Synthetic Applications of 2-(Azidomethyl)allyltrimethylsilane

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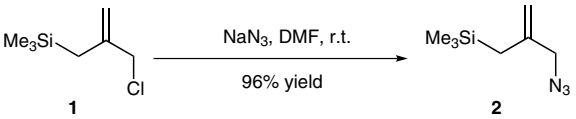
Abstract: Starting from commercially available 2-(chloromethyl)-allyltrimethylsilane, the corresponding 2-(azidomethyl)allylsilane was prepared through reaction with NaN_3. The product was stable upon isolation and storage and could be used for thermal cycloaddition of the azido group with alkenes to give allylsilane-containing triazolines or aziridines. This reaction was not accelerated by microwave (MW) dielectric heating, however, the azide fragment undergoes MW-assisted Cu(I)-catalyzed cycloaddition with a range of alkynes (including ynamides). Lewis acid mediated Hosomi–Sakurai reaction of the allylsilane with aldehydes was also possible. A one-pot transformation into different triazolo-containing homoallyl alcohols was carried out through a sequence of Cu(I)-catalyzed azide cycloaddition under MW dielectric heating and BCl_3-mediated reaction with aromatic aldehydes.

Key words: microwaves, click chemistry, azides, cycloaddition, allylation

Azides have been widely applied in organic synthesis, exploiting their versatility in cycloaddition reactions.[1] Azides are readily applicable to the preparation of small molecule libraries for biological applications and for bioconjugation within large biomolecules,[2–5] so that the term 'click chemistry' has been coined based on azide reactivity.[6] Allylsilanes are another class of very versatile molecules. They are stable, electron-rich compounds that may react in the presence of electrophiles (generally carbonyl compounds activated by Lewis acids)[7,8] or as nucleophiles, triggering the silane reactivity with fluoride through the formation of pentacoordinate silicon.[9] However, allylsilanes and azides do not react together and so can be considered as two compatible groups that can be introduced into the same molecule for further selective functionalization.

Following our long-term interest in allylsilane chemisty[10,11] and, more recently, in azide chemistry,[12] we were intrigued to develop a molecule in which the two groups coexist and can be selectively and sequentially functionalized. After a click reaction of the azide and a nucleophilic reaction of the allylsilane, a double bond and an alcohol function would still be present on the scaffold for additional transformations. 2-(Azidomethyl)allyltrimethylsilane **2** is an ideal substrate for this strategy, providing a methallyl scaffold linked to the two moieties in a suitable form for elaboration. Surprisingly, this simple molecule has never been reported before,[13] although its synthesis can be readily accomplished from commercially available 2-(chloromethyl)allyltrimethylsilane (**1**). In fact, reaction of **1** in DMF in the presence of NaN_3 at room temperature gave product **2** in almost quantitative yield (Scheme 1). Compound **2** was found to be stable at room temperature and could be stored at 4 °C for several months without decomposition.



1 2

Scheme 1 Preparation of azidoallylsilane **2**

The differing reactivity of the two functional groups was first studied independently in order to explore the potential and scope of this novel reagent. Initially, standard cycloaddition with alkenes was investigated, reacting compound **2** with a range of alkenes (Table 1). The reaction of azide with alkenes is known to proceed with the formation of triazolines or aziridines (or other products derived from these intermediates) depending on the reaction modes.[14,15] Generally, [3+2] cycloaddition under thermal conditions initially gives the sometimes unstable triazoline that can be further transformed into an aziridine.[16–21] However, under photochemical conditions, the aziridine is the major product.[22,23] To find the optimal reaction conditions, the cycloaddition of **2** with *N*-phenylmaleimide **3** was investigated.[24] Reaction did not take place in polar solvents (THF, CH_2Cl_2) or under attempted transition-metal catalysis. A poor reactivity was also observed under photochemical irradiation. Using a low-pressure Hg lamp at 254 nm in MeCN, compound **2** and *N*-phenylmaleimide gave a very low yield of aziridine **9** with several by-products arising from photodegradation of **2**, with the majority of **3** being recovered. However, reaction of **2** and **3** in toluene at 115 °C for 12 h gave triazoline **8** in acceptable yield (Table 1, entry 1), whereas only aziridine **9** was isolated in 65% yield when the reaction temperature was increased to 140° (Table 1, entry 2). Using ethyl acrylate **4** and acrylonitrile **5** as alkenes, aziridines **10** and **11** were formed at 115 °C, whilst γ-crotolactone **6** gave aziridine **12** in good yield. On the other hand, acyclic α,β-unsaturated aldehydes and ketones (cinnamaldehyde or cyclopentanone) did not react at all. When an electron-rich alkene such as dihydrofuran **7** was submitted to the thermal reaction, aziridine **13** was obtained as the sole product.[25,26]

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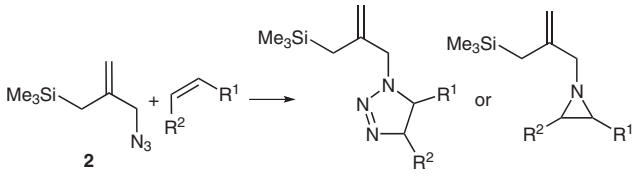
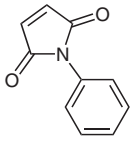
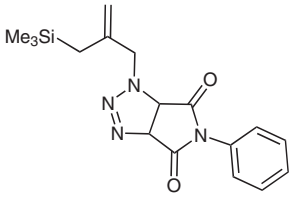
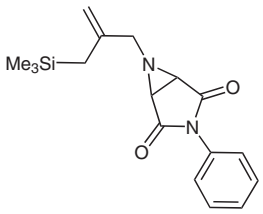
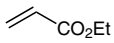
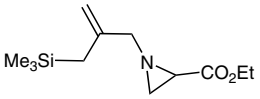
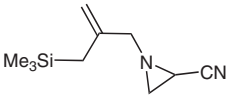
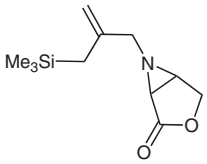
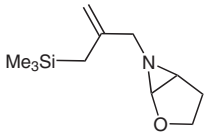
Attempts to accelerate the cycloaddition by using microwave dielectric heating were unsuccessful. Using toluene as the solvent, it was not possible to reach the internal temperature required for the cycloaddition; whereas heating in a more polar solvent (MeOH, DMF, DCE) allowed a temperature of 140 °C to be achieved, but cycloaddition still did not occur. The addition of a heating adjuvant to the toluene (a few drops of ionic liquid or a carbon fiber plug-in)[28,29] allowed the temperature to increase, but starting materials were recovered unchanged after 2 h of MW

Table 1 Thermal Reaction of Azidoallylsilane **2** and Alkenes



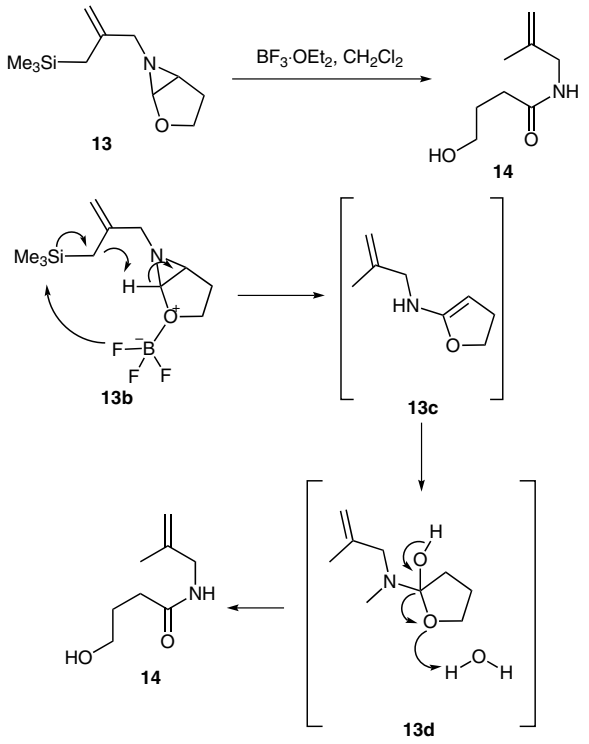
2

Entry	Alkene	Conditions[a]	Product[b]	Yield (%)[c]
1	 **3**	A	 **8**	72
2	**3**	B	 **9**	65
3	 **4**	A	 **10**	68
4	 **5**	A	 **11**	73
5	 **6**	A	 **12**	62
6	 **7**	A	 **13**	66

[a] Reacion conditions A: toluene, 115 °C, 12 h. Conditions B: toluene, 140 °C, 12 h. In both cases, the tube containing the reaction mixture was immersed in the heating bath until it reached the required temperature.
[b] The regiochemistry of compounds **10**[19] and **11**[21] was assumed on the basis of previous reports. Compounds **8**, **9**, **12** and **13** were isolated as single diastereomers, probably the *cis*-isomers.
[c] Yield of isolated and fully characterized products.

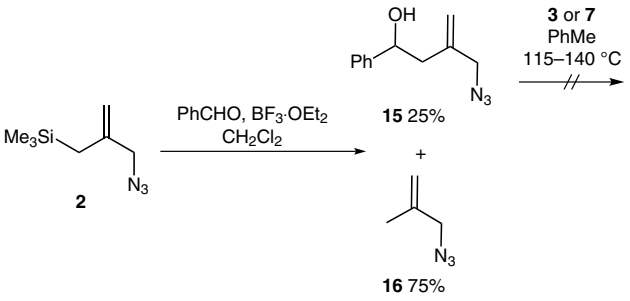
heating at 150 °C. Although rare, the ineffectiveness of microwave heating to accelerate a thermal reaction has been observed previously.[27]

After initial functionalization of the azide moiety, the reactivity of the aziridine allylsilanes was explored. However, when aziridines **9–12** were mixed with benzaldehyde in the presence of $BF_3{\cdot}OEt_2$, protodesilylation products were formed exclusively. An analogous result was obtained with other Lewis acids such as $Sc(OTf)_2$, BCl_3, $TiCl_4$ or $ZnCl_2$ or in the presence of trifluoroacetic acid (TFA), tetrabutylammonium fluoride (TBAF) or CsF. A different reactivity was observed with aziridine **13** derived from dihydrofuran. When submitted to $BF_3{\cdot}OEt_2$-mediated reaction with benzaldehyde, the hydroxymethallyl amide **14** was isolated in 62% yield (Scheme 2) and was also obtained with $BF_3{\cdot}OEt_2$ alone. The formation of this γ-hydroxymethallyl amide is proposed to occur through initial coordination of BF_3 to the ethereal oxygen (**13b**), followed by fluoride-mediated desilylation. Further abstraction of the acidic proton between the two heteroatoms yields intermediate enaminal **13c**, which undergoes attack by water to generate the final amide **14** through ring opening of the dihydrofuran ring (Scheme 2).



Scheme 2 Proposed mechanism for the formation of γ-hydroxyamide **14**

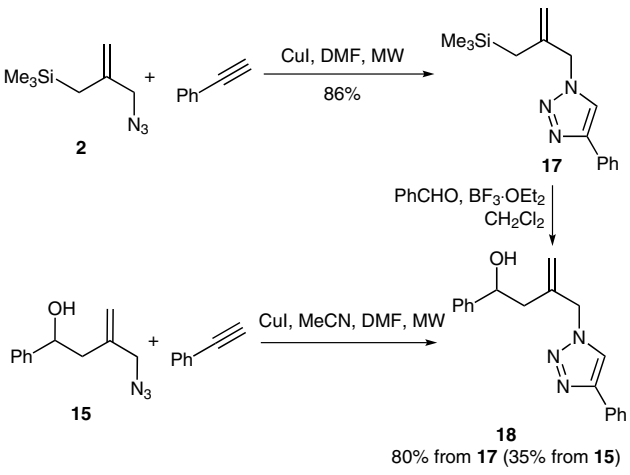
As the allylsilane functionalization appeared to be problematic, we decided to invert the sequence of events, performing an initial Hosomi–Sakurai reaction on azidoallylsilane **2** followed by [3+2] cycloaddition with alkenes (Scheme 3). Compound **2** reacted with benzaldehyde at 0 °C in the presence of $BF_3{\cdot}OEt_2$ to give homoallyl alcohol **15**, which was isolated in poor yield (ca. 25%) together with derivative **16** (Scheme 3). However, when azidoalcohol **15** was submitted to cyclization with alkenes **3** or **7**, the reaction did not proceed cleanly (Scheme 3).



Scheme 3 Attempted sequence: Hosomi–Sakuari reaction / cycloaddition with alkenes

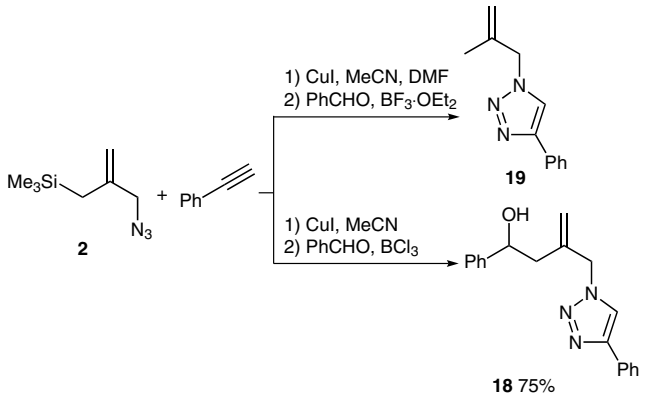
Attributing this unsatisfactory behavior to the high reactivity of the triazoline/aziridine rings, we decided to investigate the reaction of azidoallylsilane **2** with alkynes (Scheme 4). In this instance, Cu-mediated cycloaddition of **2** with phenylacetylene (DMF, CuI) occurred under MW dielectric heating, giving compound **17** in good yield. It is worth noting that the cycloaddition worked exclusively using CuI in DMF, and no reaction was observed using Cu(I) generated in situ from $CuSO_4$ and ascorbic acid. On isolation, **17** was submitted to the Hosomi–Sakurai reaction with benzaldehyde in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$, to form the corresponding triazole homoallyl alcohol **18** in 80% yield. However, when homoallyl alcohol **15** was submitted to cycloaddition with phenylacetylene, the reaction gave a very low yield of triazole **18**, with the homoallyl alcohol decomposing rapidly (Scheme 4).

Looking to the possibility of performing a multicomponent reaction, we tried mixing compound **2**, benzaldehyde and phenylacetylene in the presence of different Lewis acids and Cu(I) salts, or using CuOTf alone.[30] However, formation of compound **18** was never observed.[31]



Scheme 4 Exploration of the sequence of events for the Cu(I)-mediated cycloaddition

Subsequently, a one-pot multistep operation was attempted.[32] Allylsilane azide **2** was mixed with phenylacetylene in DMF with a catalytic amount of CuI and submitted to MW-assisted cycloaddition. Then, without opening, the microwave vial was cooled and benzaldehyde plus $BF_3{\cdot}OEt_2$ were added by using a syringe. However, exclusive desilylation of the intermediate occurred with formation of the methallyl triazole **19**.[33] Assuming that the cycloaddition reaction medium was not compatible with the Lewis acid, the protocol developed for the click reaction was adapted to conditions more compatible with the second step (Scheme 5).

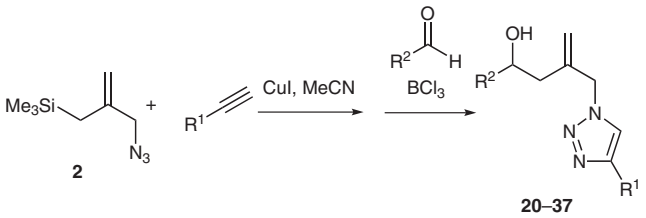


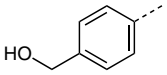
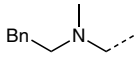
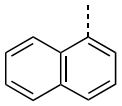
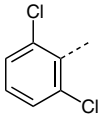
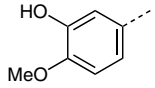
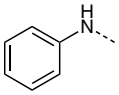
Scheme 5 One-pot operation from azidoallylsilane **2** to triazole homoallyl alcohol **20**; the choice of MeCN and BCl_3

After much optimization, CuI and acetonitrile were found to be the best combination for the first step; while a 75% yield of **18** was obtained in the second step using BCl_3 (1 M in CH_2Cl_2). Thus, the established procedure consisted of reacting the alkyne with azidoallylsilane **2** in MeCN in the presence of CuI under MW dielectric heating, followed by addition of the aldehyde and BCl_3 (Scheme 5).[34] This two-step, one-pot sequence was extended to a range of aromatic aldehydes (Table 2) and the corresponding triazolyl methallyl alcohols **20**–**37** were obtained in good yields. Aromatic and aliphatic alkynes could be successfully employed but the use of BCl_3 was incompatible with enolizable aldehydes. The presence of carboxymethyl or benzyl groups, alcohols or tertiary amines was compatible with the reaction conditions (Table 2, entries 1, 6, 7, and 9), thus expanding the potential of the reaction. Boc protection on the nitrogen was removed (Table 2, entries 8 and 18), whereas benzylated phenol suffered partial debenzylation (entry 14); both results being attributable to the presence of BCl_3. Ynamides could also be successfully employed, as in the case of *N*-Boc-*N*-phenyl aminoacetylene,[35] which gave the 4-anilino-substituted triazole **37** in 63% yield. In all cases, the products were obtained in an acceptable purity and could be isolated in yields of more than 60% (except Table 2, entry 14). However, column chromatography was necessary to obtain analytically pure samples.

In conclusion, the synthesis and synthetic applications of novel azidoallylsilane **2** have been described with a focus on the multistep, one-pot preparation of methallyltriazole derivatives. Some limitations in the reactivity of the azi-

Table 2 One-Pot Preparation of Triazole Homoallyl Alcohols



Entry	R^1	R^2	Product	Yield (%)[a]
1	MeO_2C	Ph-	**20**	66
2	$Me(CH_2)_3$	Ph	**21**	61
3	4-PhC_6H_4	Ph	**22**	68
4	4-$MeOC_6H_4$	Ph	**23**	72
5		Ph	**24**	64
6		Ph	**25**	65
7		Ph	**26**	70
8	$H_2NC_6H_4$	Ph	**27**	62[b]
9	BnO_2CCH_2	Ph	**28**	70
10	Ph	4-$MeOC_6H_4$	**29**	74
11	Ph	4-BrC_6H_4	**30**	68
12	Ph	4-CNC_6H_4	**31**	68
13	Ph	2-$NO_2C_6H_4$	**32**	62
14	Ph	4-$BnOC_6H_4$	**33**	42[c]
15	Ph		**34**	79
16	Ph		**35**	60
17	Ph		**36**	66
18		4-$MeOC_6H_4$	**37**	63[d]

[a] Yield of isolated and fully characterized products.
[b] Starting alkyne R1 = *p*-$BocNHC_6H_4$.
[c] Partial debenzylation occurred.
[d] Starting alkyne R^1= Ph(Boc)N.

doallylsilane highlight the real scope of the new scaffold, which can be considered as a useful multi-reactive system for application in diversity-oriented synthesis.

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(34) **1-Phenyl-3-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]but-3-en-1-ol (18); Typical Procedure:** In a vial suitable for MW reactions, azidoallylsilane **2** (100 mg, 0.59 mmol) was dissolved in anhydrous MeCN (2 mL) and phenylacetylene (60 mg, 0.6 mmol) was added, followed by CuI (10 mg, 0.05 mol). The vial was closed and inserted in a MW oven (Discover from CEM) and heated to 120 °C for 15 min (max power 200 W, max internal pressure 200 psi). The vial was cooled to 0 °C and anhydrous benzaldehyde (60 mg, 0.56 mmol) dissolved in anhydrous MeCN (0.5 mL) was added by using a syringe. BCl_3 (1 M in toluene, 0.6 mL, 0.6 mmol) was slowly added by using a syringe to the vial under vigorous stirring. The mixture was stirred at r.t. for 6 h, and then solid Na_2CO_3 (150 mg) was added followed by EtOAc (5 mL). The mixture was stirred at r.t. for 10 min then water (2 mL) was added. The organic layer was separated, washed with 1 M aq Na_2CO_3 (3 mL), 1 M aq NH_4Cl (3 mL) and brine (3 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and the solvent evaporated. Compound **18** (135 mg, 75%) was isolated as a waxy material by flash chromatography (hexane–EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.1 Hz, 2 H), 7.72 (s, 1 H,), 7.46–7.21 (m, 8 H), 5.15 (s, 1 H), 5.08–4.90 (m, 3 H,), 4.87 (dd, *J* = 8.4, 4.3 Hz, 1 H), 2.67 (br s, 1 H, OH), 2.42 (dd, *J* = 19.5, 6.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 143.8, 140.6, 128.8 (2C), 128.2 (2C), 127.8 (2C), 125.7 (4C), 120.0 (2C), 117.6, 72.9, 55.3, 43.1. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{19}N_3ONa^+$: 328.1426; found: 328.1424.
(35) Pizzetti, M.; Russo, A.; Petricci, E. *Chem. Eur. J.* **2011**, *17*, 4523.