Tetrahedron Letters 49 (2008) 7030–7032

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Monosubstituted 1,2,3-triazoles from two-step one-pot deprotection/click additions of trimethylsilylacetylene

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ARTICLE INFO

Article history:
Received 7 August 2008
Accepted 23 September 2008
Available online 27 September 2008

Keywords:
Click chemistry
1,2,3-Triazoles
One-pot reaction

ABSTRACT

Two-step one-pot reaction conditions have been developed for synthesizing 1-substituted-1,2,3-triazoles. This transformation involves the base-catalyzed deprotection of trimethylsilylacetylene followed by Cu-catalyzed Huisgen 1,3-dipolar cycloaddition under aqueous reaction conditions. Utilization of potassium carbonate as the base and methanol as the alcoholic aqueous co-solvent resulted in optimal yields of the desired products. The reaction conditions were found to be successful for both alkyl and aryl azide reactants, including analogs with electron-donating and electron-withdrawing functionality. This procedure stands as a simple and regioselective means by which to prepare 1-substituted-1,2,3-triazole compounds directly from azide precursors.

As the product resulting from common click reactions, the 1,2,3-triazole ring has found widespread recent utility in the fields of bioconjugation, materials science, and small molecule synthesis.[1] Deriving from the robust Cu-catalyzed Huisgen 1,3-dipolar cycloaddition,[2] 1,4-disubstituted-1,2,3-triazoles are more commonly reported, while 1,5-disubstituted isomers can also be prepared via Ru-catalyzed reaction[3] or from Grignard reagent synthons.[4] While 1,4- and 1,5-disubstituted triazole isomers can each be synthesized efficiently, no general methods for preparing isomerically pure monosubstituted 1,2,3-triazole rings using a click approach currently exist in the literature. Direct alkylation of the 1,2,3-triazole ring generally results in mixtures of regioisomers,[5] and while 1-alkyl-1,2,3-triazoles can be prepared using multiple-step reaction sequences, such approaches are limited to alkyl substituents that are reactive toward nucleophilic substitution.[6]

Due to the chemoselectivity of the Cu-catalyzed Huisgen 1,3-dipolar cycloaddition toward terminal alkyne and azide reactants, this click reaction is highly efficient even in complex chemical environments. Benefiting from such orthogonal reactivity, two-step one-pot transformations employing click reaction steps have recently been demonstrated as useful in preparing 1,4-disubstituted-1,2,3-triazoles.[7] While successful for synthesizing disubstituted triazole products, no analogous two-step one-pot methods for synthesizing monosubstituted triazoles have been reported. Herein, we describe the development of two-step one-pot reaction conditions as a general means by which to synthesize 1-substituted-1,2,3-triazole products directly from trimethylsilylacetylene and both aliphatic and aromatic azide reactants.

With the goal of efficiently synthesizing 1,2,3-triazole rings unsubstituted at the 4- and 5-position, we investigated several different approaches for incorporating an acetylene unit into the product. Direct usage of acetylene gas via bubbling into standard aqueous click reaction conditions was unsuccessful, likely due to the poor acetylene solubility. Attempts to use ethynylmagnesium bromide with reported Grignard click reaction conditions also produced no significant amounts of triazole products. We then shifted our focus to using protected acetylenes that were liquids at room temperature, including trimethylsilylacetylene. As deprotection of the trimethylsilyl (TMS) protecting group from alkynes is promoted by simple treatment with K_2CO_3 in methanol, we examined whether simple addition of this inorganic base to standard H_2O/*t*-BuOH click reaction conditions would promote TMS deprotection while not interfering with the Cu-catalyzed Huisgen 1,3-dipolar cycloaddition. As shown in Table 1,[8,9] for both alkyl (**1**) and aryl (**2**) azide reactants this led to the formation of the desired 4,5-unsubstituted 1,2,3-triazole products, but each was produced as a mixture with its 4-TMS-substituted analog.

We then examined whether the distribution of TMS- and non-TMS-containing products derived from this two-step one-pot transformation could be influenced by the identity of either the alcohol co-solvent or the base employed. As summarized in Table 1, it was found that as the degree of alcohol substitution decreases, the yield of desired non-TMS product increases. This can be explained by the fact that methanol is more acidic than *t*-butanol and its alkoxide a better nucleophile to perform TMS deprotection, hence increasing the rate of the TMS deprotection step in the methanol co-solvent system. Influence of base strength on TMS

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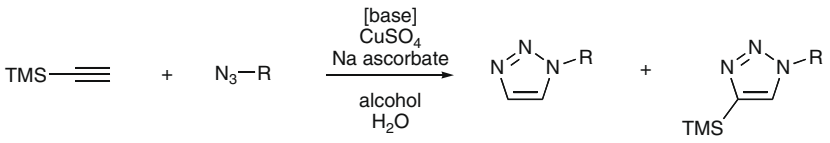
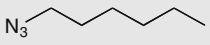
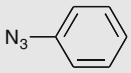
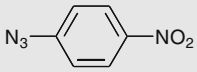
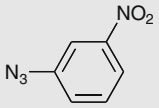
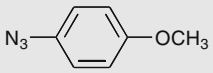
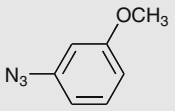
doi:10.1016/j.tetlet.2008.09.136

Table 1
Evaluation of reaction conditions[a]



Product	Azide	Base	Alcohol	% Yield[b]	
				a	**b**
1		K_2CO_3	*t*-BuOH	50	25
		K_2CO_3	*i*-PrOH	51	37
		K_2CO_3	EtOH	62	3
		K_2CO_3	MeOH	69	0
		KOH	MeOH	50	0
		Triethylamine	MeOH	78	5
		Pyridine	MeOH	40	36
		None	MeOH	24	68
2		K_2CO_3	*t*-BuOH	26	42
		K_2CO_3	*i*-PrOH	55	23
		K_2CO_3	EtOH	50	4
		K_2CO_3	MeOH	66	0
		KOH	MeOH	11	0
		Triethylamine	MeOH	75	3
		Pyridine	MeOH	44	44
		None	MeOH	12	43
3		K_2CO_3	MeOH	41	0
4		K_2CO_3	MeOH	73	0
5		K_2CO_3	MeOH	85	0
6		K_2CO_3	MeOH	79	0

[a] All reactions were carried out using 1.0 mmol azide, 1.2 mmol TMS acetylene, 1.2 mmol base, 0.1 mmol $CuSO_4$, 0.2 mmol sodium ascorbate, 5 mL alcohol, and 5 mL H_2O stirred at room temperature for 24 h.
[b] Yields were calculated from the isolated mass of product mixtures and the product ratios as measured by ^1H NMR spectroscopy.

deprotection rates was also evident. While KOH and K_2CO_3 produced no TMS-incorporated products, triethylamine resulted in small but detectable amounts of TMS-incorporated products. Pyridine, the weakest base in the series, produced relatively large amounts of triazole products with TMS incorporation.

In studying the effects of varying both alcohol co-solvent and base, it is evident that increasing the rate of TMS deprotection relative to the rate of click addition results in less TMS incorporation into the triazole products. We propose that these observations support a two-step one-pot process whereby alkyne deprotection (either before and/or after being sequestered by Cu in the reaction media) precedes the click addition step (Fig. 1). This reaction sequence is further supported by the fact that subjecting 4-TMS triazole products to K_2CO_3 methanol/H_2O reaction conditions did not promote TMS removal (Fig. 2, second step).

Collectively, these results indicate that the relative rates of the two tandem reaction steps must be balanced if the desired non-TMS product is to be formed in significant yield. One caveat is that if the TMS deprotection occurs too quickly relative to the Cu-catalyzed click addition, the overall product yield suffers. This likely derives from the loss of gaseous acetylene intermediate reactant that is not consumed quickly enough in the second click reaction step.[10]

Two observations support this hypothesis. First, while only non-TMS products are formed when using KOH as the base (which promotes TMS deprotection significantly more quickly than K_2CO_3), such products are formed in lower overall yields than with the other bases used in this investigation. Second, as the amount of copper catalyst is reduced, slowing down the rate of the click reaction step and allowing more time for the acetylene intermediate to diffuse away, overall product yield also decreases (Table 2). These observed relationships between rate of the TMS deprotection step, the click reaction step, and the overall yield of triazole products also support the proposed two-step sequence in Figure 1.

Upon identifying a synthetic method useful for both 1-alkyl- and 1-aryl-1,2,3-triazole products, this study also examined the tolerance of these conditions toward electron-poor and electron-rich aryl azide reactants. The optimal reaction conditions (K_2CO_3/MeOH) were applied to a series of nitro- and methoxy-substituted azidobenzenes (Table 1, products **3**–**6**). For each analog, only the 1-aryl-1,2,3-triazole product was observed, and only **3** showed a

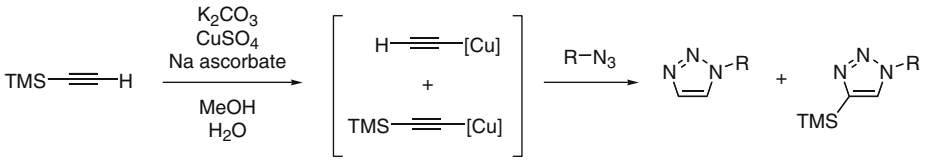


Figure 1. Proposed reaction step sequence of the two-step one-pot transformation involving base-catalyzed TMS deprotection followed by Cu-catalyzed click addition.

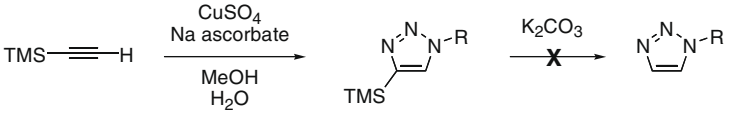


Figure 2. Alternative reaction step sequence for the two-step one-pot transformation involving Cu-catalyzed click addition followed by base-catalyzed TMS deprotection. Experimental results do not support this order of reaction steps.

Table 2
Evaluation of catalyst stoichiometry[a]

Mol % $CuSO_4$	% Yield[b]	
	1a	**1b**
20	70	0
10	37	0
5	22	0

[a] All reactions were carried out using 1.0 mmol azide, 1.2 mmol TMS acetylene, 1.2 mmol K_2CO_3, a 1:2 ratio of $CuSO_4$:sodium ascorbate, 5 mL methanol and 5 mL H_2O stirred at room temperature for 24 h.

[b] Yields were calculated from the isolated mass of product mixtures and the product ratios as measured by ^1H NMR spectroscopy.

significant amount of unreacted azide in the isolated product mixture (32% recovery as observed by NMR).

This investigation has identified general reaction conditions leading to the regioselective formation of 1-substituted-1,2,3-triazoles using a two-step one-pot TMS deprotection/click synthetic approach. It is proposed that this two-step transformation involves an initial TMS-deprotection step followed by click addition, and that balancing the relative rates of these steps via selection of alcohol co-solvent, base, and amount of catalyst is important in producing the desired 1-substituted-1,2,3-triazole products in appreciable yields. Using methanol co-solvent and K_2CO_3 base, this simple click approach is tolerant to both aromatic and aliphatic substitution and should be of general utility for synthesizing a wide range of 1-substituted-1,2,3-triazole products.

Acknowledgments

J.T.F. acknowledges the Research Corporation Cottrell College Science Award Program (CC6349) and Creighton University for financial support.

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8. To a 20 mL vial were added azide (1.0 mmol), trimethylsilylacetylene (1.2 mmol), potassium carbonate (1.2 mol), $CuSO_4$ (0.2 mmol), sodium ascorbate (0.4 mmol), methanol (5 mL), and water (5 mL). The vial was sealed with a screw cap and stirred rapidly for 24 h at room temperature. The resulting suspension was extracted between CH_2Cl_2 and 5% aqueous ammonium hydroxide, the organic layer was separated, dried over $MgSO_4$, filtered, and volatiles removed via rotovap. Those products that were brown in color (due to traces of dissolved copper from the extraction process) were treated with a 1:3 mixture of CH_2Cl_2/hexanes to precipitate a brown residue, filtered, and the solvent was evaporated to give triazole product(s). *CAUTION*: While the authors did not encounter any problems with handling the azides on the scale utilized in this study, all small organic azides should be considered shock-sensitive and, therefore, handled with requisite caution.
9. Spectroscopic characterization of products:
Compound **1a**: ^1H NMR ($CDCl_3$): δ = 7.73 (s, 1H), 7.57 (s, 1H), 4.41 (t, J = 7.2, 2H), 1.93 (m, 2H), 1.38 (m, 6H), 0.90 (t, J = 6.9, 3H). ^{13}C NMR ($CDCl_3$): δ = 134.98, 124.0, 50.5, 31.3, 30.5, 26.3, 22.6, 14.1. MS (EI): m/z = 152 ($M-H^+$) (calcd for $C_8H_{15}N_3$ = 153).
Compound **1b**: ^1H NMR ($CDCl_3$): δ = 7.52 (s, 1H), 4.40 (t, J = 7.2, 2H), 1.93 (m, 2H), 1.35 (m, 6H), 0.91 (t, J = 6.9, 3H), 0.36 (s, 9H). ^{13}C NMR ($CDCl_3$): δ = 146.6, 128.9, 50.0, 31.4, 30.6, 26.5, 22.6, 14.1, −0.9. MS (EI): m/z = 224 ($M-H^+$) (calcd for $C_{11}H_{23}N_3Si$ = 225).
Compound **2a**: ^1H NMR ($CDCl_3$): δ = 8.04 (s, 1H), 7.88 (s, 1H), 7.77 (m, 2H), 7.56 (m, 2H), 7.47 (m, 1H). ^{13}C NMR ($CDCl_3$): δ = 137.5, 135.7, 130.0, 129.0, 122.8, 121.0. MS (EI): m/z = 145 (M^+) (calcd for $C_8H_7N_3$ = 145).
Compound **2b**: ^1H NMR ($CDCl_3$): δ = 7.98 (s, 1H), 7.76 (m, 2H), 7.52 (m, 2H), 7.45 (m, 1H), 0.41 (s, 9H). ^{13}C NMR ($CDCl_3$): δ = 147.6, 137.5, 129.9, 128.7, 127.5, 121.1, −0.9. MS (EI): m/z = 217 (M^+) (calcd for $C_{11}H_{15}N_3Si$ = 217).
Compound **3a**: ^1H NMR ($CDCl_3$): δ = 8.47 (d, J = 8.8, 2H), 8.19 (s, 1H), 8.04 (d, J = 8.8, 2H), 7.98 (s, 1H). ^{13}C NMR ($CDCl_3$): insufficient solubility. MS (EI): m/z = 190 (M^+) (calcd for $C_8H_6N_4O_2$ = 190).
Compound **4a**: ^1H NMR ($CDCl_3$): δ = 8.65 (t, J = 2.1, 1H), 8.35 (dd, J_1 = 8.1, J_2 = 1.2, 1H), 8.24 (dd, J_1 = 8.1, J_2 = 1.2, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.80 (t, J = 8.1, 1H). ^{13}C NMR ($CDCl_3$): insufficient solubility. MS (EI): m/z = 190 (M^+) (calcd for $C_8H_6N_4O_2$ = 190).
Compound **5a**: ^1H NMR ($CDCl_3$): δ = 7.94 (s, 1H), 7.85 (s, 1H), 7.65 (dd, J_1 = 6.9, J_2 = 2.1, 2H), 7.03 (dd, J_1 = 6.9, J_2 = 2.1, 2H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 160.1, 135.7, 131.1, 123.0, 122.6, 115.1, 55.9. MS (EI): m/z = 175 (M^+) (calcd for $C_9H_9N_3O$ = 175).
Compound **6a**: ^1H NMR ($CDCl_3$): δ = 8.03 (s, 1H), 7.87 (s, 1H), 7.44 (t, J = 8.1, 1H), 7.38 (t, J = 2.1, 1H), 7.27 (dd, J_1 = 8.1, J_2 = 0.9, 1H), 7.00 (dd, J_1 = 8.1, J_2 = 2.1, 1H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 160.9, 138.4, 135.3, 130.8, 122.6, 114.8, 112.8, 106.8, 55.9. MS (EI): m/z = 175 (M^+) (calcd for $C_9H_9N_3O$ = 175).
10. It should be noted that no gas evolution was visually evident during any of the reactions performed in this study.