R =	ID	Ratio 2 (%)	ID	Ratio 4 (%)
1	NO ₂	2a	100	4a	0
2	CF ₃	2b	57	4b	43
3	H	2c	38	4c	62
4	CH ₃	2d	45	4d	55
5	OCH ₃	2e	33	4e	67
6	NEt ₂	2f	13	4f	87

^aReaction conditions: **2** (1.0 mmol), amine (1.0 mmol) in 1:1 t-BuOH:H₂O (10 ml) under air for 24 h.

Table 5Evaluation of substituent and addition time on three-step tandem condensation^a

Entry	R =	Add time	ID	Ratio (%)	ID	Ratio (%)	ID	Ratio (%)
1	NO ₂	0	1a	0	2a	100	4a	0
2	CF ₃	0	1b	0	2b	56	4b	44
3	H	0	1c	11	2c	22	4c	67
4	CH ₃	0	1d	44	2d	12	4d	44
5	OCH ₃	0	1e	45	2e	10	4e	45
6	NEt ₂	0	1f	90	2f	0	4f	10
7	NO ₂	20 h	1a	0	2a	100	4a	0
8	CF ₃	20 h	1b	0	2b	61	4b	39
9	H	20 h	1c	0	2c	25	4c	75
10	CH ₃	20 h	1d	0	2d	10	4d	90
11	OCH ₃	20 h	1e	0	2e	17	4e	83
12	NEt ₂	20 h	1f	0	2f	0	4f	100

^aReaction conditions: organic azide (1.0 mmol), alkyne (1.0 mmol), CuSO₄ (0.2 mmol), sodium ascorbate (0.4 mmol) in 1:1 t-BuOH:H₂O (10 ml) under air for 24 h. Amine (1.0 mmol) added either at reaction onset or after 20 h of stirring.