# Steric Effects on the Regioselectivity of an Azide–Alkyne Dipolar Cycloaddition Reaction: The Synthesis of Human Leukocyte Elastase Inhibitors[1]

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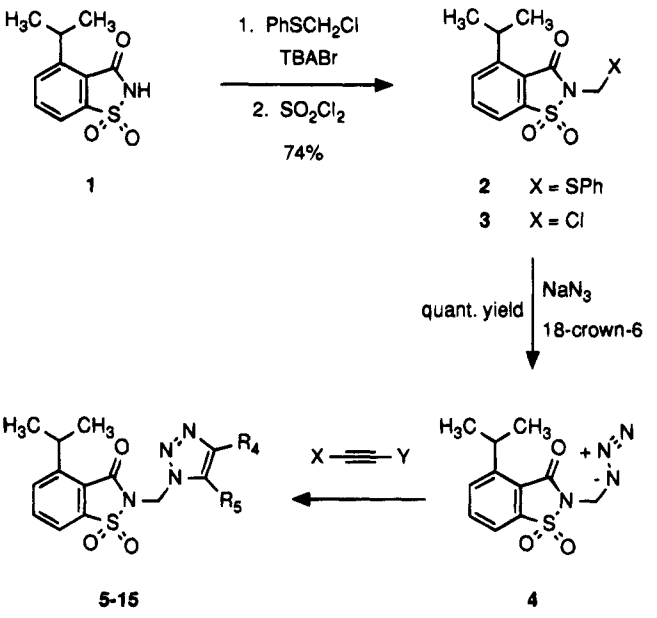
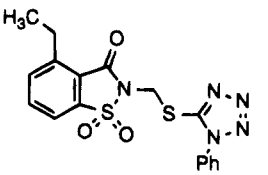
The cycloaddition reaction of *N*-(azidomethyl)benzisothiazolone **4** with various electron-deficient acetylenes gave a novel series of 1,2,3-triazoles **5–15** that were prepared for testing as inhibitors of human leukocyte elastase (HLE). Steric effects controlled the reaction regioselectivity, since as the acetylene substituent size increased from hydrogen to phenyl, *tert*-butyl, and trimethylsilyl, the regioisomer ratios reversed. An electronic effect of silicon appears to be responsible for the formation of only one isomer with the trimethylsilyl acetylenecarboxylate and ethynyl sulfone. For example, the 5-(phenylsulfonyl)triazole **13b** was the only regioisomer detected in the reaction of phenyl 2-(trimethylsilyl)ethynyl sulfone with the azide **4**. The strongly electron-withdrawing sulfone exerted no control over the regioselectivity of the cycloaddition reaction in comparison to the dominating effect of the trimethylsilyl group. High pressure and water as solvent were separately shown to accelerate the rate of product formation. The structures were unambiguously assigned on the basis of an X-ray crystal structure determination and NOE difference experiments. The derivative **12a**, WIN 68123, is a potent HLE inhibitor with an apparent binding constant ($K_i$*) of 0.38 nM.

## Introduction

Human leukocyte elastase (HLE) has been proposed to be a primary mediator of pulmonary emphysema. Endogenous regulatory proteins, e.g., $\alpha_1$-protease inhibitor, normally inactivate the free HLE that may be present in the lung. An imbalance between HLE and the endogenous regulatory proteins is postulated to occur in emphysema, where the deficiency of the $\alpha_1$-protease inhibitor leads to elastin connective tissue destruction in the lung by HLE.[2] An inhibitor of HLE should prove useful as a therapeutic agent for the treatment of emphysema and inflammatory pulmonary diseases where HLE is implicated in the pathophysiology.[3] Previously, we have discussed the synthesis of a series of benzisothiazolones and the structure–activity study that led to the discovery of WIN 62225, a potent, mechanism-based inhibitor of HLE ($K_i$* = 2.0 nM).[4] This paper discusses the synthesis of a new class of inhibitors (**5–15**) (Scheme I) that are structurally related to WIN 62225 and that possess the 1,2,3-triazole leaving group. These compounds are prepared via a 1,3-dipolar cycloaddition reaction of an *N*-(azidomethyl)benzisothiazolone derivative (**4**) with various electron-deficient acetylenes. In the course of preparing these analogs for biological testing, surprisingly large steric effects were noted for acetylenes with bulky substituents. For example, the reaction of phenyl 2-(trimethylsilyl)ethynyl sulfone with the azide **4** gave the 5-(phenylsulfonyl)-4-(trimethylsilyl)triazole **13b** as the only regioisomer detected in the reaction. The strongly electron-withdrawing sulfone exerted no control over the regiochemical outcome of the cycloaddition reaction in comparison to the dominating effect of the trimethylsilyl group.

**Scheme 1**



WIN 62225

## Results and Discussion

The target compounds **5–15** (Tables 1 and 3) were desired for testing as potential inhibitors of HLE. A

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(1) Presented in part at the 204th National Meeting of the American Chemical Society, Washington, DC, August 26, 1992; ORGN 356.

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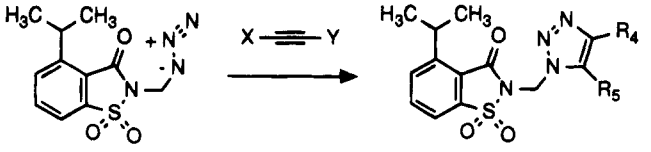
0022-3263/94/1959-6184$04.50/0 

**Table 1. Cycloaddition Reactions with Acetylenecarboxylates**



4 5-15

| alkyne | | equiv of | reactn | | triazole | | isolated yield |
|---|---|---|---|---|---|---|---|
| X = | Y = | alkyne | time[a] | compd | $R_5$ = | $R_4$ = | (%) |
| $COOCH_3$ | $COOCH_3$ | 3 | 6 h | **5** | $COOCH_3$ | $COOCH_3$ | 84 |
| H | $COOCH_3$ | 19 | 18 h | **6a** | H | $COOCH_3$ | 66 |
| | | | | **6b** | $COOCH_3$ | H | 23 |
| Ph | $COOCH_2CH_3$ | 10 | 7 d | **7a** | Ph | $COOCH_2CH_3$ | 37 |
| | | | | **7b** | $COOCH_2CH_3$ | Ph | 56 |
| TMS | $COOCH_3$ | 3 | 7 d | **8b** | $COOCH_3$ | TMS | 68 |

[a] Reactions were run at 0.02–0.04 M in benzene at reflux using 1–3 mmol of starting azide.

synthetic method was needed that would permit the synthesis of a large number of analogs through a central intermediate, while providing flexibility to permit the introduction of a variety of functional groups. The use of the intermediate azide **4** in 1,3-dipolar cycloaddition reactions with various substituted acetylenes permitted the preparation of these derivatives in one reaction step (Scheme 1).

The cycloaddition reaction of the azide **4** with acetylenecarboxylates proceeded in very good yield (Table 1). The reaction conditions and the regioisomer ratios obtained were similar to those reported for related examples.[5] The more electron deficient dipolarophiles react with faster reaction rates compared to the less electron deficient and sterically hindered dipolarophiles (Table 1). For example, dimethyl acetylenedicarboxylate afforded the triazole **5** in 6 h, while ethyl phenylpropiolate required 7 days for the complete formation of the triazoles **7a** and **7b** in good yield. A similar result was obtained for methyl (trimethylsilyl)propiolate, although the trimethylsilyl group completely dominated the selectivity of the reaction to afford triazole **8b** as the only isolable product. This type of dominating effect by a trimethylsilyl substituent has been noted in the cycloaddition reaction of diazoalkanes.[6,7] During the course of this work, Padwa reported[7] that in the reaction of diazomethane with acetylenes, the steric effect of the trimethylsilyl substituent dominates over the electron-withdrawing effects of sulfones. In the reaction of 2-diazopropane with a series of 3-substituted propiolates, as the 3-substituent increases in size from hydrogen to *tert*-butyl, steric effects control the regioselectivity. Thus, methyl propiolate affords only a 5-carboxypyrazole, while methyl 3-*tert*-butylpropiolate gave only a 4-carboxypyrazole.[8] In a series of (arylsulfonyl)acetylenes, the steric effect of trimethylsilyl was even more dominant, and a complete reversal of regioselectivity occurred between trimethylsilyl and methyl or phenyl.[7] In our experiments, a more gradual steric effect is observed between the hydrogen, phenyl, and trimethylsilyl examples (Table 1).

The 1,3-dipolar cycloaddition reaction, like the Diels–Alder reaction, has a highly negative volume of activation.[9,10] Reaction conditions that serve to compress the transition state, such as high pressure, aqueous conditions, sonication, etc., should increase the reaction rate. Additionally, since the use of unconventional solvents[11–13] and special conditions[9,14] have been shown to accelerate or enhance selectivity of Diels–Alder reactions, we chose to examine the effect of some of these new reaction conditions to control the reaction rate and possibly regioselectivity of the dipolar cycloaddition reaction of the azide **4** with ethyl phenylpropiolate. 1,3-Dipolar cycloadditions have shown relatively small solvent effects on reaction rate.[15] Only high pressure has been reported to accelerate the reaction rate significantly, but relatively few examples are known. During the course of this work, Weinreb reported[16] that high pressure accelerated the reaction of azides with olefins. Reaction conditions are reported to have little effect on regioselectivity ratios; nonetheless, some of these new methods could have given interesting results. Also, sterically-hindered acetylenes reacted with the azide **4** at a slow rate. Attempts to increase product formation by increasing the reaction temperature beyond ~100 °C gave multiple decomposition products and very low product yields in some examples.

We chose to study the reaction of the dipolarophile ethyl phenylpropiolate, since reaction with the azide **4** required 7 days to go to completion in refluxing benzene affording a nearly equal mixture of the 4- and 5-carboxytriazoles **7a** and **7b**. This reaction would provide the best example to determine if the reaction rate or the regioisomer ratio could be modified by reaction conditions. The

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**Table 2. Effect of Reaction Conditions on Rates of Formation**

| entry | reactn conditions[a] | temp (°C) | time, h | isolated yield **7a**:**7b** |
|---|---|---|---|---|
| 1 | $PhCH_3$ | 80 | 144 | 43:54 |
| 2 | $PhCH_3/H_2O$[b,c] | 80 | 144 | 39:51 |
| 3 | dioxane/$H_2O$[c] | 80 | 72 | 44:43 |
| 4 | $H_2O$[c] | 80 | 24 | 43:47 |
| 5 | neat | 80 | 24 | 42:49 |
| 6 | $PhCH_3$, 10 kbar[d] | rt | 144 | 36:54 |
| 7 | 5 M LiCl/$H_2O$[c] | 80 | 24 | 41:48 |
| 8 | 5 M $LiClO_4/Et_2O$ | rt | 144 | <5% |
| 9 | neat, sonicate | 40 | 24 | <5% |

[a] Reactions were run with 1 mmol of azide **4** and 10 equiv of alkyne in 10 mL of solvent. [b] 10 mL each of toluene and water were used. [c] These reactions were biphasic. [d] Reaction under these conditions for 55 h gave 24:40% isolated yield of **7a**:**7b** and recovered starting material.

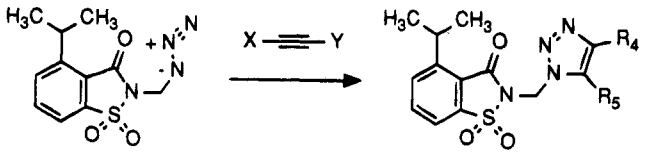
series of reaction conditions listed in Table 2 showed *no significant effect on the regioisomer ratio*; however, an *increase in the reaction rate,* as detected by a shortening of the reaction time to completion, was noted for entries 4, 5, 6, and 7. The reaction under neat conditions (entry 5) went to completion within 24 h at 80 °C. With water as the reaction solvent, a similar result was obtained (entry 4). We attribute this effect predominately to a neat reaction occurring in the biphasic reaction medium. If water did cause a significant increase in the reaction rate, then the biphasic toluene/water reaction of entry 2 should have resulted in a faster time to reaction completion. Instead this reaction gave similar results to those of the toluene solution reaction in entry 1. This result suggests that the reactants form product predominately in the toluene phase with no effect by water. Aqueous 5 M lithium chloride has been reported to increase the reaction rate of Diels–Alder reactions by greater than 2-fold; no effect was noted (compare entry 7 with entry 4).[11] The dioxane/water reaction (entry 3) gave an intermediate time to completion, but this result is difficult to interpret since the reaction was biphasic. High pressure (entry 6) did cause a significant rate increase, since the reaction was complete after 144 h *at room temperature*, compared to entry 1 in toluene which was complete in 144 h *at 80 °C*. However, sonication did not produce a significant effect on reaction rate (entry 9). The Lewis acid effect of the 5 M lithium perchlorate in ether was also insignificant (entry 8), since little reaction occurred. The findings in Table 2 are consistent with literature reports. The use of water as a solvent/reaction medium dispersant agent should be useful for sluggish reaction where neat conditions are not practical, as with solid reactants (see entry 6, Table 3).

The cycloaddition reaction of ethynylsulfones with the azide **4** was also examined (Table 3). Even though the sulfonyl group is a stronger electron-withdrawing group than a carboxy group, similar regiochemical effects were noted. The monosubstituted acetylenes of entries 1 and 2 afforded predominately the 4-substituted-triazoles. An increasing steric effect was noted as the size of the acetylene substituent increased from H to phenyl to *tert*-butyl. The ratio of regioisomers changed from predominately the 4-sulfonyltriazoles **a** to the 5-sulfonyltriazoles **b** in entries 2–4.

A particularly troublesome reaction was the acetylene of entry 6 in Table 3. The reaction of *N,N*-dimethyl 2-*tert*-butylethynesulfonamide with the azide **4** in benzene at reflux for 24 h gave only a trace of product by TLC. The reaction in DMF at reflux for 2 days led to substantial decomposition. The triazoles **14a** and **14b** were isolated in 3% and 7% yields, respectively. The heterogeneous reaction of entry 6 in water at 100 °C for 24 h afforded the triazoles **14a** and **14b** in 34% and 61% isolated yield, respectively. A similar result was obtained for the phenyl 2-*tert*-butylethynyl sulfone of entry 4, where the triazoles **12a** and **12b** were isolated in 36% and 63% yield, respectively. Since these reactions were biphasic, we attribute the rate acceleration and high yields to reaction in the neat phase and the fact that water only serves as a reaction dispersant agent. These reactions could not be conveniently carried out under neat conditions, since the acetylenes were crystalline solids. This represents a new use for water as a biphasic reaction medium for sluggish cycloaddition reactions.

The Verloop steric parameters (STERIMOL parameters)[17] characterize the size and shape of a substituent.

**Table 3. Steric Effects of Substituted Sulfonylacetylenes on Product Ratios**




**4** **5-15**

| entry | alkyne X = | alkyne Y = | condn[a] | equiv of alkyne | time | compd | triazole $R_5$ = | triazole $R_4$ = | isolated yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | H | TMS | A | 5 | 7 d | **9a** | H | TMS | 81 |
| 2 | H | $SO_2Ph$ | A | 4 | 16 h | **10a** | H | $SO_2Ph$ | 72 |
| | | | | | | **10b** | $SO_2Ph$ | H | (~5)[b] |
| 3 | Ph | $SO_2$-Tol | A | 1 | 7 d | **11a** | Ph | $SO_2Tol$ | 40 |
| | | | | | | **11b** | $SO_2Tol$ | Ph | 32 |
| 4 | t-Bu | $SO_2Ph$ | B | 2 | 4 h | **12a** | t-Bu | $SO_2Ph$ | 36 |
| | | | | | | **12b** | $SO_2Ph$ | t-Bu | 63 |
| 5 | TMS | $SO_2Ph$ | A | 3 | 5 h | **13b** | $SO_2Ph$ | TMS | 73 |
| 6 | t-Bu | $SO_2NMe_2$ | B[c] | 2 | 24 h | **14a** | t-Bu | $SO_2NMe_2$ | 34 |
| | | | | | | **14b** | $SO_2NMe_2$ | t-Bu | 61 |
| 7 | TMS | $SO_2NMe_2$ | A | 2 | 6 d | **15b** | $SO_2NMe_2$ | TMS | 82 |

[a] The reaction concentrations were 0.02–0.06 M in **4**. A = refluxing benzene, B = water at 100 °C. [b] A minor amount of **10b** (~5%) was detected by NMR in the crude reaction mixture. See ref 27. [c] Reaction in benzene at reflux for 24 h gave <5% reaction by TLC, while reaction in DMF at reflux for 2 days gave 3%:7% yield of **14a**:**14b** and numerous decomposition products.

**Table 4. STERIMOL Minimum Length ($B_1$) Steric Parameters[28]**

| | $B_1$, Å | | $B_1$, Å |
|---|---|---|---|
| H | 1.00 | COOR | 1.78 |
| Ph | 1.54 | $SO_2Ph$ | 2.05 |
| $C(CH_3)_3$ | 2.84 | $SO_2NMe_2$ | 2.05 |
| $Si(CH_3)_3$ | 3.04 | | |

In the calculation of these parameters, consideration of standard bond angles, van der Waals radii, bond lengths, and user-determined reasonable conformations are used to build the model of the substituent in space. The STERIMOL minimum width ($B_1$) is the shortest distance in angstroms from the van der Waals surface to the bond axis. Thus, the $B_1$ parameter is a measure of the minimum distance from the centroid of a substituent to its van der Waals surface. These parameters (Table 4) show that in the reaction transition state of the azide **4** with the acetylenes, the steric crowding around the *tert*-butyl and trimethylsilyl substituents would be considerable compared to either the phenylsulfonyl or sulfonamido substituents. Therefore, steric effects adequately account for the observed regioselectivities. Also, the *tert*-Bu and TMS groups should exert similar steric effects in the transition state since their $B_1$ values are similar; therefore, the ability of silicon to stabilize the transition state appears to be responsible for the exclusive formation of **13b** (entry 5), whereas the *tert*-Bu acetylene gave a 1:2 ratio of regioisomers **12a**:**12b** (entry 4). The ability of silicon to stabilize a positive charge on a $\beta$-carbon atom through $d/\pi$ interactions[18] would stabilize the transition state, leading to the formation of isomer **13b**. The substituent rank order for the STERIMOL minimum width, $B_1$, is TMS ~ *tert*-Bu > $SO_2$ > Ph > H, thus the regioisomer ratios listed in Table 3 can be rationalized predominately on the basis of steric effects with an electronic component for TMS.

**1,2,3-Triazole Structure Assignments.** The structure of **13b** was confirmed by single crystal X-ray diffraction.[19] The structures of the related compounds **8b** and **15b** were assigned on the basis of putative reactivity analogous to that which formed **13b**. NOE difference experiments were used to assign the structures of **6a,b**, **9a**, **10a,b**, **12a,b**, and **14a,b**. Irradiation of the linking $CH_2$ protons of compounds **6a**, **9a**, and **10a** led to enhancement of the triazole 5-position proton. Irradiation of the triazole 5-position *tert*-butyl protons led to enhancement of the linking $CH_2$ protons of compounds **12a** and **14a**. No enhancement was detected in the related irradiation experiments with compounds **6b**, **10b**, **12b**, and **14b**. The structures of **7a,b** and **11a,b** were assigned on the basis of comparison of the $^1$H-NMR data with compounds **6a,b** and **12a,b**. Comparison of the $^1$H-NMR chemical shifts of the $CH_2$ protons of compounds **7a,b** with **6a,b** showed that the **b** isomer $CH_2$ shift is 0.61 ppm and 0.49 ppm further downfield relative to the **a** isomer $CH_2$ shift. The same comparison of the $CH_2$ proton chemical shifts of compounds **11a,b** with **12a,b** showed a similar effect. Consistent with these assignments was the observation that the **b** isomer in every example was less polar than the **a** isomer, based on silica TLC $R_f$.

**Summary.** In the 1,3-dipolar cycloaddition reaction of an (azidomethyl)benzisothiazolone **4** with acetylenes, trimethylsilyl dominates over the electron deficient sulfonyl group to control the regioselectivity of this reaction. This result appears to be due mainly to a steric effect; however, electronic effects by trimethylsilyl cannot be ruled out. The steric effect of the TMS group, combined with the stabilization of a partial positive charge on the acetylene $\beta$ carbon by TMS in the transition state, could account for the exclusive formation of the 4-(trimethylsilyl)triazoles **13b** and **15b**. The rate of sluggish 1,3-dipolar cycloaddition reactions can be accelerated by running the reactions either neat or in a biphasic reaction with water as the reaction solvent. The rate increases noted for the aqueous reactions have been attributed to a reaction taking place in the neat phase of the reaction; water serves only as a reaction dispersant agent. High pressure (10 kbar) has also been shown to increase the reaction rate significantly. The 1,2,3-triazoles **5–15** prepared by this 1,3-dipolar cycloaddition reaction are a new class of human leukocyte elastase inhibitors. The triazole **12a**, WIN 68123, is a potent time-dependent inhibitor with an apparent binding constant ($K_i$*) of 0.38 nM.[20]

## Experimental Section

**4-(1-Methylethyl)-2-[(phenylthio)methyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (2).** A mixture of 4-(1-methylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (**1**)[21] (37.9 g, 0.168 mol), chloromethyl phenyl sulfide (33.3 g, 0.21 mol), tetrabutylammonium bromide (5.4 g, 17 mmol), and 200 mL of toluene was stirred and refluxed for 24 h. Heating was stopped, and the mixture was evaporated under reduced pressure. The residue was taken up in 1:1 $CH_2Cl_2$:hexane and added to a column of 485 g of silica gel. The column was eluted with hexane and then 1:1 $CH_2Cl_2$:hexane. Evaporation of the 1:1 $CH_2Cl_2$:hexane fractions gave 53.5 g (92%) of **2** as a yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (d, $J$ = 6 Hz, 6H), 4.21 (m, 1H), 5.13 (s, 2H), 7.32 (m, 3H), 7.61 (m, 2H), 7.75 (m, 3H); MS 348 ($MH^+$).

**2-(Chloromethyl)-4-(1-methylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (3).** The benzisothiazolone **2** (53.5 g, 0.154 mol), sulfuryl chloride (67.2 g, 0.50 mol), and 250 mL of $CH_2Cl_2$ were stirred together for 1 h and allowed to stand overnight. The solvent was removed under reduced pressure, and the residue was taken up in 100 mL of hexane and scratched. Solid separated and was collected after cooling to afford 38.55 g of an off-white solid. Recrystallization from 2-isopropanol–cyclohexane gave 33.5 (80%) of **3** as a colorless solid: mp 101–102.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.33 (d, $J$ = 6 Hz, 6H), 4.30 (m, 1H), 5.56 (s, 2H), 7.81 (m, 3H); MS 274 ($MH^+$), 238 ($M^+$ – 35). Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.27; H, 4.42; N, 5.12. Found: C, 48.37; H, 4.55; N, 5.14.

**2-(Azidomethyl)-4-(1-methylethyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (4).** CAUTION! Extreme care must be taken when handling any organo-azide due to the potential for explosive character.[22] We have not experienced any problems with handling the azide **3**; nonetheless, all reactions using azides were conducted in a hood behind a safety shield.

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(18) Zanirato, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2789. Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621.

(19) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(20) The kinetics of HLE inhibition by **12a** was determined using the method described in ref 4.

(21) The benzisothiazolone **1** was prepared by our method: Hlasta, D. J.; Court, J. J.; Desai, R. C. *Tetrahedron Lett.* **1991**, *32*, 7179.

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A mixture of 0.53 g (2.0 mmol) of 18-crown-6 and 25 mL of benzene was refluxed for 2 h with a water trap. Sodium azide (0.65 g, 10 mmol) and the benzisothiazolone **3** (2.73 g, 10 mmol) were added at rt, and the mixture was stirred for 60 h at rt. The reaction mixture was added to a column of 64 g of silica gel and elution with benzene gave the azido compound as a colorless solution in benzene (250 mL total volume). The azido compound was stored and usually used as a solution in benzene. CAUTIOUSLY, concentration of 10.0 mL of this solution and drying the residue under vacuum gave 106 mg of the azide **4** as a colorless oil (95% yield): IR (film) 2109, 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.34 (d, $J$ = 6 Hz, 6H), 4.31 (m, 1H), 5.13 (s, 2H), 7.82 (cm, 3H); MS (FAB) 281 ($MH^+$), 253 ($MH^+$ − 28), 238 ($M^+$ − 42). Anal. Calcd for $C_{11}H_{12}N_4O_3S$: C, 47.14; H, 4.32; N, 19.99. Found: C, 47.07; H, 4.27; N, 20.00.

***N,N*-Dimethyl-2-(trimethylsilyl)ethynesulfonamide.** *N,N*-Dimethylsulfamoyl chloride (7.18 g, 50 mmol) was added to a stirred suspension of aluminum chloride (6.67 g, 50 mmol) in 50 mL of $CH_2Cl_2$. A solution formed and was stirred for 15 min and filtered through glass wool. The solution was added slowly to a cooled solution of bis(trimethylsilyl)acetylene (7.67 g, 45 mmol) in 50 mL of $CH_2Cl_2$. The mixture was stirred for 90 min and allowed to stand overnight at rt. After the mixture was poured into ice water, the layers were separated. The organic layer was washed with saturated NaCl and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to leave 9.4 g of an amber oil, which partly crystallized. Trituration with hexane gave 3.0 g of a brown solid. Two recrystallizations from hexane gave 1.05 g (11%) of an off-white solid: mp 64−67 °C; IR (KBr) 2124, 1471, 1354 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.26 (s, 9H), 2.80 (s, 6H); MS 206 ($MH^+$). Anal. Calcd for $C_7H_{15}NO_2SSi$: C, 40.94; H, 7.36; N, 6.82. Found: C, 41.15; H, 7.41; N, 6.80.

***N,N*,3,3-Tetramethyl-1-butyne-1-sulfonamide.** *N,N*-Dimethylsulfamoyl chloride (14.35 g, 100 mmol) was added to a stirred suspension of aluminum chloride (13.33 g, 100 mmol) in 100 mL of $CH_2Cl_2$. A solution formed after stirring for 20 min and was filtered through glass wool. This solution was added dropwise to a cooled solution (0 °C) of (3,3-dimethyl-1-butynyl)trimethylsilane[23] (13.86 g, 90 mmol) in 100 mL of $CH_2Cl_2$ under $N_2$. The mixture was stirred for 2 h and allowed to stand overnight at rt. The darkened mixture was poured into ice water. The layers were separated, the organic layer was dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. The brown solid residue (8 g) was triturated with hexane to afford 5.3 g (31%) of tan solid; mp 94−96 °C. An analytical sample was obtained after two recrystallizations from hexane, the second after charcoal treatment, to give colorless solid: mp 96.5−97 °C; IR (KBr) 2977, 2211, 2173, 1349 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.33 (s, 9H), 2.80 (s, 6H); MS (DCI) 190 ($MH^+$). Anal. Calcd for $C_8H_{15}NO_2S$ : C, 50.77; H, 7.99; N, 7.40. Found: C, 50.96; H, 8.04; N, 7.33.

**[(3,3-Dimethyl-1-butynyl)sulfonyl]benzene.** Benzenesulfonyl chloride (4.85 g, 28 mmol) was added to a stirred suspension of aluminum chloride (3.7 g, 28 mmol) in 25 mL of $CH_2Cl_2$. A solution formed and was filtered through glass wool. This solution was added dropwise to a cooled solution (0 °C) of (3,3-dimethyl-1-butynyl)trimethylsilane[23] (3.85 g, 25 mmol) in 25 mL of $CH_2Cl_2$ under $N_2$. The dark brown mixture was stirred overnight at rt and then poured onto ice−1 N HCl. The organic layer was separated, washed with water (2×), dried over $Na_2SO_4$, and concentrated. The residue was chromatographed on silica gel with gradient elution (25% benzene in cyclohexane to benzene) to afford 382 mg (7%) of the acetylene[24] as a pale yellow oil: silica TLC (benzene) $R_f$ = 0.3; $^1H$ NMR ($CDCl_3$) $\delta$ 1.26 (s, 9H), 7.60 (m, 3H), 8.00 (m, 2H).

**Triazole 5.** A mixture of 285 mg (1.0 mmol) of the azide **4** and 426 mg (3.0 mmol) of dimethyl acetylenedicarboxyate in 12 mL of benzene was heated at reflux for 6 h. Crystallization from benzene/cyclohexane gave 354 mg (84%) of triazole **5** as a white solid: mp 153−154 °C (EtOAc/cyclohexane); IR (KBr) 1745, 1728 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.31 (d, $J$ = 6 Hz, 6H), 3.96 (s, 3H), 4.10 (s, 3H), 4.29 (m, 1H), 6.63 (s, 2H), 7.80 (cm, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 160.1, 158.5, 158.4, 152.8, 140.2, 138.0, 135.8, 132.3, 131.0, 121.7, 118.8, 53.8, 52.8, 49.8, 28.5, 23.0; MS (DCI) 423 ($MH^+$). Anal. Calcd for $C_{17}H_{18}N_4O_7S$: C, 48.34; H, 4.30; N, 13.26. Found: C, 48.36; H, 4.17; N, 13.23.

**Triazoles 6a and 6b.** To 3.0 mmol of the azide **4** in 150 mL of benzene was added 4.7 g (56 mmol) of methyl propiolate, and the solution was refluxed 18 h. The reaction mixture was chromatographed on silica gel and eluted with methylene chloride to give 250 mg (23%) of **6b** followed by 720 mg (66%) of **6a**, both as white solids. **6b**: mp 150.5−151.5 °C (EtOAc); IR (KBr) 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.32 (d, $J$ = 6 Hz, 6H), 4.06 (s, 3H), 4.35 (m, 1H), 6.79 (s, 2H), 7.80 (cm, 3H), 8.18 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.7, 158.4, 152.7, 138.0, 137.8, 135.4, 132.2, 128.8, 121.8, 118.7, 53.0, 49.5, 28.4, 23.0; MS (DCI) 365 ($MH^+$), 364 ($M^+$). Anal. Calcd for $C_{15}H_{16}N_4O_6S$: C, 49.44; H, 4.43; N, 15.38. Found: C, 49.43; H, 4.21; N, 15.35. **6a**: mp 192−193 °C (EtOAc); IR (KBr) 1732 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.33 (d, $J$ = 6 Hz, 6H), 3.94 (s, 3H), 4.28 (m, 1H), 6.30 (s, 2H), 7.85 (cm, 3H), 8.48 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 160.7, 158.9, 152.9, 140.7, 138.0, 135.8, 132.4, 128.5, 121.5, 119.0, 52.2, 50.5, 28.5, 22.9; MS (DCI) 365 ($MH^+$), 364 ($M^+$). Anal. Calcd for $C_{15}H_{16}N_4O_5S$: C, 49.44; H, 4.43; N, 15.38. Found: C, 49.67; H, 4.35; N, 15.56.

**Triazoles 7a and 7b.** To 3.0 mmol of the azide **4** in 140 mL of benzene was added 5.0 g (29 mmol) of ethyl phenylpropiolate, and the solution was refluxed 7 d. The reaction mixture was chromatographed on silica gel and gradient eluted with 1:1 hexanes−methylene chloride to 2:1 $CH_2Cl_2$−EtOAc to give 760 mg (56%) of **7b** followed by 500 mg (37%) of **7a** both as white solids. **7b**: mp 117−119 °C (EtOAc/cyclohexane); IR (KBr) 1738, 1715 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.33 (d, $J$ = 6 Hz) and 1.36 (t, $J$ = 6 Hz) (9H), 4.34 (m, 1H), 4.47 (q, $J$ = 6 Hz, 2H), 6.79 (s, 2H), 7.44 (m, 3H), 7.78 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.1, 158.5, 152.7, 150.2, 138.1, 135.4, 132.1, 129.6, 129.5, 129.1, 127.9, 125.1, 121.7, 118.7, 62.5, 50.3, 28.4, 23.0, 13.8; MS (DCI) 455 ($MH^+$), 454 ($M^+$). Anal. Calcd for $C_{22}H_{22}N_4O_5S$: C, 58.14; H, 4.88; N, 12.33. Found: C, 58.10; H, 4.73; N, 12.29. **7a**: mp 177.5−179 °C (EtOAc); IR (KBr) 1749, 1726 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.24 (t, $J$ = 6 Hz) and 1.28 (d, $J$ = 6 Hz) (9H), 4.16 (m, 1H), 4.29 (q, $J$ = 6 Hz, 2H), 6.18 (s, 2H), 7.48 (m, 5H), 7.76 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 160.6, 157.8, 152.6, 141.8, 137.9, 137.4, 135.4, 132.1, 130.3, 130.0, 128.7, 125.0, 121.6, 118.7, 61.0, 49.1, 28.4, 22.9, 14.0; MS (DCI) 455 ($MH^+$). Anal. Calcd for $C_{22}H_{22}N_4O_5S$: C, 58.14; H, 4.88; N, 12.33. Found: C, 58.14; H, 4.75; N, 12.37.

**Triazole 8b.** To 1.1 mmol of the azide **4** in 30 mL of benzene was added 480 mg (3.1 mmol) of methyl (trimethylsilyl)propiolate,[25] and the solution was refluxed 7 d. The reaction mixture was chromatographed on silica gel and gradient eluted with 10% to 25% cyclohexane in EtOAc to give 410 mg of a colorless oil. Crystallization from cyclohexane afforded 325 mg (68%) of **8b** as white solid: mp 122.5−123.5 °C (cyclohexane); IR (KBr) 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.36 (s, 9H), 1.29 (d, $J$ = 7 Hz, 6H), 4.04 (s, 3H), 4.33 (m, 1H), 6.78 (s, 2H), 7.77 (cm, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.7, 158.4, 152.6, 152.1, 138.1, 135.3, 133.7, 132.1, 121.9, 118.6, 52.6, 49.8, 28.4, 23.0, −1.5; MS (DCI) 437 ($M^+$). Anal. Calcd for $C_{18}H_{24}N_4O_5SSi$: C, 49.52; H, 5.54; N, 12.83. Found: C, 49.58; H, 5.48; N, 12.80.

**Triazole 9a.** A solution of 1.44 mmol of the azide **4** in 40 mL of benzene and 695 mg (7.09 mmol) of (trimethylsilyl)-acetylene was refluxed for 7 d. The reaction mixture was chromatographed on silica gel and gradient eluted with 15% to 40% EtOAc in cyclohexane to give 440 mg (81%) of **9a** as a colorless oil: IR (KBr) 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.31 (s, 9H), 1.31 (d, $J$ = 7 Hz, 6H), 4.28 (m, 1H), 6.27 (s, 2H), 7.80 (cm) and 7.86 (s) (4H); MS (DCI) 379 ($MH^+$). Anal. Calcd for $C_{16}H_{22}N_4O_3SSi$: C, 50.77; H, 5.86; N, 14.80. Found: C, 51.19; H, 5.87; N, 14.74.

**Triazole 10a.** A solution of 3.0 mmol of the azide **4** in 110 mL of benzene and 1.9 g (11 mmol) of (ethynylsulfonyl)-benzene[26] was refluxed for 16 h. The reaction mixture was

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concentrated and the residue (~5% of **10b** was detected in the NMR of the crude product) recrystallized from ethyl acetate to afford 960 mg (72%) of **10a** as white solid: mp 219.5–220.5 °C (EtOAc); IR (KBr) 1741 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.27 (d, $J$ = 6 Hz, 6H), 4.19 (m, 1H), 6.46 (s, 2H), 7.72 (cm, 3H), 8.00 (m, 4H), 8.16 (m, 1H), 9.09 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 158.4, 151.3, 147.6, 139.8, 137.1, 136.2, 134.3, 132.7, 129.8, 129.0, 127.4, 121.5, 119.4, 50.8, 27.9, 22.6; MS (DCI) 447 ($MH^+$). Anal. Calcd for $C_{19}H_{18}N_4O_5S_2$: C, 51.11; H, 4.06; N, 12.55. Found: C, 51.18; H, 3.91; N, 12.61.

**Triazoles 10b and 13b.** A solution of 3.0 mmol of the azide **4** in 125 mL of benzene and 4.85 g (20 mmol) of phenyl 2-(trimethylsilyl)ethynyl sulfone (Aldrich) was stirred at rt for 6 d. The reaction mixture was chromatographed on silica gel, and 340 mg (22%) of **13b** was obtained on elution with benzene, followed by 430 mg (32%) of **10b** on elution with EtOAc, both as a white solids. **10b**: mp 170–172 °C (EtOAc); IR (KBr) 1748 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.32 (d, $J$ = 7 Hz, 6H), 4.21 (m, 1H), 6.58 (s, 2H), 7.68 (cm, 3H), 8.04 (m, 5H), 8.62 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 158.2, 151.7, 139.2, 137.5, 137.3, 136.8, 135.4, 133.1, 130.1, 128.0, 121.3, 119.7, 51.3, 28.4, 23.0; MS (DCI) 447 ($MH^+$) 446 ($M^+$). Anal. Calcd for $C_{19}H_{18}N_4O_5S_2$: C, 51.11; H, 4.06; N, 12.55. Found: C, 51.09; H, 4.00; N, 12.48. **13b**: mp 200.5–201.5 °C (EtOAc); IR (KBr) 1742 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.49 (s, 9H), 1.32 (d, $J$ = 6 Hz, 6H), 4.26 (m, 1H), 6.39 (s, 2H), 7.5–8.0 (cm, 8H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.3, 152.8, 152.5, 140.7, 139.9, 138.1, 135.4, 134.2, 132.0, 129.6, 127.1, 121.8, 118.6, 50.6, 28.5, 22.9, −0.9; MS (DCI) 518 ($M^+$). Anal. Calcd for $C_{22}H_{26}N_4O_5S_2Si$: C, 50.95; H, 5.05; N, 10.80. Found: C, 50.79; H, 4.97; N, 10.75.

**Triazoles 11a and 11b.** A solution of 3.0 mmol of the azide **4** in 53 mL of benzene and 881 mg (3.44 mmol) of phenylethynyl $p$-tolyl sulfone was refluxed for 7 d. The reaction mixture was chromatographed on silica gel, and 510 mg (32%) of **11b** was obtained on elution with benzene, followed by 640 mg (40%) of **11a** on elution with 25% EtOAc in benzene both as a white solids. **11a**: mp 179–181.5 °C (EtOAc); IR (KBr) 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.26 (d, $J$ = 7 Hz, 6H), 2.38 (s, 3H), 4.13 (m, 1H), 6.07 (s, 2H), 7.2–7.9 (cm, 12H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 157.8, 152.6, 146.2, 144.8, 139.5, 137.8, 137.6, 135.5, 132.2, 131.0, 130.3, 129.7, 128.8, 128.0, 123.2, 121.5, 118.7, 49.2, 28.4, 22.9, 21.6; MS (DCI) 537 ($MH^+$), 536 ($M^+$). Anal. Calcd for $C_{26}H_{24}N_4O_5S_2$: C, 58.20; H, 4.51; N, 10.44. Found: C, 57.99; H, 4.31; N, 10.43. **11b**: mp 173–174.5 °C (EtOAc); IR (KBr) 1744 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.35 (d, $J$ = 7 Hz, 6H), 2.34 (s, 3H), 4.37 (m, 1H), 6.84 (s, 2H), 7.09 (m, 2H), 7.3–7.6 (cm, 7H), 7.80 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.7, 152.7, 149.7, 145.7, 138.2, 136.4, 135.4, 133.4, 132.2, 130.0, 129.6, 129.5, 128.3, 128.0, 127.7, 122.0, 118.8, 51.2, 28.5, 23.0, 21.6; MS (DCI) 537 ($MH^+$), 536 ($M^+$). Anal. Calcd for $C_{26}H_{24}N_4O_5S_2$: C, 58.20; H, 4.51; N, 10.44. Found: C, 57.96; H, 4.34; N, 10.40.

**Triazoles 12a and 12b.** A suspension of 200 mg (0.71 mmol) of the azide **4** and 272 mg (1.22 mmol) of [(3,3-dimethyl-1-butynyl)sulfonyl]benzene[24] in 10 mL of water was vigorously stirred at 100 °C for 4 h. The reaction mixture was concentrated in vacuo, and the residue was purified by chromatographed on silica gel eluted with 1:5 EtOAc in cyclohexane and then 1:3 EtOAc in cyclohexane to give 224 mg (63%) of **12b** followed by 130 mg (36%) of **12a** both as white solids. **12a**: mp 205-206 °C (benzene/cyclohexane); IR (KBr) 1754 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.32 (d, $J$ = 6 Hz, 6H), 1.81 (s, 9H), 4.26 (m, 1H), 6.37 (s, 2H), 7.57 (m, 3H), 7.78 (m, 3H), 8.02 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.7, 152.8, 146.1, 140.2, 138.0, 135.6, 133.8, 132.3, 129.2, 128.8, 128.3, 121.8, 118.9, 52.0, 32.6, 30.8, 28.5, 23.0; MS (DCI) 503 ($MH^+$) 502 ($M^+$). Anal. Calcd for $C_{23}H_{26}N_4O_5S_2$: C, 54.96; H, 5.21; N, 11.15. Found: C, 54.88; H, 5.15; N, 11.21. **12b**: mp 186.5–187.5 °C (benzene/cyclohexane); IR (KBr) 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.32 (d, $J$ = 6 Hz, 6H), 1.48 (s, 9H), 4.26 (m, 1H), 6.47 (s, 2H), 7.5–8.0 (cm, 8H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.2, 158.6, 152.6, 141.0, 138.2, 135.4, 134.1, 132.1, 131.3, 129.6, 126.6, 122.0, 118.7, 52.1, 33.5, 30.1, 28.5, 23.0; MS (DCI) 502 ($M^+$). Anal. Calcd for $C_{23}H_{26}N_4O_5S_2$: C, 54.96; H, 5.21; N, 11.15. Found: C, 55.16; H, 5.16; N, 11.07.

**Triazole 13b.** A solution of 1.0 mmol of the azide **4** in 21 mL of benzene and 710 mg (3.0 mmol) of phenyl 2-(trimethylsilyl)ethynyl sulfone[26,27] was refluxed for 5 h. The reaction mixture was chromatographed on silica gel and eluted with benzene to give 380 mg (73%) of **13b** as a white solids: mp 200.5–201.5 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 0.47 (s, 9H), 1.31 (d, $J$ = 6 Hz, 6H), 4.26 (m, 1H), 6.39 (s, 2H), 7.5–8.0 (cm, 8H).

**Triazoles 14a and 14b.** A suspension of 517 mg (1.84 mmol) of the azide **4** and 700 mg (3.7 mmol) of *N,N*,3,3-tetramethyl-1-butyne-1-sulfonamide in 30 mL of water was vigorously stirred at 100 °C for 24 h. The reaction mixture was extracted with $CHCl_3$, and the organic layer was separated and dried over $Na_2SO_4$, filtered, and concentrated. Crystallization from EtOAc/cyclohexane gave 336 mg (39%) of **14b** as a white solid: mp 210–212 °C. The mother liquor was purified by chromatography on silica gel eluted with 10% EtOAc in cyclohexane to give 190 mg (22%) of **14b** followed by 290 mg (34%) of **14a** both as white solids. **14a**: mp 201–202 °C (EtOAc/cyclohexane); IR (KBr) 1727 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.35 (d, $J$ = 6 Hz, 6H), 1.72 (s, 9H), 3.13 (s, 6H), 4.32 (m, 1H), 6.38 (s, 2H), 7.83 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.8, 152.7, 138.0, 135.5, 132.2, 121.7, 118.9, 52.0, 38.7, 32.0, 30.3, 28.5, 23.0; MS (DCI) 470 ($MH^+$). Anal. Calcd for $C_{19}H_{27}N_5O_5S_2$: C, 48.60; H, 5.80; N, 14.91. Found: C, 48.68; H, 5.80; N, 14.85. **14b**: mp 211–212 °C (EtOAc/cyclohexane); IR (KBr) 1749 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.33 (d, $J$ = 6 Hz, 6H), 1.50 (s, 9H), 2.94 (s, 6H), 4.35 (m, 1H), 6.41 (s, 2H), 7.79 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.8, 158.6, 152.8, 138.2, 135.4, 132.2, 129.7, 122.1, 118.7, 50.8, 36.8, 33.2, 29.8, 28.5, 23.0. Anal. Calcd for $C_{19}H_{27}N_5O_5S_2$: C, 48.60; H, 5.80; N, 14.91. Found: C, 48.70; H, 5.78; N, 14.96.

**Triazole 15b.** A solution of 3.18 mmol of the azide **4** in 100 mL of benzene and 1.30 g (6.3 mmol) of *N,N*-dimethyl-2-(trimethylsilyl)ethynesulfonamide was refluxed for 6 d. The reaction mixture was chromatographed on silica gel and eluted with benzene and then 20% EtOAc in benzene to give 1.27 g (82%) of **15b** as a white solid: mp 196–198 °C ($CH_3CN$); IR (KBr) 1749 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.43 (s, 9H), 1.35 (d, $J$ = 7 Hz, 6H), 2.94 (s, 6H), 4.36 (m, 1H), 6.39 (s, 2H), 7.78 (cm, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.4, 152.7, 152.3, 138.5, 137.9, 135.4, 132.2, 121.9, 118.6, 49.7, 36.9, 28.5, 23.0, −1.2; MS (DCI) 486 ($MH^+$), 485 ($M^+$). Anal. Calcd for $C_{18}H_{27}N_5O_5S_2Si$: C, 44.52; H, 5.60; N, 14.42. Found: C, 44.77; H, 5.58; N, 14.44.

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(27) Freshly prepared 1-(phenylsulfonyl)-2-(trimethylsilyl)acetylene was used. Commercially available acetylene (Aldrich) under identical conditions gave a mixture of **13b** (22%) and **10b** (32%), even though the spectral data were consistent for pure material.

(28) The minimum lengths $B_1$ were calculated using the STERIMOL program for this series of substituted acetylenes. Our calculated values vary only slightly from the original generic values calculated by Verloop (see ref 17).