

One-Pot Three-Step Synthesis of 1,2,3-Triazoles by Copper-Catalyzed Cycloaddition of Azides with Alkynes formed by a Sonogashira Cross-Coupling and Desilylation

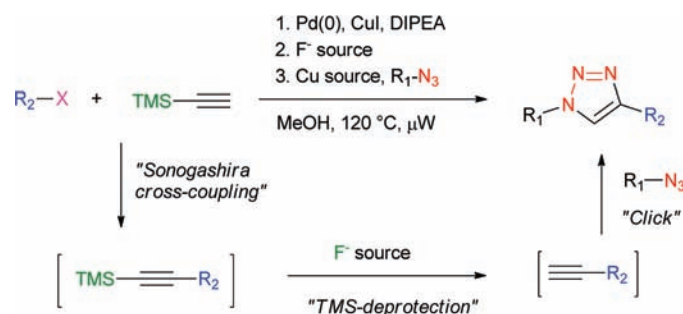
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ABSTRACT



A microwave-assisted, one-pot, three-step Sonogashira cross-coupling–desilylation–cycloaddition sequence was developed for the convenient preparation of 1,4-disubstituted 1,2,3-triazoles starting from a range of halides, acyl chlorides, ethynyltrimethylsilane, and azides.

The exquisite regioselectivity, high tolerance to the presence of functional groups, and exceptional high yields of Cu(I)-catalyzed 1,3-dipolar cycloadditions of azides with terminal alkynes (CuAAC) to give 1,4-disubstituted triazoles¹ have made it a powerful approach for bioconjugation,² construction, and modification of materials³ and the parallel combinatorial synthesis of libraries of compounds for drug dis-

covery.⁴ Recent efforts to further develop CuAAC have focused on one-pot multicomponent reactions in which azides are prepared in situ prior to the cycloaddition. The attraction of such an approach is that it minimizes time-consuming workup and purification protocols and avoids handling of potentially explosive azides. Most methods for in situ preparation of azides take advantage of the nucleophilicity of sodium azide toward electrophiles such as aromatic fluorides, iodides, benzylic bromides, as well as epoxides and boronic acids.⁵ Organic azides have also been generated in situ by Cu(II)-catalyzed diazo transfer of triflyl azide or azidotrimethylsilane to amines.⁶ Surprisingly, one-pot mul-

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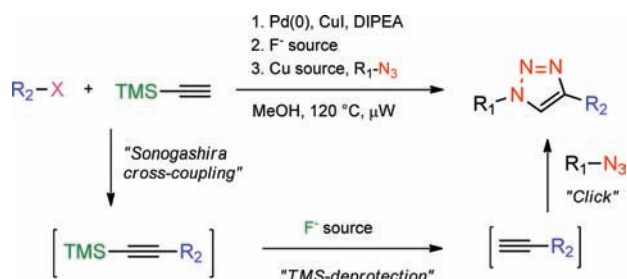
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timestep reactions involving in situ generation of terminal alkynes for click chemistry have not been reported. The attraction of such an approach is that a wide variety of alkynes can be generated from simple and readily available starting materials, such as aromatic halides.

Herein, we describe a microwave-assisted one-pot, three-step procedure entailing Sonogashira cross-coupling of aromatic halides with ethynyltrimethylsilane (TMS-acetylene) to give TMS-protected alkynes, which were desilylated and then employed in 1,3-dipolar cycloadditions with various azides to give a range of 1,2,3-triazoles (Scheme 1). In

Scheme 1. One-Pot Three-Step Synthesis of 1,2,3-Triazoles by in Situ Formation of a Terminal Alkyne by Sonogashira Cross-Coupling and Desilylation Followed by a Cycloaddition with an Azide



addition, it was found that the use of aromatic acyl chlorides in the Sonogashira cross-coupling gave TMS-protected ynones, which after desilylation and Cu(I)-catalyzed cycloadditions with azides led to the regioselective formation of 1-substituted 4-phenylacyl-1*H*-1,2,3-triazoles.

First, optimal reaction conditions were established for a fast and high-yielding one-pot desilylation–cycloaddition reaction sequence (Table 1). It has been reported that TMS-

Table 1. Microwave-Assisted One-Pot TMS-Deprotection of Compounds **1a–g** and Cycloaddition with Azides **2a–c** to Give Triazoles **3a–i**

entry	R	R'	method A ^a yield (%)	method B ^b yield (%)
1	C ₆ H ₅	Bn	98	98 ^c
2	4-MeO-C ₆ H ₄	Bn	97	96
3	4-CF ₃ -C ₆ H ₄	Bn	98	97
4	4-Cl-C ₆ H ₄	Bn	89	95
5	4-Br-C ₆ H ₄	Bn	81	91
6	2-Br-C ₆ H ₄	Bn	89	90
7	CH ₂ OH	Bn	82	98
8	C ₆ H ₅	4-MeO-Bn	87	98
9	C ₆ H ₅	4-NO ₂ -Bn	98	99

^a A mixture of TBAF (1.0 M, 1.0 equiv), CuI (10 mol %), and DIPEA (20 mol %) was used. ^b CuF₂ (2.0 equiv) was used. ^c **3a** was isolated in yields of 22% and 57% when the reaction was performed at 60 or 90 °C, respectively.

modified acetylenes can readily be deprotected using reagents such as tetrabutylammonium fluoride (TBAF)⁷ or silver salts⁸ to give terminal alkynes, which can then undergo cycloadditions with azides. It was expected that these two steps can be performed as a one-pot process and accelerated by microwave irradiation.⁹ A temperature survey revealed that reaction of trimethyl(phenylethynyl)silane (**1a**) with benzyl azide (**2a**) in the presence of TBAF (1 equiv), CuI (10 mol %), and *N,N*-diisopropylethylamine (20 mol %) in methanol under microwave irradiation at 120 °C was complete within 20 min to afford the 1,4-disubstituted triazole **3a** in an almost quantitative yield as a single regioisomer (Table 1, entry 1, method A). A similar reaction without TBAF resulted in no triazole formation, clearly establishing that the TMS-alkyne must be deprotected to undergo a 1,3-dipolar cycloaddition. Furthermore, when the transformation was performed in the absence of CuI, only a trace amount of triazole was isolated as a mixture of regioisomers.¹⁰ The desilylation–cycloaddition reaction could also be performed at ambient temperature; however, in this case a prolonged reaction time of 12 h was required to achieve complete conversion of the starting materials.

We have found that CuF₂ is an efficient reagent for deprotecting TMS-modified alkynes and promoting 1,3-dipolar cycloadditions with azides to give 1,4-disubstituted triazoles.¹¹ As expected, the use of CuF₂ (2 equiv) also gave the 1,2,3-triazole **3a** in an excellent yield (Table 1, entry 1, method B). It was found that the scope of the one-pot process is excellent, and 1,4-disubstituted triazoles containing electron-donating (entry 2), -withdrawing (entry 3), and bulky functionalities (entry 6) could be obtained in excellent yield. Furthermore, the use of CuF₂ was found to be most convenient and gave in general slightly higher yields of product compared to the use of TBAF/CuI. It is also possible to employ a catalytic amount of CuF₂ (10 mol %); however, in this case the addition of TBAF (1 equiv) is required to facilitate desilylation.

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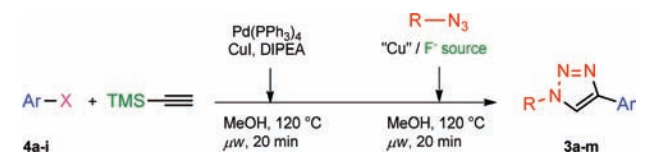
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(10) Heating under microwave irradiation trimethyl(phenylethynyl)silane (**1a**) with benzyl azide (**2a**) in the presence of TBAF (1 equiv) at 120 °C for 20 min resulted in less than 5% yield of the corresponding triazole in a 1:1 mixture of regioisomers.

(11) Mechanistic studies and DFT calculations support the notion that CuF₂ catalyzes the cycloaddition. Friscourt, F.; Ledin, P. A.; Boons, G.-J. In *Abstracts of Papers, 239th ACS National Meeting* (March 21–25) San Francisco, CA, USA, 2010 and manuscript in preparation.

TMS-substituted alkynes are readily accessible by Sonogashira cross-coupling between aromatic halides and ethynyltrimethylsilane.¹² Furthermore, it has been found that microwave irradiation can significantly reduce the reaction time of metal-catalyzed cross-coupling reactions.¹³ Thus, we explored whether Sonogashira cross-coupling, desilylation, and cycloaddition can be performed under microwave conditions as a one-pot procedure. Various aromatic iodides (Table 2, entries 1–6 and 10–11) were reacted with

Table 2. One-Pot, Three-Step Synthesis of 1,4-Disubstituted Triazoles **3**



entry	Ar-X	R	method A ^a yield (%)	method B ^b yield (%)
1	Ph-I	Bn	96	91
2	4-MeO-C ₆ H ₄ -I	Bn	41	54
3	4-CF ₃ -C ₆ H ₄ -I	Bn	97	98
4	4-F-C ₆ H ₄ -I	Bn	98	98
5	4-Me-C ₆ H ₄ -I	Bn	93	95
6	2-Me-C ₆ H ₄ -I	Bn	97	98
7	Ph-Br	Bn	42	65
8	4-MeO-C ₆ H ₄ -Br	Bn	13	15 (57 ^c)
9	4-NO ₂ -C ₆ H ₄ -Br	Bn	12	11 (53 ^c)
10	Ph-I	4-MeO-Bn	84	91
11	Ph-I	4-NO ₂ -Bn	97	98

^a A mixture of TBAF (1.0 M, 2.0 equiv) and CuI (10 mol %) was used. ^b CuF₂ (2.0 equiv) was used. ^c The Sonogashira cross-coupling was performed using Pd(PPh₃)₂Cl₂ (5 mol %) and CuI (10 mol %) in refluxing Et₃N for 10 h.

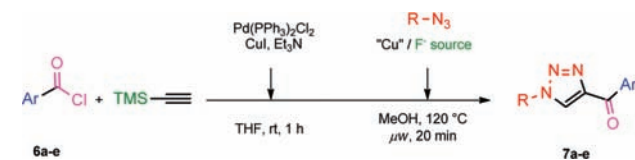
ethynyltrimethylsilane using a catalytic amount of Pd(PPh₃)₄ (5 mol %) and CuI (10 mol %) in the presence of *N,N*-diisopropylethylamine (2 equiv) in methanol under microwave irradiation at 120 °C for 20 min, followed by the introduction of an azide and TBAF/CuI or CuF₂ and further microwave irradiation at 120 °C for 20 min. Gratifyingly, the one-pot, three-step process produced the expected 1,4-disubstituted triazoles (**3**) in most cases in high yield. As expected, aromatic bromides (entries 7–9), which are known to couple poorly under classical Sonogashira cross-coupling conditions, required optimization of the palladium source, choice of amine, and reaction time. It was found that triazoles were obtained in acceptable yields when a mixture of an aromatic bromide, ethynyltrimethylsilane, Pd(PPh₃)₂Cl₂ (5 mol %), and CuI (10 mol %) in Et₃N was heated under reflux prior to the desilylation–cycloaddition protocol (entries 8 and 9).

The scope of the one-pot, three-step protocol was further extended to the synthesis of 1-substituted 4-acyl-1*H*-1,2,3-triazoles by using acyl chlorides as the starting material in

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Table 3. One-Pot, Three-Step Synthesis of 1-Substituted 4-Acyl-1*H*-1,2,3-triazoles **7a–e**



entry	Ar	R	method A ^a yield (%)	method B ^b yield (%)
1	Ph	Bn	40	42
2	4-MeO-C ₆ H ₄	Bn	80	83
3	4-F-C ₆ H ₄	Bn	82	88
4	4-NO ₂ -C ₆ H ₄	Bn	32	36
5	2-Me-C ₆ H ₄	Bn	35	34

^a A mixture of TBAF (1.0 M, 2.0 equiv) and CuI (10 mol %) was used. ^b CuF₂ (2.0 equiv) was used.

the Sonogashira cross-coupling reaction (**7**, Table 3).^{12b,14} Acyl chlorides did not tolerate the use of microwave irradiation;¹⁵ however, the desired TMS-protected ynones could be obtained by simply reacting an acyl chloride (**6**) with ethynyltrimethylsilane in the presence of Pd(PPh₃)₂Cl₂ and triethylamine in THF at room temperature for 1 h. The resulting compounds were not isolated but immediately submitted to the deprotection–cycloaddition protocol and reaction with benzyl azide in the presence of CuF₂ or the TBAF/CuI-afforded 1-benzyl,4-acyl-1*H*-1,2,3-triazoles (**7**). The Sonogashira cross-coupling reaction was found to be sensitive to the nature of the employed acyl chloride, and the use of electron-rich acyl chlorides (entries 2 and 3 vs entry 4) gave the best conversions of the starting materials. Full conversions of the 1-substituted 4-acyl-1*H*-1,2,3-triazoles were achieved when TMS-modified ynones were purified prior to reaction with azides, establishing the Sonogashira coupling of the acyl chlorides with ethynyltrimethylsilane as the yield-limiting step of the one-pot, three-step protocol.

It is important to note that 1-substituted 4-acyl-1*H*-1,2,3-triazoles have rarely been prepared by CuAAC due to side product formation.¹⁶ Previous syntheses of this class of triazoles involved classical thermal Huisgen 1,3-dipolar cycloadditions with the inconvenience of separating the two triazole regioisomers^{17a} and condensation of amines with α -diazo-1,3-dicarbonyls.^{16b} The microwave conditions reported here provide easy and regioselective access to this class of biomedically important compounds.

In conclusion, an expedient one-pot, three-step protocol has been developed for the preparation of 1,4-disubstituted

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triazoles involving Sonogashira cross-coupling to generate in situ a variety of TMS-protected alkynes, which could immediately be desilylated and reacted with azides in the presence of a mixture of TBAF/CuI or CuF₂. The reaction sequence could be completed within 1 h by employing microwave-assisted heating. Furthermore, we have shown that 2-yn-1-ones, which were obtained by Sonogashira cross-coupling of aromatic acyl chlorides with ethynyltrimethylsilane, undergo Cu-catalyzed cycloadditions with azides when subjected to microwave heating to give regioselective formation of 1-substituted 4-phenylacyl-1*H*-1,2,3-triazoles. The new one-pot, three-step process will make it possible to rapidly prepare compound libraries for drug discovery programs as it avoids time-consuming and costly purification

protocols of synthetic intermediates. Furthermore, it is to be expected that the one-pot procedure can be combined with in situ formation of azides⁵ thereby further increasing the convenience of CuAAC.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ¹H NMR and ¹³C NMR spectra of all products are available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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