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Trimethylsilyl-Directed 1,3-Dipolar Cycloaddition Reactions in the Solid-Phase Synthesis of 1,2,3-Triazoles

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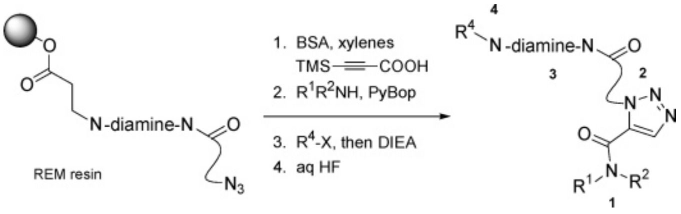
ABSTRACT

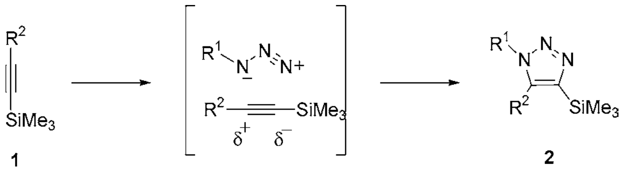


A regioselective method for the preparation of 1,5-trisubstituted 1*H*-1,2,3-triazoles via a 1,3-dipolar cycloaddition of 1-trimethylsilylacetylenes with organoazides is described. Immobilization of the azide on REM resin and subsequent cycloaddition afforded a 2 × 2 × 4 × 3 membered 1,5-disubstituted 1*H*-1,2,3-triazole library with an average purified yield of 68%.

The most versatile method for the synthesis of 1,2,3-triazoles has been the 1,3-dipolar cycloaddition reaction between an azide and an acetylene. Until recently, a significant drawback was that unsymmetrical acetylenes gave regioisomer mixtures of triazoles.[1] These mixtures tend to favor triazoles where the electron-withdrawing group occupies the 4-position and the electron-donating group occupies the 5-position. As a consequence of this problem, the cycloaddition reaction has found limited use in solid-phase synthesis and in drug discovery for the synthesis of triazole libraries to expand compound screening collections. A Wang resin-bound azide has been used in a cycloaddition reaction with acetylenes; however, an electron-withdrawing group on the acetylene was required to selectively obtain 1,4-disubstituted triazoles.[2]

The use of group IVA elements as regiodirecting groups in cycloaddition reactions has seen limited use thus far. The directing effect of the trimethylsilyl group in 1,3-dipolar cycloaddition reactions was first reported in 1972, when Birkhofer and Franz noted that the reaction between 4-(trimethylsilyl)-3-butyn-2-one and diazomethane produced a regioenhanced 4:1 mixture of pyrazoles.[3] This type of directing effect by 1-trimethylsilylacetylenes,[3−5] has been noted in the cycloaddition reactions of diazoalkanes and nitrile oxides. Typically, single isomers are obtained; however, mixtures were afforded with diazomethane.[3,4]

Scheme 1. Directed 1,3-Dipolar Cycloaddition



In our earlier work, we demonstrated that substituted organic azides when heated in the presence of 1-trimethylsilylacetylenes **1** exclusively yield the 1,5-disubstituted 4-trimethylsilyltriazoles **2**. We proposed that the trimethylsilyl group controlled the regioselectivity by a combination of steric hindrance and the ability of silicon to stabilize a partial positive charge on the acetylene β-carbon in the transition state (Scheme 1).[6] As a continuation of our study,

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[1] Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33−85 and references therein.

[2] Blass, E.; Coburn, K. R.; Faulkner, A. L.; Hunn, C. L.; Natchus, M. G.; Parker, M. S.; Portlock, D. E.; Tullis, J. S.; Wood, R. *Tetrahedron Lett.* **2002**, *43*, 4059−4061.

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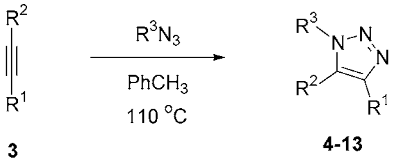
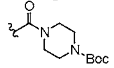
we wish to report the application of this process using solid-phase methods toward the generation of 1,5-disubstituted 1*H*-1,2,3-triazole libraries bearing four diversity centers.[7] During the course of our work, Sharpless and Meldal reported the use of copper(I) catalysis to control the regioselective synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles from terminal acetylenes and azides.[8,9] More recently, 1-bromomagnesium acetylenes were shown to react selectively with organoazides in good yield to form 1,5-disubstituted triazoles; however, reactive functional groups such as carbonyl are not compatible.[10] These methods complement our method described herein, since our work selectively provides 1,5-disubstituted 1*H*-1,2,3-triazoles and is compatible with 1-trimethylsilylacetylenes bearing aliphatic, aryl, or carbonyl groups in the 2-position.

To define the scope of this reaction, representative triazoles were synthesized in solution and characterized to determine the extent of regioselectivity observed in each case. As shown in Table 1, complete regioselectivity was obtained with 1-trimethylsilyl acetylenes.[11] Conversely, when nonsilylated acetylenes (entries 6 and 7) were used, regiomeric mixtures of triazoles were observed. The cycloadditions were run in refluxing toluene with reaction times ranging between 12 and 46 h.

Table 1. 1,3-Dipolar Cycloaddition of Acetylenes **3** to Form Triazoles **4**−**13**



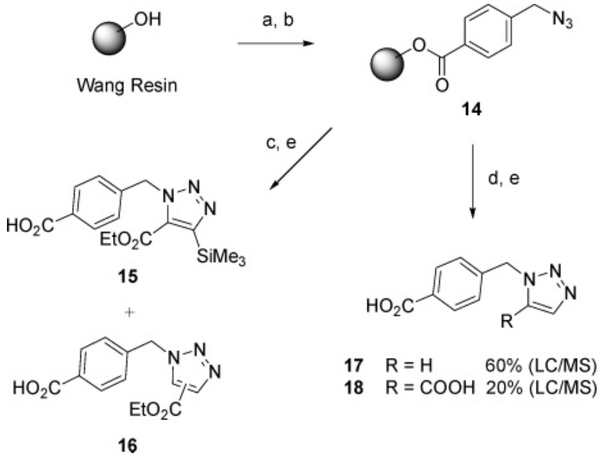
3 **4-13**

entry	R^1 =	R^2 =	R^3 =	time (h)	prdt	yield (%)
1	$SiMe_3$	SO_2-tol	Bn	12	**4**	82
2	$SiMe_3$	COMe	Bn	14	**5**	62
3	$SiMe_3$	COMe	TMS	14	**6**	(74)[a]
4	$SiMe_3$	CO_2Et	3-pyr	14	**7**	91
5	$SiMe_3$	CO_2Et	Bn	14	**8**	91
6	CO_2Et	H	Bn	14	**9a**	33
	H	CO_2Et	Bn		**9b**	35
7	CO_2Et	CF_3	Bn	14	**10a**	46
	CF_3	CO_2Et	Bn		**10b**	44
8	$SiMe_3$	CO_2H	Bn	22	**11**	60[b]
9	$SiMe_3$	CH_2OH	Bn	46	**12**	60
10	$SiMe_3$		Bn	14	**13**	42[c]

[a] Product obtained was desilylated **6** (R^3 = H). [b] Minor amount (15%) of desilylated **11** (R^1 = H) was isolated. [c] Minor amount (~20%) of the deprotected piperazinyl triazole **13** was isolated.

Entries 1, 2, 5, 8, and 9 show a range of examples where the electron-withdrawing ability of the R^2 group is varied. Electron-withdrawing groups on acetylenes are well-known to increase the cycloaddition reaction rate with azides. The electron-neutral $-CH_2OH$ example (entry 9) as expected required extended reaction time to obtain a reasonable yield. The 4-trimethylsilyl group was stable in all examples, except for entry 8 where 15% of the desilylated triazole **11** was obtained as a byproduct.

Scheme 2. Wang Resin Chemistry[a]



[a] Conditions: (a) 4-(chloromethyl)benzoyl chloride (5 equiv), DIEA (6 equiv), rt, DCM, 23 h; (b) TBAF (10 equiv), trimethylsilyl azide (10 equiv), rt, THF, 24 h; (c) ethyl trimethylsilyl-propynoate (5 equiv), 110 °C, toluene, 14 h; (d) trimethylsilyl-propynoic acid (2.5 equiv), 110 °C, toluene, 22 h; (e) TFA:DCM (1:1), 1 h.

Wang resin was chosen for our initial solid-phase studies due to its rapid and efficient cleavage protocol. Acylation of the resin with chloromethylbenzoyl chloride yielded the resin-bound benzyl chloride that was converted with trimethylsilyl azide to the resin-bound benzyl azide **14** (Scheme 2). We found that resin **14** was stable for more than seven months when stored at 4 °C on the basis of FT-IR analysis and subsequent chemical yields. The cycloaddition of **14** with ethyl trimethylsilyl-propynoate provided complete conversion to the resin-bound triazole after refluxing in toluene for 16 h. The progress of the cycloaddition reactions with **14** was monitored by FT-IR spectroscopy (azide stretch 2095 cm^{-1} relative to the carbonyl stretch at 1717 cm^{-1}). However, we

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(3) Birkhofer, L.; Franz, M. *Chem. Ber.* **1972**, *105*, 1759−1767.

(4) Guillerm, G.; L'Honore, A.; Veniard, L.; Pourcelot, G.; Benaim, J. *Bull. Soc. Chim. Fr.* **1973**, *105*, 2739−2746.

(5) Padwa, A.; Wannamaker, M. W. *Tetrahedron* **1990**, *46*, 1145−1162.

(6) Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem.* **1994**, *59*, 6184−6189.

(7) This work was presented in a preliminary form: Link, J. S.; Coats, S. J.; Hlasta, D. J. *Metal Directed 1,3-Dipolar Cycloadditions in Solution and Solid-Phase Synthesis*; Abstract at the 223rd National Meeting of the American Chemical Society, Orlando, FL, April 7−11, 2002; ORGN 228.

(8) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064.

(9) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897−3899. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128−1137 and references therein.

(10) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237−1240.

(11) Regiochemical assignments were made in accordance with ^1H, ^{13}C, and two-dimensional NMR studies. For example, triazole **8** in an HMBC experiment shows a three-bond proton−carbon correlation between the benzylic protons and the carbon of the triazole ring with the carbonyl attached, whereas no correlation is seen to the carbon with the trimethylsilyl group attached.

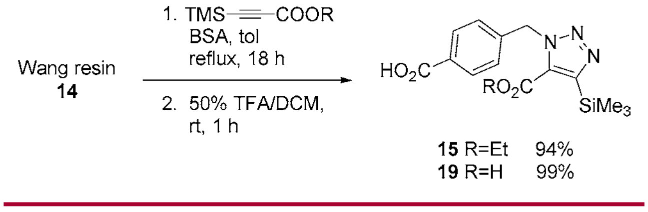
were surprised to find that cleavage with 50% TFA/DCM yielded both the desired 1,5-disubstituted 1,2,3-triazole, **15**, and varying amounts (from 5%−30%) of a mixture of the desilylated 1,5- and 1,4-disubstituted 1,2,3-triazoles **16**, albeit in combined excellent yield (based on initial loading of Wang resin).

Our solution-phase efforts had clearly shown clean regioselective cycloadditions to provide the 1,5-substituted triazoles. First, we determined that the 1,5-triazole **15** was stable to rearrangement during the resin cleavage reaction. The regiointegrity of the 1,5-triazole **15** was maintained when exposed to the cleavage conditions. In addition, there was no detectable loss of the TMS group.[12]

We repeated the cycloaddition of **14** with ethyl trimethylsilyl-propynoate in toluene-d_8 and found that *ethyl propynoate was formed* in the filtrate as evidenced by ^{1}H NMR analysis. We reasoned that TBAF from the azide formation reaction was not completely removed from the resin despite extensive washing of the resin. The resin **14** was treated with 10 equiv of bis(trimethylsilyl)acetamide (BSA) in DCM for 7 h at room temperature. When the cycloaddition was carried out with azide **14** that had been pretreated with BSA, we observed the regioselective formation of 1,5-triazole **15** in near quantitative isolated yield, while the amount of desilylated 1,5- and 1,4-disubstituted 1,2,3-triazoles **16** was extremely low on the basis of LC/MS and ^{1}H NMR analysis.

When BSA pretreated resin **14** was allowed to react with trimethylsilyl-propynoic acid, we obtained the desilylated, decarboxylated, 1-substituted triazole **17** in 42% isolated yield (60% by LC/MS) and desilylated 1,5-triazole **18** (20% by LC/MS) (Scheme 2). None of the desired triazole **19** was detected.[12] The solution-phase reaction of benzyl azide with trimethylsilyl-propynoic acid (Table 1, entry 8) gave the desired trimethylsilyl triazole **11**; however, a significant amount (15%) of desilylated triazole was isolated.[13] We later found that triazole **19** was not stable to the cycloaddition reaction conditions. When triazole **19** was refluxed in toluene for 14 h, we observed the same mixture of **17** and **18** by LC/MS analysis.

Scheme 3. BSA Protects Against Desilylation/ Decarboxylation

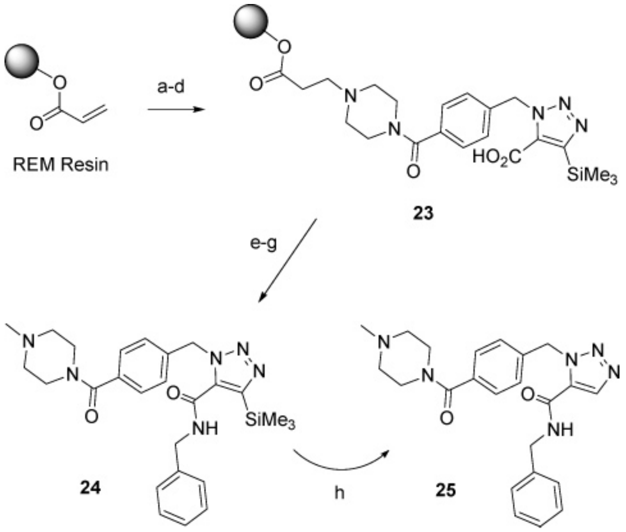


When resin **14** was allowed to react with trimethylsilyl-propynoic acid in the presence of BSA, we observed high regioselectivity and obtained the 1,5-triazole **19** in near quantitative yield and greater than 98% purity after removal of the TFA/DCM cleavage solution (Scheme 3). Clearly, BSA protects against desilylation and decarboxylation of our triazole system by rapid and complete formation of the silyl ester, which blocks both deleterious pathways. Tetrabutylammonium azide, although quite expensive, could also be substituted for the Me_3SiN_3/TBAF mixture with equally effective results.

We also found that when 5 equiv of ethyl trimethylsilyl-propynoate was allowed to react with resin **14** in the presence of 10 equiv of BSA for 16 h in toluene at 110 °C and then washed and cleaved with 50% TFA/DCM, we obtained after silica gel purification a 94% isolated yield of 1,5-triazole **15** (Scheme 3). We were unable to detect any of the 1,4-regioisomer or desilylation under these conditions.

We were unable to find desilylation conditions that would allow for removal of the TMS group that did not also cause significant cleavage from Wang resin. We did, however, find that after cleavage from resin, the TMS group in the triazole **15** could be removed in 79% yield with 10 equiv of 50% aq HF in THF.

Scheme 4. REM Resin Chemistry[a]



[a] Conditions: (a) piperazine (20 equiv), DMF, 96 h; (b) 4-(chloromethyl)benzoyl chloride (4 equiv), DIEA (6 equiv), DCM, 23 h, rt; (c) trimethylsilyl azide (9 equiv), TBAF:THF (1 M, 9 equiv), 24 h; (d) trimethylsilyl-propynoic acid (5 equiv), BSA (10 equiv), xylenes, 105 °C, 24 h; (e) benzylamine (5 equiv), PyBop (5 equiv), DIEA (10 equiv), DMF, 24 h; (f) MeI (10 equiv), DMSO, 19 h; (g) DIEA (4 equiv), DCM, 6 h; (h) aq HF (10 equiv), THF, 4 h.

The solution-phase and the Wang solid-phase chemistry demonstrated the feasibility of our approach. We chose to pursue REM resin as our solid support (Scheme 4). REM resin is a particularly attractive solid support, because an additional site of diversity can be created during the quarternization/elimination protocol, and the products are obtained in a traceless fashion.[14,15] The 1,4-addition of pipera-

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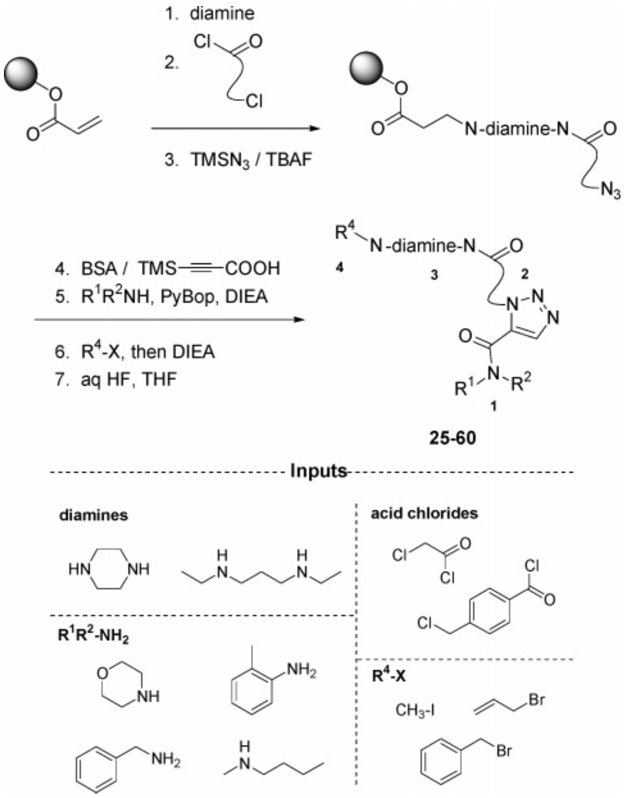
[12] Ethyl trimethylsilyl-propynoate and trimethylsilyl-propynoic acid did not contain minor amounts of desilylated acetylene and were stable after heating at 110 °C in toluene-d_8 for 24 h. Because we used 5 equiv of the 1-trimethylsilylacetylene in the cycloaddition reaction and the fact that ethyl propynoate undergoes a more rapid cycloaddition with **14**, a small impurity of desilylated acetylene would have explained our leakage of regioselectivity.

zine onto REM resin swelled in DMF yielded the resin-bound diamine. Coupling of the azido group was accomplished in the two-step procedure developed above on Wang resin involving amide formation under basic conditions with 4-(chloromethyl)benzoyl chloride followed by nucleophilic displacement of the primary chloride with in situ-generated tetrabutylammonium azide. Cycloaddition of the resin-bound azide with trimethylsilyl-propynoic acid in the presence of BSA yielded the trisubstituted triazole **23**. Coupling of the carboxylic acid of **23** with benzylamine was found to be quite difficult to drive to completion.[16] The desired amide was formed completely using PyBop in the presence of DIEA as evidenced by quaternization with MeI and subsequent elimination with DIEA to provide **24**, which did not contain any of the carboxylic acid as determined by LC/MS analysis.

Our last remaining issue to resolve before proceeding with the preparation of compound sets was the removal of the trimethylsilyl group from the triazole ring system. When triazole **24** was exposed to 10 equiv of HF (50% aq) in THF for 4 h at room-temperature, we observed smooth removal of the TMS group to afford triazole **25** (Scheme 4).[17]

A small library (2 × 2 × 4 × 3) of 1,5-disubstituted triazoles was prepared with the inputs shown in Scheme 5. All expected products were obtained except in the examples where *N*,*N*′-diethyl-propane-1,3-diamine was paired with chloroacetyl chloride. In these examples, 1,4-diethyl-[1,4]-diazepan-2-one was detected by LC/MS during the acylation step. Apparently, after acylation of the REM-bound diamine with chloroacetyl chloride, an intramolecular quaternization cyclization occurs, leading to elimination of the diazepan-2-one off-resin. We confirmed this side pathway by isolation of the diazepan-2-one from the washings after reaction of the REM-bound *N*,*N*′-diethyl-propane-1,3-diamine with chloroacetyl chloride (see Supporting Information). For the 36 successful reactions, we found that the products were obtained with excellent crude purities (LC/HRMS) and with excellent isolated yields for this eight-step process on REM resin.[14,15] The average crude purity was 87% on the basis of analysis of the PDA chromatogram, and the average isolated yield was 68% after reverse-phase HPLC purification (yield range from 27% to quantitative, calculated on the basis of the initial loading of REM resin).

Scheme 5. Synthesis of a 2 × 2 × 4 × 3 1,5-Disubstituted 1*H*-1,2,3-Triazole Library on REM Resin



In conclusion, we have shown that 1-trimethylsilyl acetylenes in the dipolar cycloaddition with a resin-bound azide produce one isomer of the corresponding 1,2,3-triazole. This methodology has been used on REM resin to prepare a small library of 1,5-disubstituted 1*H*-1,2,3-triazoles. REM resin is a technically difficult platform to use in long reaction schemes. To our knowledge, no one has conducted an eight-step reaction sequence with isolated yields as robust as those obtained in this study (68% average isolated yield).

Acknowledgment. We thank Greg Leo for assistance in the two-dimensional NMR structure assignments of these compounds.

Supporting Information Available: Experimental details and characterization data for new compounds and LC/HRMS results, isolated yields, and rule-of-five calculated properties for the 2 × 2 × 4 × 3 triazole library. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In a solution-phase reaction designed to mimic the Wang resin linker, a benzyl azide **20** on reaction with trimethylsilyl-propynoic acid gave two desilylated triazoles **21** and **22**, analogous to **17** and **18** (see Supporting Information).

(14) Brown, A. R.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288−3295. Cameron, K. S.; Morphy, J. R.; Rankovic, Z.; York, M. *J. Comb. Chem.* **2002**, *4*, 199−203.

(15) Barn, D.; Caulfield, W.; Cowley, P.; Dickins, R.; Bakker, W. I.; McGuire, R.; Morphy, J. R.; Rankovic, Z.; Thorn, M. *J. Comb. Chem.* **2001**, *3*, 534−541.

(16) A series of coupling agents were evaluated for their ability to form this sterically hindered amide bond. The following coupling agents are listed in order of increasing coupling efficiency for the reaction of **23** with 5 equiv of benzylamine: EEDQ < 1,3-dimethyl-2-fluoropyridinium toluene-4-sulfonate < MSNT < 2-chloro-1,3-dimethylimidazolinium chloride < DIC/HOBT < PyBrop < PyBop.

(17) Recently, we have found that precleavage desilylation can be accomplished by exposure of the REM trimethylsilyl triazole **23** to KF/aq HCl in THF (see Supporting Information).