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β-Tosylethylazide: a useful synthon for preparation of *N*-protected 1,2,3-triazoles via click chemistry

Amy H. Yap and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, USA

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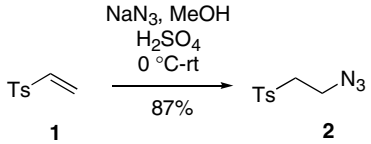
Abstract—β-Tosylethylazide (TSE-N_3), which can be prepared in one step from *p*-tolyl vinyl sulfone and sodium azide/H_2SO_4, undergoes metal-catalyzed 1,3-dipolar cycloadditions with alkynes to produce TSE-protected 1,2,3-triazoles. The protecting group can be removed using potassium *tert*-butoxide in THF at −78 to 0 °C.

1,2,3-Triazoles are nitrogen heterocycles, which have a number of important industrial, agrochemical, and pharmaceutical uses.[1] One of the most attractive ways to prepare these compounds involves the thermal 1,3-dipolar cycloaddition of azides with alkynes, pioneered by Huisgen.[2] One of the main drawbacks of this chemistry has been a lack of regioselectivity when utilizing unsymmetrical alkynes, as well as a requirement for elevated reaction temperatures. However, an important advance in this field was the recent discovery that cycloadditions of terminal alkynes with alkyl azides catalyzed by Cu(I) can be conducted at room temperature and are highly regioselective, leading to 4-substituted-1,2,3-triazoles.[3] It is believed that this process occurs via the stepwise addition of the azide to a copper acetylide intermediate, rather than by a concerted cycloaddition.[3c] This type of cycloaddition has been classified by Sharpless as a kind of 'click' reaction, whereby heteroatom links between molecules can be generated under very mild experimental conditions.[4] Various applications of this methodology are beginning to appear at a rapid rate.[4b]

During the past few years we have been exploring the use of β-tosylethyl (TSE)-containing synthons for preparation of various kinds of N-protected systems.[5,6] For example, readily prepared β-tosylethylamine (TSE-NH_2) can be used to synthesize a number of types of N-protected amido compounds.[5a,b] We have introduced β-tosylethylhydroxylamine (TSE-NHOH) and demonstrated that it can be applied in amidyl radical/olefin cyclizations.[5c] More recently, β-tosylethylhydrazine (TSE-$NHNH_2$) was shown to be effective in synthesis of TSE-protected pyrazoles and 5-aminopyrazoles.[5d] In all of these cases the TSE-protecting group can be removed via a retro-Michael reaction promoted by potassium *tert*-butoxide. In this letter we now report the synthesis of β-tosylethylazide (TSE-N_3) and its application to the generation of protected 1,2,3-triazoles via metal-catalyzed 1,3-dipolar cycloadditions with alkynes.[7]

β-Tosylethylazide (**2**) can be easily synthesized as a crystalline solid in one step in good yield from commercially available *p*-tolyl vinyl sulfone (**1**) and sodium azide/sulfuric acid in methanol (Eq. 1).[8–10] This material is purified by chromatography and can be stored indefinitely in the freezer:



(1)

Using the Sharpless protocol,[3a] it was found that treatment of TSE-N_3 (**2**) with terminal alkynes in the presence of cupric sulfate/sodium ascorbate (to generate Cu(I) in situ) in aqueous *tert*-butanol at room temperature led to the 4-substituted-1,2,3-triazoles **3** (Scheme 1).[11] Several examples of this cycloaddition are shown

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* Corresponding author. Tel.: +1 814 863 0189; fax: +1 814 865 3292; e-mail: smw@chem.psu.edu

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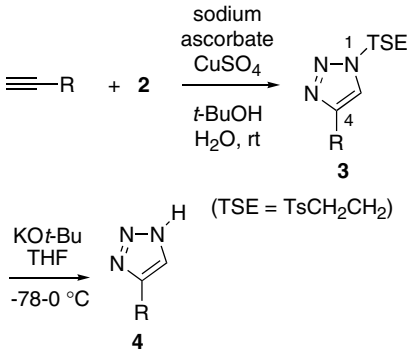
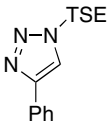
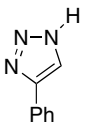
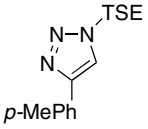
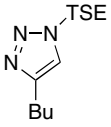
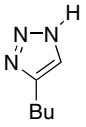
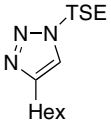
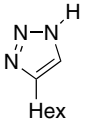
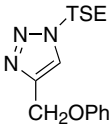
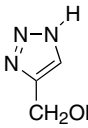
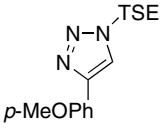
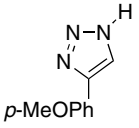
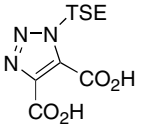
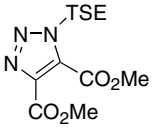
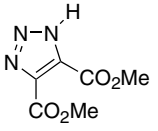


Scheme 1.

in Table 1. The products in these cases crystallized out of the reaction mixture in sufficiently pure form for utilization without further purification. Yields of the 1,2,3-triazoles generally ranged from 75% to 97%. Interestingly, these conditions also promoted the cycloadditions of acetylene dicarboxylic acid (entry g) and dimethyl acetylenedicarboxylate (entry h) with azide **2**. If either the cupric sulfate or the sodium ascorbate was omitted from the reaction mixture, only starting materials were recovered. Since these alkynes cannot form copper acetylides, it is not clear exactly how these reactions are occurring. In order to firmly establish that the regioselectivity of the cycloaddition with terminal alkynes occurred as expected, the adduct of TSE-N_3 with phenylacetylene was analyzed by both ^{1}H NMR NOE studies and X-ray crystallography, and was found to indeed have the 4-substituted triazole structure as shown in entry a.[12]

It was possible to remove the TSE-protecting group by exposure of triazoles **3** to potassium *tert*-butoxide in THF at −78 °C and then letting the reaction mixture slowly warm to 0 °C, producing the unprotected tri-

Table 1. Preparation of TSE-protected triazoles by Cu(I)-catalyzed cycloadditions of TSE-N_3 with alkynes, and deprotection with KO*t*-Bu/THF

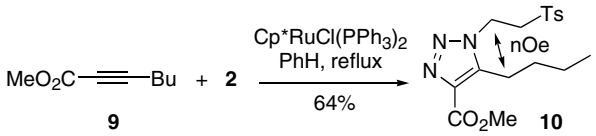
Entry	Alkyne	TSE-protected triazole	Isolated yield (%)	Deprotected triazole	Isolated yield (%)
a	Ph—		92		77
b	*p*-MePh—		89		
c	Bu—		93		93
d	Hex—		97		61
e	$PhOH_2C$—		93		80
f	*p*-MeOPh—		85		77
g	HO_2C—CO_2H		75		
h	MeO_2C—CO_2Me		86		88

azoles **4**.[13] *p*-Tolyl vinyl sulfone is presumably formed in this step, but polymerizes under the reaction conditions. A few examples of such deprotections are shown in Table 1.

More recently, the Sharpless group has discovered that $Cp^*RuCl(PPh_3)_2$ and related ruthenium complexes efficiently catalyze the cycloaddition of alkyl azides with both terminal and internal alkynes to produce 1,2,3-triazoles.[14] However, it was found that with the ruthenium catalysts, the regioselectivity of the reaction with terminal alkynes is reversed, leading to 5-substituted-1,2,3-triazoles. We have applied this new methodology to cycloadditions of TSE-N_3 (**2**) with alkynes. Thus, treatment of phenylacetylene with azide **2** and $Cp^*RuCl(PPh_3)_2$ in refluxing benzene leads to the 5-phenyl-1,2,3-triazole **5** in good yield (Scheme 2).[15] That adduct **5** is in fact the 5-substitited 1,2,3-triazole was established by ^1H NMR NOE experiments.

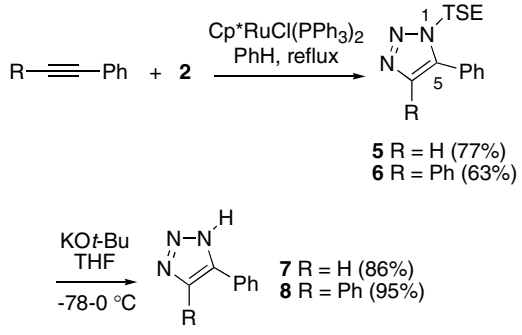
Similarly, with diphenylacetylene, the protected triazole **6** could be prepared. Removal of the TSE-protecting groups of **5** and **6** with potassium *tert*-butoxide under the usual conditions afforded triazoles **7** and **8**, respectively.

Finally, since the Sharpless group had not reported a ruthenium-catalyzed cycloaddition of an alkyl azide with an unsymmetrical internal alkyne,[14] we were prompted to explore the reaction of TSE-N_3 with alkyne **9** (Eq. 2). Interestingly, this cycloaddition gave only one detectable 1,2,3-triazole in moderate yield, which was proven to be the regioisomer **10** by ^1H NMR NOE analysis. It should also be noted that the cycloaddition of azide **2** and alkyne **9** does not occur under Cu(I) catalysis:



(2)

In conclusion, we have demonstrated that readily prepared β-tosylethylazide undergoes regioselective cycloadditions with a variety of alkynes under either copper or ruthenium catalysis to afford *N*-protected 1,2,3-triazoles. The TSE-protecting group on these adducts can be removed under mildly basic conditions via a retro-Michael reaction using potassium *tert*-butoxide.



Scheme 2.

Acknowledgments

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8. Cf. Bera, S.; Sakthivel, K.; Pathak, T.; Langley, G. J. *Tetrahedron* **1995**, *51*, 7857.
9. We thank David Dastrup for developing this synthesis of TSE-N_3.

10. Preparation of TSE-N_3 (**2**). A solution of concentrated H_2SO_4 (0.27 mL, 19.2 mmol) in MeOH (30 mL) was added slowly to a solution of sodium azide (2.86 g, 44 mmol) in MeOH (120 mL) at 0 °C and the mixture was stirred for 15 min. A solution of *p*-tolyl vinyl sulfone (**1**, 0.73 g, 4.0 mmol) in MeOH (60 mL) was slowly added and the mixture was stirred for 72 h at rt. The reaction mixture was diluted with 20 mL of H_2O and the aqueous layer was extracted with CH_2Cl_2. The organic extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (20:80 EtOAc/hexanes) to afford TSE-N_3 (**2**) as a white crystalline solid (0.78 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, $J = 8.2$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H), 3,67 (t, $J = 6.9$ Hz, 2H), 3.31 (t, $J = 6.9$ Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 135.8, 130.0, 127.9, 54.9, 44.7, 21.6; HRMS calcd for $C_9H_{11}N_3SO_2$ 226.0650 (MH^+), found 226.0643.
11. General procedure for Cu(I)-catalyzed Cycloaddition of TSE-$N_3$with alkynes. The alkyne (3.0 mmol) and TSE-N_3 (**2**, 0.68 g, 3.0 mmol) were added to a solution of water/*t*-BuOH (8 mL/4 mL). Solutions of sodium ascorbate (1.0 M in H_2O, 300 μL, 0.3 mmol) and copper(II) sulfate (0.3 M in H_2O, 100 μL, 0.03 mmol) were added sequentially and the reaction mixture was stirred rapidly at rt for 8 h. The triazole precipitated out of the reaction mixture, which was then diluted with 5 mL of H_2O and chilled in ice. The triazole product **3** was isolated via filtration, washed with cold H_2O, and was dried in vacuo.
12. We thank Dr. Hemant Yennawar (Penn State Small Molecule X-Ray Crystallographic Facility) for this crystal structure determination. CCDC 600036 contains the supplementary crystallographic data, which can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
13. General deprotection procedure. A solution of *t*-BuOK in THF (1.0 M, 0.86 mL) was slowly added to a solution of protected triazole (200 μmol) in THF (10 mL) at −78 °C. The solution was slowly warmed to 0 °C over a period of 1–3 h. The reaction mixture was neutralized with glacial acetic acid (24.7 μL, 100 μmol) at 0 °C. The mixture was concentrated in vacuo and the residue was purified by flash column chromatography (30:70 EtOAc/hexanes) to afford the deprotected 1,2,3-triazole.
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15. General procedure for ruthenium-catalyzed synthesis of TSE-protected 1,2,3-triazoles. The alkyne (0.50 mmol) was added to a solution of TSE-N_3 (**2**, 0.168 g, 0.75 mmol) and $Cp^*RuCl(PPh_3)_2$ (0.04 g, 0.05 mmol) in benzene (2.5 mL). The reaction mixture was stirred and heated at reflux for 2 h. After cooling the mixture to rt, the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (50:50 ether/hexanes to 100% ether gradient) to yield the TSE-protected 1,2,3-triazole.