Selective Formation of 1,5-Substituted Sulfonyl Triazoles Using Acetylides and Sulfonyl Azides

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Abstract:

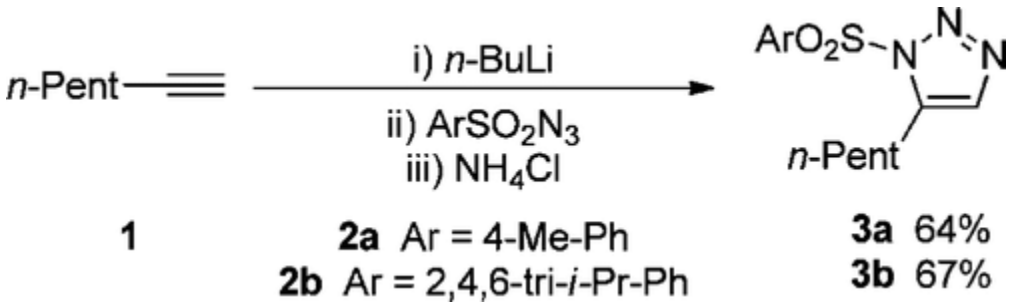
The reaction of acetylides with sulfonyl azides was found to selectively form 1,5-substituted sulfonyl triazoles. This reaction thus provides access to the regioisomeric product as compared to the popular copper-catalyzed azide–alkyne cycloaddition. The reaction is efficient and selective with a variety of alkyne sources and sulfonyl azides and can incorporate an additional electrophile to yield 1,4,5-trisubstituted sulfonyl triazoles.

Keywords: chemistry | biochemistry | sulfonyl triazoles | acetylides | solfonyl aziders

Article:

The copper-catalyzed reaction of terminal alkynes with azides to yield 1,2,3-triazoles has deservedly received much attention in recent years.(1) This reaction regioselectively forms 1,4-substituted triazoles using alkyl, aryl, or sulfonyl azides.(2) Although it was reported that 1,4-substituted sulfonyl triazoles could be converted to 2,4-substituted triazoles using amine bases,(3) there are no efficient methods to selectively convert terminal alkynes and sulfonyl azides to 1,5-substituted triazoles.(4-6) In 2004, there was an excellent report for the reaction of alkynyl Grignard reagents with carbon-substituted azides to yield 1,5-disubstituted triazoles and 1,4,5-trisubstituted triazoles.(7) Interestingly, no reactions were reported with sulfonyl azides despite the authors' expertise with this electrophilic azide source.(8) Additionally, the copper-catalyzed reaction with sulfonyl azides often forms products other than the typical triazoles.(8) Due to the significance of substituted triazoles in ligand design, drug discovery, and biochemical applications,(1) it is attractive to have a facile, regioselective, and efficient route to 1,5-substituted sulfonyl triazoles. In this report we describe an efficient method for the selective synthesis of 1,5-substituted sulfonyl triazoles from terminal alkynes and sulfonyl azides.

During our initial study of the reactivity of acetylides and sulfonyl azides, it was determined that the major product of the reaction with 1-heptyne was 1,5-triazole 3 (Scheme 1). This was true for both sulfonyl azides 2a and 2b. The structures were determined by comparison to the 1,4-triazoles formed by reaction with CuI and 2,6-lutidine along with X-ray crystallographic analysis of 3a (see Supporting Information).



Scheme 1. Synthesis of 1,5-Substituted Triazoles

Although this reaction appears similar to the frequently employed copper-catalyzed azide–alkyne cycloaddition (CuAAC) and complementary ruthenium-catalyzed cycloaddition (RuAAC),(4) there are two main differences. First, the reaction described herein produces 1,5-substituted triazoles whereas the CuAAC yields 1,4-substituted triazoles. Second, this reaction works efficiently with sulfonyl azides, whereas the RuAAC has not been reported with sulfonyl azides. Based on these differences, it was decided to optimize this reaction and study its scope.

Optimization of the reaction conditions determined that if the reaction was not kept at −78 °C, mixtures of differentially substituted triazoles (mostly the 1,4-substituted triazoles) were isolated (Table 1, entry 1 versus 2; see the Supporting Information for a more detailed optimization table). Interestingly, it was found that other counterions, including sodium and potassium, allowed for the formation of 1,5-triazoles; however the reactions were not as efficient, potentially due to the poor solubility of the anions at −78 °C (entry 1 versus 3 and 4). A very poor yield was observed with a Grignard reagent (not shown) which likely illustrates why the reactions described herein were not described in prior reports.(7) A final key reaction condition for the optimization was to use a slight excess of the alkyne, relative to the sulfonyl azide source (entry 5). With these optimal conditions, other sulfonyl azide sources (2a and 2c) were examined and the reaction was found to maintain efficiency (entries 6 and 7).

Table 1. Optimization for Synthesis of 1,5-Triazoles 3[a]

entry	heptyne (equiv)/ $ArSO_2N_3$ (equiv)	base (equiv)	time (h)	yield of 3[b]

entry	heptyne (equiv)/ $ArSO_2N_3$ (equiv)	base (equiv)	time (h)	yield of 3[b]
1	**1** (1.0)/**2a** (1)	*n*-BuLi (1.2)	2	64% **3a**
2[c]	**1** (1.0)/**2a** (1)	*n*-BuLi (1.2)	5	39% **3a**
3	**1** (1.0)/**2a** (1)	NaHMDS (1.2)	2	23% **3a**
4	**1** (1.0)/**2a** (1)	KHMDS (1.2)	2	27% **3a**
5	**1** (1.2)/**2a** (1)	*n*-BuLi (1.2)	0.3	90% **3a**
6	**1** (1.2)/**2b** (1)	*n*-BuLi (1.2)	0.3	67% **3b**
7[d]	**1** (1.2)/**2c** (1)	*n*-BuLi (1.2)	2	79% **3c**

A Reaction conditions (unless otherwise noted): The indicated base was added to a solution of heptyne in THF at −78 °C. After 15 min, the indicated sulfonyl azide (1 equiv) was added, and the reaction was stirred for the time indicated.

B Isolated yield.

C The reaction temperature was increased to ambient temperature after 2 h.

D **2c**, Ar = *p*-NO_2-Ph.

With conditions in hand for the efficient transformation of heptyne into 1,5-triazoles, a variety of different alkynes were studied in the reaction (Table 2). Importantly, the reaction with phenylacetylene was also efficient with all three of the sulfonyl azide sources (entries 1–3). It was determined that electron-rich arenes worked better in this reaction than electron-poor arenes (entry 4 versus 6), although the more sterically hinderered ortho-anisole substrate was not as efficient (entry 5). Although a nitro-group was tolerated on the sulfonyl azide, the nitro-

substituted aryl acetylide did not yield any desired product and only starting material was isolated (entry 7). The silyl-substituted acetylide was low yielding for this reaction (entry 8), whereas the tert-butyl acetylide was highly efficient (entry 9).

Table 2. Alkyne Screen[a]

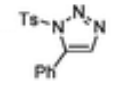
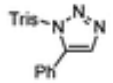
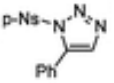
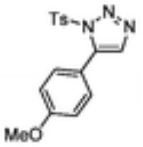
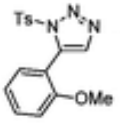
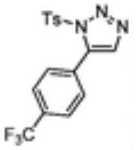
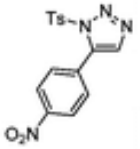
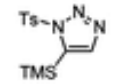
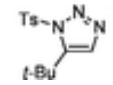
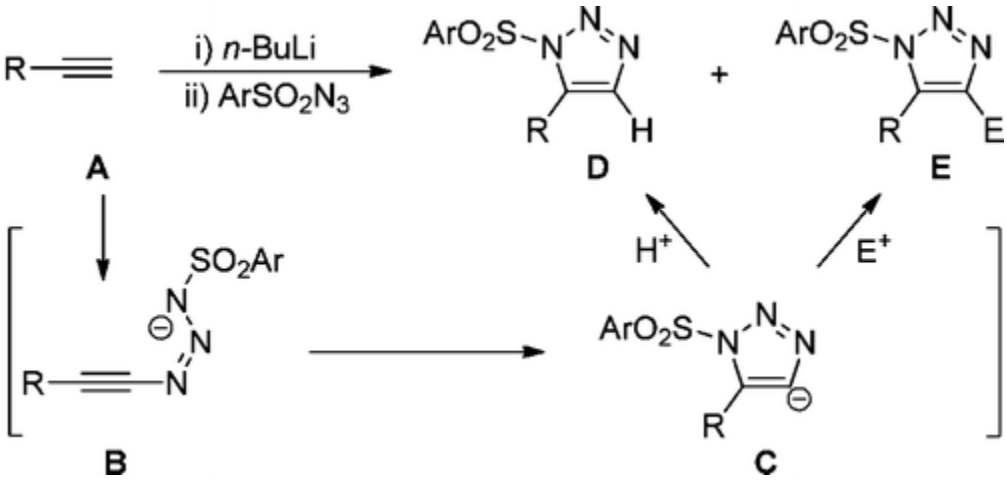
entry	substrate	$ArSO_2N_3$	time	yield[b]	product
1	Ph—	**2a**	40 min	79% (**4a**)	
2	Ph—	**2b**	25 min	85% (**4b**)	
3	Ph—	**2c**	25 min	87% (**4c**)	
4	MeO—	**2a**	45 min	80% (**5**)	
5	OMe	**2a**	25 min	24% (**6**)	
6	F_3C—	**2a**	25 min	53% (**7**)	
7[c]	O_2N—	**2a**	3 hr	0% (**8**)	
8	TMS—	**2a**	25 min	14% (**9**)	
9	*t*-Bu—	**2a**	45 min	87% (**10**)	

Table aReaction conditions (unless otherwise noted): 1.2 equiv of n-BuLi was added to a solution of the indicated alkyne (1.2 equiv) in THF at −78 °C. After 15 min, 1 equiv of the indicated sulfonyl azide was added, and the reaction was stirred for the time indicated at which point the sulfonyl azide was fully consumed as judged by TLC.

Table bIsolated yield.

Table cQuantitative recovery of starting alkyne and sulfonyl azide as judged by 1H NMR of the crude reaction mixture. Ts = p-toluenesulfonyl; Tris =2,4,6-triisopropylphenylsulfonyl; p-Ns = p-nitrophenylsulfonyl.

Based on the proposed reaction mechanism (Scheme 2), it was decided to explore the reactions of the triazole anion (C) with other electrophiles (formation of E). Using identical conditions as described earlier, the reactions were quenched with electrophiles other than a Brønsted acid (Table 3). Acid chlorides (entries 1–3) were able to yield the respective ketones with moderate efficiency. Unfortunately, the reactions with benzylchloroformate or a chlorosilane were not high yielding (entries 4 and 5), but the reaction with the iodomethane proceeded smoothly (entry 6). Unexpectedly, when the p-nitrophenylsulfonyl azide source (2c) was used in slight excess, the free triazole was isolated where the presumed anion (Scheme 2, C) reacted similarly to an intermolecular electrophilic aromatic substitution and subsequently cleaved the sulfur–nitrogen bond (Table 3, entry 7). These reactions formally represent highly regioselective cycloadditions between sulfonyl azides and internal alkynes, a reaction that is otherwise difficult.



Scheme 2. Proposed Mechanism for the Reactions

Table 3. Electrophile Screen[a]

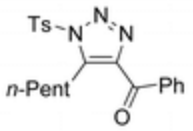
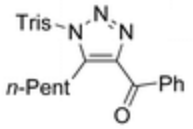
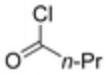
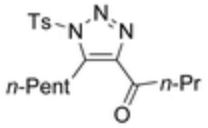
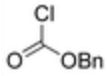
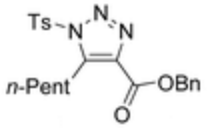
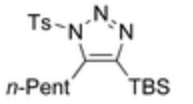
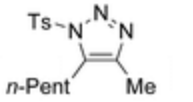
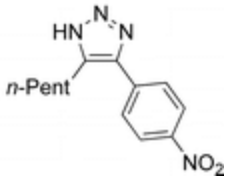
entry	Alkyne	$ArSO_2N_3$	electrophile	yield[b]	product
1	**1**	**2a**	BzCl	80% (**11a**)	
2	**1**	**2b**	BzCl	57% (**11b**)	
3	**1**	**2a**		66% (**12**)	
4	**1**	**2a**		19% (**13**)	
5	**1**	**2a**	TBSCl	17% (**14**)	
6[c]	**1**	**2a**	MeI	64% (**15**)	
7	**1**	**2c**	**2c**	52% (**16**)	

Table aReaction conditions (unless otherwise noted): 1.2 equiv of n-BuLi was added to a solution of the indicated alkyne (1.2 equiv) in THF at −78 °C. After 15 min, 1 equiv of p-toluenesulfonyl azide was added, the reaction was stirred for 30 min, and then 2 equiv of the indicated electrophile were added. The reactions were stirred at −78 °C.

Table bIsolated yield.

Table cAfter addition of MeI the reaction was warmed to ambient temperature. Ts = p-toluenesulfonyl; Tris =2,4,6-triisopropylphenylsulfonyl.

It should be noted that the 1,5-substituted sulfonyl triazoles isomerized to the 1,4-triazoles to a moderate amount when being purified by silica gel chromatography, presumably via an acid-catalyzed pathway. To circumvent this, crystallization was utilized to isolate the pure 1,5-triazoles. Surprisingly, when the crystals of some of the 1,5-triazole products were stored in a −20 °C freezer for extended periods (>1 week), isomerization to the 1,4-triazoles still occurred. When the same 1,5-triazoles were stored as solutions in CDCl3 no observable isomerization occurred (see Supporting Information for more details). These data lend evidence for the

isomerization taking place even in the crystalline form. The crystal structure of 3a further supports this hypothesis since the nitrogen atom in the 3-position is in relatively close proximity to the sulfur atom of an adjacent molecule (Figure 1). Other isomerization mechanisms are also possible, including radical reactions, but these were not explored since the isomerization did not occur to an appreciable amount in solution.

Figure 1 has been omitted from this formatted document.

Importantly, the reactions described herein combine two readily available starting materials, terminal alkynes and sulfonyl azides, to efficiently and selectively assemble 1,5-substituted sulfonyl triazoles. This reaction displays the substituents of the triazole much closer together than the complementary 1,4-triazoles and thus provides for new structural opportunities. Additionally, the putative triazole anion was trapped with various electrophiles to regioselectively form 1,4,5-trisubstituted triazoles. Further explorations into this reaction, including the isomerization of 1,5-triazoles to 1,4-triazoles, are ongoing.

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Supporting Information

Experimental data and spectroscopic characterization of all products and crystallographic data for 3a. This material is available free of charge via the Internet at http://pubs.acs.org.

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