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[3+2] Cycloaddition Reactions in the Solid-Phase Synthesis of 1,2,3-Triazoles

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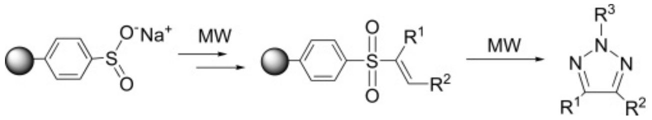
ABSTRACT

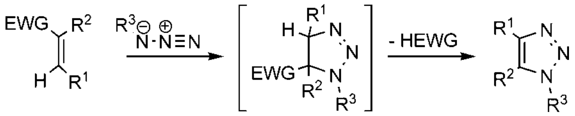


An efficient and regioselective procedure for the synthesis of 1,2,3-triazoles via a [3+2] cycloaddition of polymer-bound vinyl sulfone and sodium azide is described. Microwave irradiation provided significant rate enhancement in all steps of the three-step protocol. A representative set of 23 compounds was prepared.

1,2,3-Triazoles are attractive targets as they are associated with a wide range of applications in organic, materials, and medicinal chemistry. Numerous synthetic approaches to this class of compounds have been developed.[1] Among them, the 1,3-dipolar cycloaddition of azides and alkynes is the traditional and extensively used method. However, the efficiency of this process is dependent on the steric and electronic properties of the alkyne, and until recently, the regioselectivities of these reactions are generally low with unsymmetrical alkynes giving regioisomeric mixtures of triazoles.[2] As a consequence of these problems, such cycloaddition reactions have found limited use in the solid-phase synthesis (SPS) of triazole libraries.

Alternative solid-phase routes for the synthesis of 1,2,3-triazoles have rarely been explored.[1e,k] In particular, the [3+2] cycloaddition of azides and electron-poor alkenes (Scheme 1) has received very little attention. This may be attributed to the poor reactivities of the reactants which require harsh reaction conditions to facilitate the cycloaddition.[1b,o] Thus, finding an easy method to facilitate the solid-phase cycloaddition would be essential. We herein report a convenient solid-phase procedure for the regioselective and traceless synthesis of trisubstituted and disubstituted 1,2,3-triazoles (Scheme 2).

Scheme 1. Directed [3+2] Cycloaddition



Polystyrene/1% divinylbenzene sodium sulfinate resin **1** was chosen for our solid-phase studies because (i) the vinyl sulfone dipolarophile can be efficiently generated and (ii) the electronegative sulfone that is eliminated in the reaction may serve as a means to direct the regiochemistry of the cycloaddition as well as a traceless linker for the SPS.

To define the scope of this reaction, representative triazoles were synthesized using **1** to survey the requisite reaction

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(1) (a) Huisgen, R.; Knorr, R.; Moius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014−4021. (b) Maiorana, S.; Pocar, D.; Calla Croce, P. *Tetrahedron Lett.* **1966**, *7*, 6043−6045. (c) Meek, J. S.; Fowler, J. *J. Org. Chem.* **1968**, *33*, 985−991. (d) Chakrasali, R. T.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 851−854. (e) Li, C. L.; Huang, W. Q.; Lu, Y.; He, B. L. *Chin. Chem. Lett.* **1991**, *2*, 773−774. (f) Dong, Z.; Hellmund, K. A.; Pyne, S. G. *Aust. J. Chem.* **1993**, *46*, 1431−1436. (g) Gouault, N.; Cupif, J. F.; Sauleau, A.; David, M. *Tetrahedron Lett.* **2000**, *41*, 7293−7297. (h) Rostovtsec, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (i) Harju, K.; Vahermo, M.; Mutikainen, I.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2003**, *5*, 826−833. (j) Batanero, D. B.; Barba, F. *Heterocycles* **2004**, *65*, 1175−1180. (k) Raghavendra, M. S.; Lam, Y. *Tetrahedron Lett.* **2004**, *45*, 6129−6132. (l) Krasiñski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237−1240. (m) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem.* **2005**, *70*, 6426−6529. (n) Coats, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. J. *Org. Lett.* **2005**, *7*, 1469−1472. (o) Roque, D. R.; Neill, J. L.; Antoon, J. W.; Stevens, E. P. *Synthesis* **2005**, 2497−2502.

(2) (a) Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem.* **1994**, *59*, 6184−6189. (b) Sasaki, T.; Eguchi, S.; Yamaguchi, M.; Esaki, T. *J. Org. Chem.* **1981**, *46*, 1800−1804. (c) Howell, S. J.; Spencer, N.; Philp, D. *Tetrahedron* **2001**, *57*, 4945−4954.

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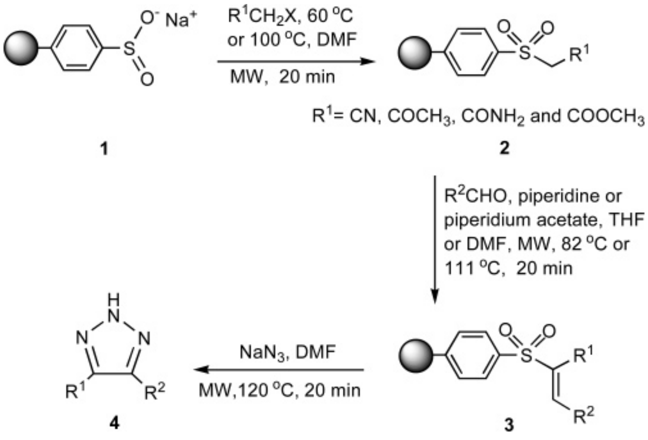
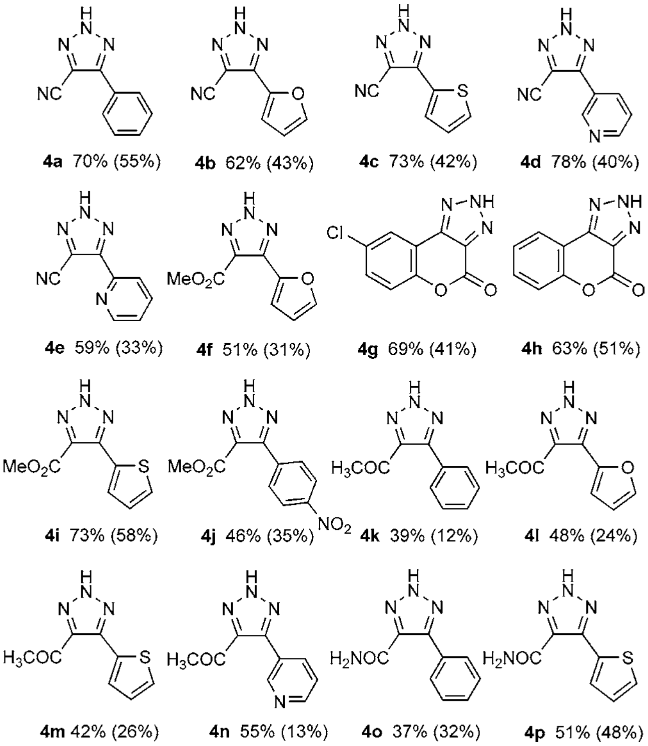
Scheme 2. Sulfinate SPS of 1,2,3-Triazoles



conditions required for SPS. Treatment of **1** with bromoacetonitrile, α-bromoketone, or α-bromoamide at 100 °C for 12 h gave **2** which was amenable to KBr FTIR monitoring (disappearance of the sulfinate stretch at 959 cm^{-1} and appearance of the sulfone stretch at 1320 and 1147 cm^{-1}, of the C═O stretch at 1746 cm^{-1}, and of the CN stretch at 2258 cm^{-1}). Subsequent Knoevenagel condensation of **2** with an aldehyde in refluxing benzene and 1 equiv of piperidine as a catalyst for 5 h[1e] gave the polymer-supported vinyl sulfone **3** which could not be reliably analyzed on the FTIR. Hence, we proceeded with the cycloaddition of **3** with NaN_3 in DMF at 120 °C for 2 h ($R^1 = CN$), 5 h ($R^1 = CO_2CH_3$ or $COCH_3$), or 12 h ($R^1 = CONH_2$) which concomitantly released the target molecule from the solid support in trace amounts. Attempts to carry out the condensation at higher temperatures led to the formation of various decomposition products. Further examination of the reaction indicated that the condensation occurred most favorably in refluxing THF for 36 h with piperidine or piperidine acetate as the catalyst.

To facilitate combinatorial synthesis, we needed to establish a methodology to prepare the 1,2,3-triazoles more expediently. Because microwave irradiation has been shown to provide a striking reduction in reaction times and cleaner reactions over conventional thermal procedures,[3] we proceeded to explore the SPS of our compounds under microwave conditions. For the initial evaluation of the microwave-assisted formation of **2**, we carried out a systematic variation of the reaction time and temperature with bromoacetonitrile as a representative example. We discovered that the reaction was completed within 20 min at a preselected temperature of 60 °C and 10 equiv of bromoacetonitrile. Microwave-assisted Knoevenagel condensation of **2** ($R^1 = CN$) with benzaldehyde in THF at 82 °C for 20 min followed by sodium azide cycloaddition at 120 °C for 20 min under microwave activation, extraction, and purification gave **4a** in 70% overall yield (vs 55% yield obtained via conventional heating). To illustrate the versatility of this methodology, a representative set of compounds (**4a**−**p**) was prepared (Figure 1). Except for **4o** and **4p** ($R^1 = CONH_2$), the microwave-assisted procedure generally led to significantly higher conversion and purity. The lower yields for the amide-substituted triazoles may be attributed to the more sluggish Knoevenagel condensation which did not proceed at 82 °C. Hence, formation of **3** ($R^1 = CONH_2$) was carried out at 111 °C in DMF.

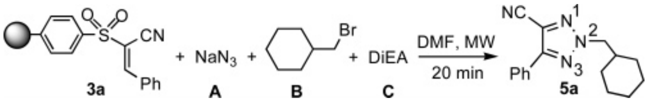


4a 70% (55%) **4b** 62% (43%) **4c** 73% (42%) **4d** 78% (40%)
4e 59% (33%) **4f** 51% (31%) **4g** 69% (41%) **4h** 63% (51%)
4i 73% (58%) **4j** 46% (35%) **4k** 39% (12%) **4l** 48% (24%)
4m 42% (26%) **4n** 55% (13%) **4o** 37% (32%) **4p** 51% (48%)

Figure 1. Library of 4,5-disubstituted-1,2,3-triazoles. The values in parentheses indicate the overall yields obtained via conventional heating.[4]

To address the regiochemistry of the cycloaddition reaction, resin **3a** was treated in a one-pot coupling procedure with sodium azide and bromomethylcyclohexane (Table 1) to give two regioisomers in a 10:1 ratio.[5] HMBC analysis

Table 1. Cycloaddition of Resin **3a** To Form Triazole **5a**



temperature (°C)	**3a**:**A**:**B**:**C**	yield (%)[a]
100	1:5:10:0	<5
35	1:5:10:5	41
70	1:5:10:5	45
100	1:5:10:5	45
120	1:5:10:5	50
150	1:5:10:5	55

[a] Overall yield of **5a**.

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(3) (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403−10432. (b) Varma, R. S. *Green Chem.* **1999**, 43−55. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105.

of the major regioisomer showed a proton−carbon correlation between the methylene proton ($CH_2C_6H_{11}$) and the nitrile carbon indicating that the major isomer could possibly be the N1 and N2 regioisomer. Further analysis by X-ray crystallography confirmed that the major isomer is 2-cyclohexylmethyl-5-phenyl-2*H*-[1,2,3]triazole-4-carbonitrile **5a** (Figure 2). Analogous cycloadditions with various resins **3** and alkyl halides were also performed (Figure 3). The regioselectivity of each crude mixture was approximately 10:1 with only polymer-bound 3-benzenesulfonyl-6-chlorochromen-2-one and benzyl bromide providing a greater amount of the second regioisomer. Regiochemical assignments based on X-ray crystallography show that **5e1** and **5e2** are the major and minor isomers, respectively (Figure 2).

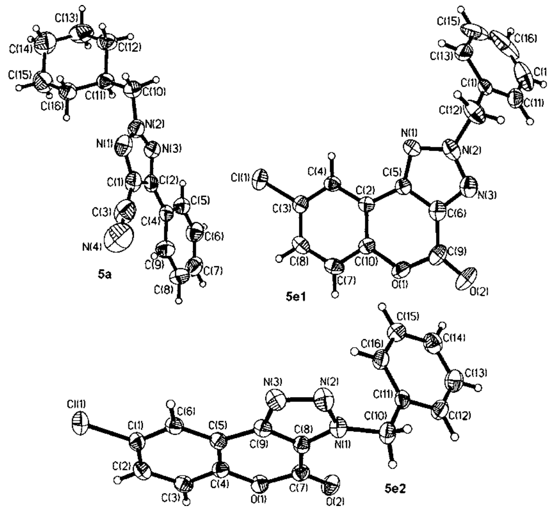


Figure 2. Crystal structures of **5a**, **5e1**, and **5e2**.

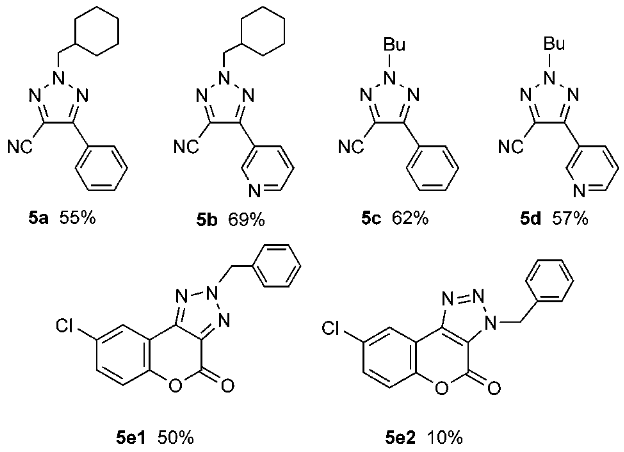
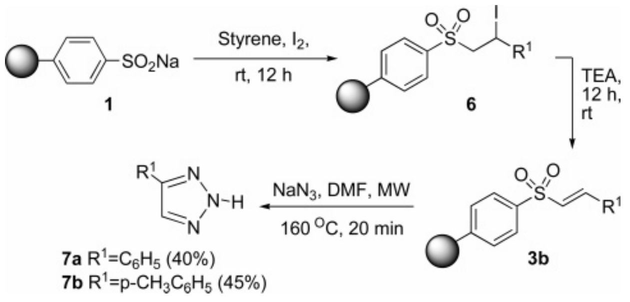

5a 55%
5b 69%
5c 62%
5d 57%
5e1 50%
5e2 10%

Figure 3. Trisubstituted-1,2,3-triazoles.

We have also examined the synthesis of **3** (R^1 = H) via the ionic addition of **1** to alkenes (Scheme 3). To our knowledge, this reaction has not been explored on the solid phase. In our experiments, **1** was treated with styrene in the presence of I_2 to yield β-iodosulfone **6** which was subsequently reacted with TEA to give the desired vinyl sulfone **3b**. Microwave-assisted cycloaddition with sodium azide in DMF at 160 °C for 20 min gave **7a** in 40% overall yield (cycloaddition at 120 °C for 20 min gave **7a** in 5% overall yield). Similarly, treatment of **1** with 1-methyl-4-vinylbenzene gave **7b** in 45% overall yield.

Scheme 3. Sulfinate SPS of Monosubstituted 1,2,3-Triazoles **7**



In summary, an efficient and regioselective traceless SPS of trisubstituted and disubstituted 1,2,3-triazoles has been devised. Using microwave irradiation, we have also shown that the total reaction time could be shortened from over 1 day to 1 h. Because a variety of reagents can be used in each step of the reaction, the overall strategy enables efficient library generation.

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Supporting Information Available: Experimental details and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Triazoles are known to undergo tautomerism. From the X-ray crystal studies of the compounds reported in this manuscript, it is clear that the position of the NH is dependent on the substituents on the triazole ring. Hence, for consistency in the drawings of our figures and schemes, we have placed all the NH on position 2.

(5) Attempts to carry out the cycloaddition with organic azides did not give the desired triazole, and the starting materials were recovered.