Table 1. Selected physical properties of compounds **2** and **3**.

2: Colorless oil; $R_f = 0.56$ (silica, 50% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2924, 2866, 1717$ (overlapping signals), 1458, 1383, 1360, 1263, 1199, 1142, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.95$ (d, $J = 2.9$ Hz, 1H), 7.34–7.32 (m, 4H), 7.29–7.25 (m, 1H), 4.59 (d, $J = 9.9$ Hz, 1H), 4.51 (d, $J = 9.9$ Hz, 1H), 4.34 (d, $J = 2.2$ Hz, 1H), 4.26–4.20 (m, 2H), 4.02 (dd, $J =$ 9.5, 2.2 Hz, 1H), 3.46 (s, 3H), 3.42–3.37 (m, 1H), 2.66–2.60 (m, 1H), 2.54–2.48 (m, 3H), 2.30–2.23 (m, 2H), 2.03–1.98 (m, 2H), 1.95–1.88 (m, 2H), 1.43–1.39 (m, 1H), 1.32 (s, 3H), 1.30 (t, $J = 5.9$ Hz, 3H), 1.27–1.23 (m, 2H), 1.17–1.14 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 200.0$, 173.4, 164.9, 162.5, 138.6, 129.7, 128.4, 127.6, 127.5, 81.0, 76.4, 75.1, 70.2, 61.5, 60.0, 57.7, 48.8, 41.7, 38.8, 35.7, 34.2, 30.1, 29.7, 28.6, 28.3, 21.2, 16.0, 14.0 ppm; HRMS (MALDI–FTMS), calcd for $C_{29}H_{36}O_7$ $[M+Na^+]$: 519.2353, found: 519.2359

3: Colorless oil; $R_f = 0.48$ (silica, 25% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2931, 2846, 1727, 1717, 1448, 1364, 1243, 1200, 1097, 1055$ cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.97$ (d, $J = 5.2$ Hz, 1H), 7.33–7.30 (m, 4H), 7.28–7.25 (m, 1H), 4.86 (d, $J = 7.0$ Hz, 1H), 4.79 (d, $J = 7.0$ Hz, 1H), 4.55 (d, $J = 11.8$ Hz, 1H), 4.49 (d, $J = 11.8$ Hz, 1H), 4.44 (dd, $J = 11.4$, 3.3 Hz, 1H), 4.29 (bd, $J = 15.4$ Hz, 1H), 4.25–4.17 (m, 2H), 4.09 (bd, $J =$ 15.0 Hz, 1H), 3.80–3.75 (m, 1H), 3.64–3.59 (m, 1H), 3.38 (d, $J = 3.0$ Hz, 1H), 3.37–3.32 (m, 1H), 2.39–2.34 (m, 1H), 2.35 (d, $J = 5.1$ Hz, 1H), 2.20–2.16 (m, 2H), 2.11–2.05 (m, 2H), 1.98–1.93 (m, 2H), 1.90–1.85 (m, 1H), 1.84–1.78 (m, 2H), 1.31 (t, $J = 7.3$ Hz, 3H), 1.27–1.23 (m, 2H), 1.21 (s, 3H), 1.14–1.09 (m, 1H), 1.00–0.93 (m, 2H), 0.02 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 203.2$, 173.9, 139.4, 138.8, 134.9, 128.3, 127.6, 127.4, 95.1, 80.2, 74.1, 70.0, 67.4, 65.1, 61.1, 60.8, 49.1, 41.3, 38.6, 35.9, 31.9, 31.8, 29.7, 28.7, 28.5, 22.3, 18.2, 16.4, 14.1, −1.4 ppm; HRMS (MALDI–FTMS), calcd for $C_{34}H_{50}O_7Si$ $[M+Na^+]$: 621.3218, found: 621.3218

conversion) (for selected physical properties of compounds **2** and **3**, see Table 1).

The described chemistry may hold the key to a successful total synthesis of azadirachtin (**1**) by providing the basis for the construction of the C8–C14 bridge. Furthermore, this study may serve as the foundation for future developments in carbon–carbon bond forming reactions, particularly in sterically congested situations and in the construction of quaternary centers.

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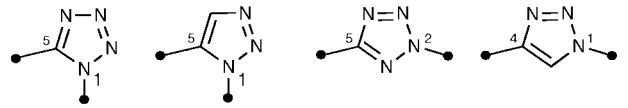
A Click Chemistry Approach to Tetrazoles by Huisgen 1,3-Dipolar Cycloaddition: Synthesis of 5-Sulfonyl Tetrazoles from Azides and Sulfonyl Cyanides**

Zachary P. Demko and K. Barry Sharpless*

Dedicated to Professor Rolf Huisgen

Stable in strongly acidic and basic media, as well as to oxidizing and reducing conditions, tetrazoles readily tolerate a wide range of chemical environments,[1] and new uses for this unique family of heterocycles continue to emerge in both materials science,[2] and pharmaceutical applications. They can serve as metabolically stable surrogates for a carboxylic acid group,[3] as precursors to a variety of nitrogen-containing heterocycles by Huisgen rearrangement,[4] and as simple lipophilic spacers displaying two substituents in the appropriate manner. In the latter example, the connectivity patterns of the embedded tetrazole units bear a striking resemblance to those of their 1,2,3-triazole analogues (Scheme 1).



Scheme 1. Spacial display of substituents in disubstituted tetrazoles and triazoles.

However, despite these structural similarities, the triazoles are much easier to synthesize, thanks to the direct Huisgen 1,3-dipolar cycloaddition route to triazoles ($RN_3 + RC{\equiv}CR$).[5] It has been argued that this [2+3] cycloaddition is among the rare organic reactions which approach perfection, or ideal "click-chemistry" status,[6] with many consequent applications.[7] The analogous [2+3] route to tetrazoles ($RN_3 + RC{\equiv}N$) is reliable for intramolecular cases,[8] but the existing intermolecular precedents for this process are neither general nor practical (see below).

Every chemist is familiar with the personal activation barrier to running "difficult" reactions, and it is well known that the value of a reaction increases dramatically if it is simple to perform. Therefore, uncovering a simple [2+3] fu-

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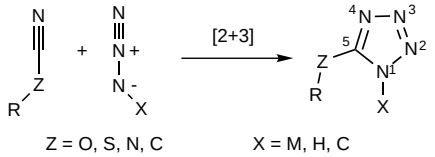
sion process, a "click" reaction, to form tetrazoles would provide a rapid entry to this useful class of compounds.

A common route to 5-functionalized-1*H*-tetrazoles is by the facile addition of metal azides to nitriles, thiocyanates, cyanates, and cyanamides (Scheme 2).[9] If one could expand the scope of this reaction to include organic azides (Scheme 2; X = C), this could serve as a powerful process for fragment assembly.



Scheme 2. [2 + 3] Cycloaddition route to tetrazoles.

Unfortunately, most nitriles are not good enough dipolarophiles to engage organic azides in an intermolecular fashion, and Lewis acid catalysis has not yet been helpful. To date, only certain highly electron-deficient nitriles are known to undergo this cycloaddition intermolecularly; namely, *N*-alkylated nitriles (nitrilium salts),[10] perfluoronitriles, and trichloroacetonitrile.[11] There is also a report involving phenyl cyanate and several other electron-poor aryl nitriles, but these reactions were performed at a pressure of 10 kbar.[12]

Initial attempts to utilize unactivated nitriles gave, as expected, poor results. The only result worth mentioning was from the use of methyl thiocyanate as the solvent and β-phenethyl azide, heated in a pressure reactor at 136 °C, from which 5-methylthio-1-phenethyltetrazole (**1**) was isolated in 32 % yield. Increasing the oxidation state of the sulfur species from II → VI (i.e. R-S^{II}-CN → R-S^{VI}O$_2$-CN) was highly beneficial.

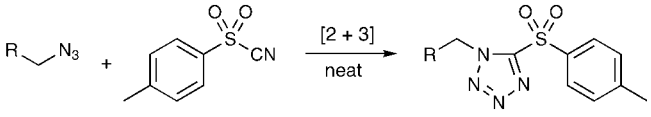
Upon simple heating of neat toluenesulfonyl cyanide with one equivalent of various unhindered azides, quantitative conversion to the 1-alkyl-5-sulfonyl tetrazole was observed; the excellent results in Table 1 establish the scope of this reaction. This procedure is the quintessence of the ideal "click-chemistry" transformation.[6] Toluenesulfonyl cyanide melts at 48 °C so, at the given reaction temperatures (80–100 °C), all the reactions performed here involved stirred, homogeneous liquids. As the reaction proceeds, the mixture solidifies as the product is formed. As the reactions are run neat and only one equivalent of each reagent is needed, there are no side products, and no workup is needed, other than chipping the stir bar away from the solid product. In addition, the reactants are not especially sensitive to air or water, so no precautions need to be taken in that respect.

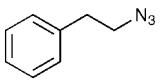
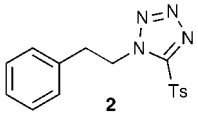
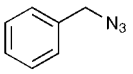
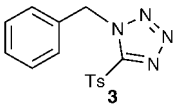
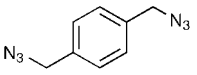
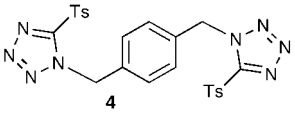
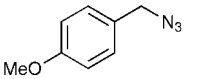
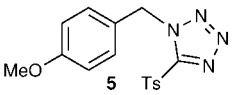
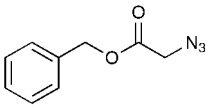
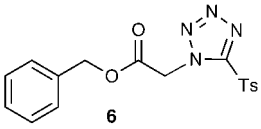
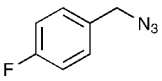
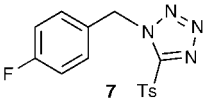
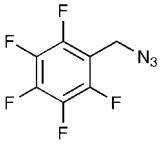
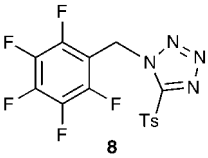
To our knowledge, these are the first examples of the direct synthesis of 1,5-substituted tetrazoles[13] by an intermolecular [2+3] cycloaddition between an organic azide and a nitrile group bound to a sulfur atom (Scheme 3). Sulfonyl cyanides were discovered in 1968,[14] and are known to be active dienophiles,[15] as well as dipolarophiles.[16]

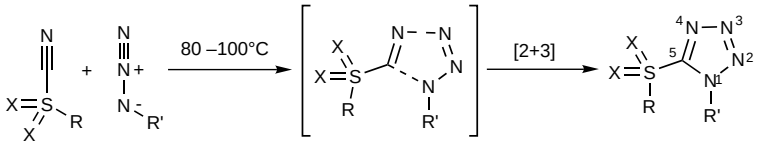
In all cases, the reaction is highly regioselective, and only one isomer is observed. Indeed, with sterically unhindered azides, the yields are virtually quantitative, and as the process is run neat, no purification is needed; truly a "click reaction"! Moreover, while the initial cycloaddition adducts **I** are stable under physiological conditions, their 5-sulfonyl substituent can be readily replaced by a variety of nucleophiles.

Sealed vials are used to ensure that the more volatile azides are not lost. In cases where the precise purity of the azide is

Table 1. [2+3] Dipolar cycloaddition of unhindered azides and toluenesulfonyl cyanide.



Reagent	Reaction conditions T [°C]	Time [h]	Product	Yield [%]
	100	16	 **2**	99
	80	16	 **3**	99
	80	16	 **4**	99
	80	16	 **5**	99
	80	16	 **6**	99
	80	16	 **7**	99
	80	40	 **8**	99



Scheme 3. Direct [2+3] cycloaddition route to 1-alkyl-5-sulfonyltetrazole.

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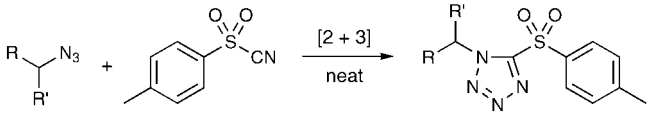
not known, a slight excess of toluenesulfonyl cyanide is added; at the end of the reaction the product is ground to a powder, and the excess TsCN reagent is simply removed by sublimation. Bulky azides and aryl azides do not react as well as unhindered azides (see Table 2 and Table 3). Yields for secondary and tertiary azides are between 46–91%, and for aryl azides, between 30–67%. Isolation of these sulfonyl tetrazoles by column chromatography is not difficult. Azides attached to electron-withdrawing groups require slightly longer reaction times or higher reaction temperatures.[11]

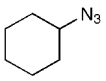
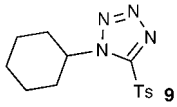
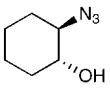
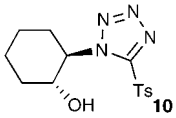
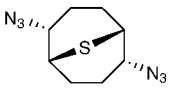
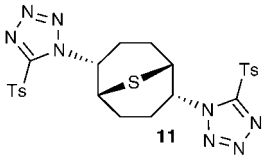
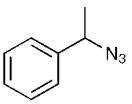
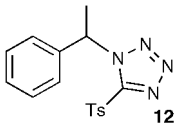
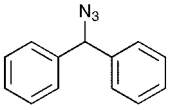
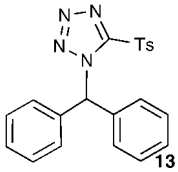
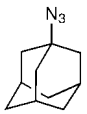
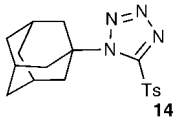
1-Substituted-5-sulfonyl tetrazoles are known to be very reactive toward nucleophilic attack by an addition–elimination pathway.[17] For example, thiophenol engages **3** at room temperature, and the corresponding adduct **19** can be isolated in 95% yield (see Scheme 4). Goltsberg and Koldobskii have demonstrated that various O, N, and C nucleophiles can add to sulfonyl tetrazoles, in yields ranging from 70–98%.[18] With this chemistry, one can functionalize sulfonyl tetrazoles with a wide range of nucleophiles. Therefore, by demonstrating a simple and expedient route to sulfonyl tetrazoles, we have provided an indirect route to a wide variety of 1,5-disubstituted tetrazoles (Scheme 5).

This chemistry enables a variety of substituents from the adjacent, or 1,5-positions of the hydrophobic tetrazole core, as shown above. This variety nicely complements the triazole cycloaddition chemistry mentioned in the introduction, as some acetylene–azide pairs are known to react to give 1,4-disubstituted triazoles with good regioselectivity[19] (Scheme 1, far right). Together, these methods provide fast access to either of the two fundamental topologies available to disubstituted azoles.

In summary, herein we extend the range of reliable dipolarophiles for intermolecular cycloadditions with organic azides, to include nitriles attached to a sulfonyl group. The examples with unhindered aliphatic azides constitute a perfect example of the ideal click-chemistry reaction—neat, thermal fusion in ≈100% yield. When sterically unhindered azides are used as the dipolar component, the reaction is virtually quantitative, and no workup procedures are necessary.

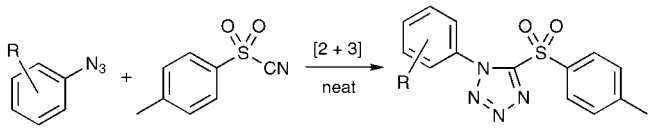
Table 2. [2+3] Dipolar cycloaddition of hindered azides and toluenesulfonyl cyanide.

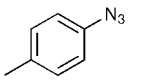
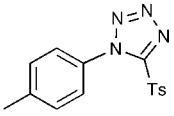
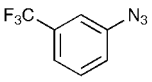
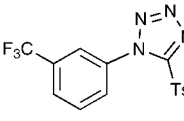
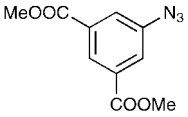
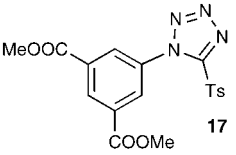
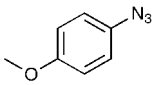
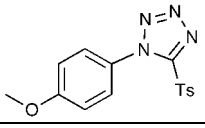


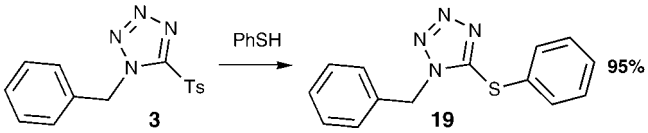
Reagent	Reaction conditions T [°C]	Time [h]	Product	Yield [%]
	80	16	 **9**	91
	80	16	 **10**	76
	80	24	 **11**	67[a]
	80	16	 **12**	59
	80	36	 **13**	48
	100	60	 **14**	46

[a] Because of the neighboring-group participation of the sulfur lone pair and the good leaving-group ability of the 5-sulfonyl tetrazole anion, a mixture of isomers is observed; see below.

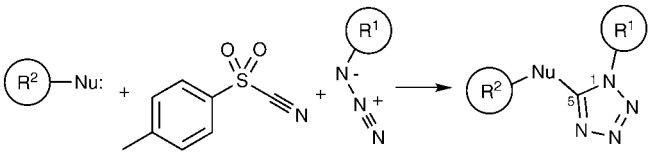
Table 3. [2+3] Dipolar cycloaddition of aryl azides and toluenesulfonyl cyanide.



Reagent	Reaction conditions T [°C]	Time [h]	Product	Yield [%]
	100	24	 **15**	62
	100	100	 **16**	67
	100	100	 **17**	43
	80	40	 **18**	30



Scheme 4. S_NAr derivatization of 5-sulfonyl tetrazoles.



Scheme 5. A general route to 1,5-disubstituted tetrazoles.

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Together with the known substitutions of the resulting sulfonyl tetrazoles, the two-step sequence is formally equivalent to regioselective cycloadditions of azides with a wide variety of nitriles. Further studies on the scope of this chemistry will be reported.[20]

Experimental Section

Note: Many low-molecular-weight azides are known to be explosive. In this lab, no problems have been encountered, but great caution should be exercised when heating compounds of this type, especially neat. The reactions described here were run on only a few grams; an increase in the scale of these reactions will decrease the efficiency of heat dissipation and explosions may result.

A vial was charged with a stir bar, *p*-toluenesulfonyl cyanide (905 mg, 5.0 mmol), and azide (5.0 mmol), and tightly capped. The reagents were stirred neat in an oil bath set to 80 °C, for 16 h. If the reaction was not complete at this time, stirring was continued, in some cases with the temperature reset to 100 °C. In the cases of unhindered azides, the crude product, a light yellow solid, was analytically pure. To remove color, the product can be dissolved in a mixture of ethyl acetate (30 %) and hexanes (70 %), and run down a short plug of silica gel to yield a white solid. If excess toluenesulfonyl cyanide was present, the product was crushed and placed under vacuum at 80 °C for four hours. In the case of hindered azides, the product was purified by column chromatography, by eluting with ethyl acetate (10 %) and hexanes (90 %), to give the product as a white or light-tan solid. In some cases (**9**, **14**) the product was sufficiently insoluble that trituration with ethyl acetate (10 %) and hexanes (90 %) was sufficient to purify the compound.

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[19] Regioselectivities observed are from 3:1 to 9:1 with propiolates (references a, b). Recent work in our laboratory (V. Rostovsev et al., unpublished results) as well as in reference c has shown that copper acetylides add to azides with complete regioselectivity; a) D. Clarke, R. W. Mares, H. J. McNab, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1799 – 1804; b) K. Hirota, H. Hosono, Y. Kitade, Y. Maki, C. K. Chu, R. F. Schinazi, H. Nakane, K. Ono, *Chem. Pharm. Bull.* **1990**, *39*, 2597 – 2601; c) C. W. Torne, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*(9), 3057 – 3064.

[20] Note added in proof: We have recently become aware of a patent which describes the [2 + 3] cycloaddition of a number of sulfonyl cyanides and azides. Only one yield is given, and the yield and procedure are not as efficient as described here; see D. H. Klaubert, J. H. Sellstedt, US Pat. 4,526,978, July 2, **1985**.

A Click Chemistry Approach to Tetrazoles by Huisgen 1,3-Dipolar Cycloaddition: Synthesis of 5-Acyltetrazoles from Azides and Acyl Cyanides**

Zachary P. Demko and K. Barry Sharpless*

Dedicated to Professor Rolf Huisgen

The preceding communication[1] describes the facile [2+3] cycloaddition of azides and *p*-toluenesulfonyl cyanide to form 5-sulfonyl tetrazoles, interesting compounds in their

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