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Azide cyclizations with acetylenic silyl ketone: a general access to functionalized-1,2,3-triazolylacylsilanes and aldehydes.

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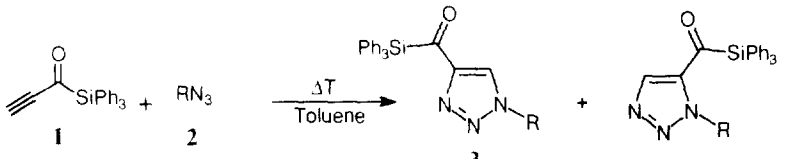
Abstract: Reaction of several azido compounds with acetylenic silyl ketone affords a simple and direct entry to triazolylacylsilanes and, after desilylation, to the corresponding functionalized triazolylaldehydes

Acylsilanes have been shown versatile reagents in synthetic organic chemistry.[1] They may provide regio and stereoselective access to a number of polyfunctionalized molecules, and thus may act as effective building blocks in organic synthesis.

Our interest in such chemistry has been recently focused on α,β-unsaturated acylsilanes which show an interesting and versatile reactivity, participating in a number of useful transformations, ranging from Michael additions with different silylated nucleophiles[2] to the acetylenic silyl ketone based stereopredetermined synthesis of polyenals and polyenes.[3] Furthermore, although acetylenic silyl ketone may be considered a synthetic equivalent of propargylaldehyde, their reactivities have been shown to be quite different.

On the other hand, in spite of the structural features that outline acetylenic silyl ketone **1** as a potentially good dienophile, only a few cycloaddition reactions have been reported on such compound and on the parent



1 2 3 4

Scheme 1

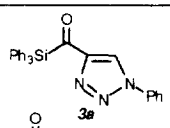
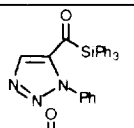
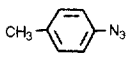
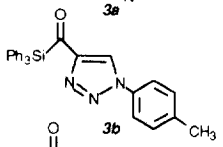
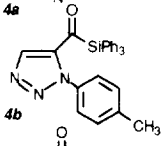
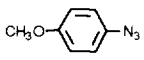
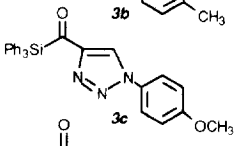
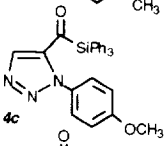
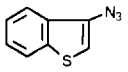
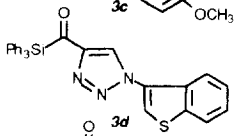
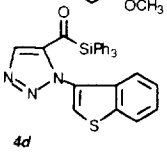
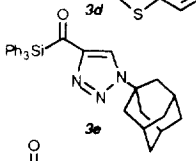
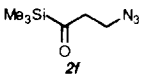
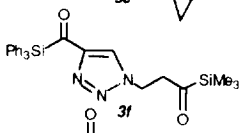
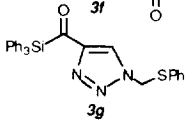
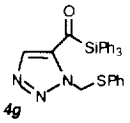
ethylenic derivative.[4] Our recent interest in the chemistry and the reactivity of azido group containing molecules[5] led us to evaluate the chemical behaviour of acetylenic silyl ketone **1** toward a variety of azides.

Addition of azides to acetylenes or activated methylene compounds is a well established method for the synthesis of 1,2,3-triazoles.[6] Indeed, the cycloaddition of azides with compounds with an activated triple bond has been investigated primarily for the esters of acetylenic acids,[7] and more recently for α–acetylenic acids and α–acetylenic ketones.[8] In contrast, only one example of phenyl azide cycloaddition with propargylaldehyde to

give 1-phenyl-1,2,3-triazol-4-carbaldehyde has been reported,[9] but in order to avoid difficulties connected with the isolation of propiolaldehyde, different synthetic procedures avoiding the use of propynal have been devised to such triazolyl carbaldehyde.[10]

We now report that acetylenic silyl ketone **1** can act as an efficient 1,3-dipolarophile, reacting smoothly in refluxing toluene with different azido derivatives affording in high yields 1-substituted-1,2,3-triazolyl- 4- and -5-acylsilanes.[11] The reactions occurred smoothly with both aromatic and aliphatic azides, to afford the desired compounds in reasonable yields, thus allowing a simple access to a novel class of heteroacylsilanes.[12] The chemical reactivity of the product acylsilane may prove interesting, in that the typical reactivity of the acylsilane moiety is linked to the important triazole ring system.[13] Results are summarized in Table 1.

Table 1. Synthesis of triazolyl acylsilanes

Reagent	Product		Ratio *3:4*	Conditions (T°C/Time h)	Yield[a] (%)
 *2a*	 *3a*	 *4a*	75:25	110/12	68
 *2b*	 *3b*	 *4b*	80:20	110/12	69
 *2c*	 *3c*	 *4c*	80:20	110/16	59
 *2d*	 *3d*	 *4d*	80:20	80/12	60
 *2e*	 *3e*			110/10	47
 *2f*	 *3f*			110/16	59
PhSCH$_2$N$_3$ *2g*	 *3g*	 *4g*	72:28	110/10	66

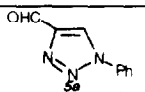
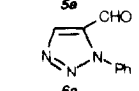
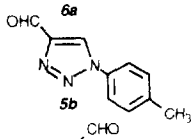
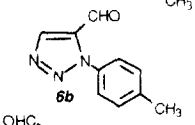
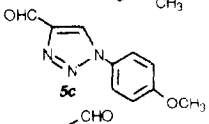
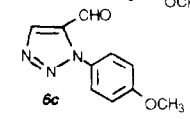
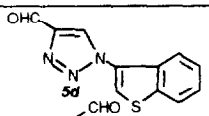
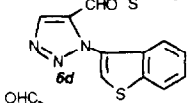
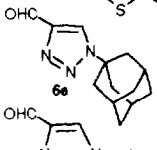
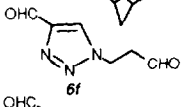
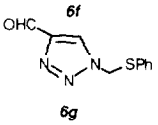
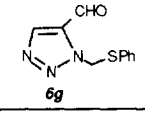
[a]Yields of chromatographycally pure material. All compounds showed spectroscopical and analytical data consistent with assigned structure

From the regiochemical point of view, it must be stated that generally mixtures of 1,4- and 1,5- isomers were obtained, although, as expected from the high degree of polarization of acetylenic silyl ketone **1**, the 1,4-isomer was always largely predominant. The two isomers could be easily separated by usual chromatographic

techniques (tlc, column chromatography). In the case anyway of the sterically hindered azide **2e** and the acylsilane azide **2f** a single regioisomer was detected in the crude reaction mixture.

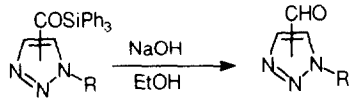
The regiochemical assignement was performed on the basis of the chemical shifts of the H-4 and H-5 proton resonances, which have been reported to be diagnostic for 5 and 4 substituted triazoles,[14] the 1,4-disubstituted systems showing an H-5 resonance in the range of 7.7-8.2 ppm, while for 1,5-disustituted ones the H-4 resonance is hidden in the aromatic signals.[15]

Table 2. Synthesis of 4- and 5-formyl-1-substituted triazoles.

Reagent	Desilylated Product	Yield[a] (%)	^{1}H-NMR δ (CHO)	δ (H)
3a	 **5a**	77	10.24	8.53
4a	 **6a**	66	9.98	8.39
3b	 **5b**	80	10.2	8.5
4b	 **6b**	60	9.85	8.4
3c	 **5c**	90	10.22	8.45
4c	 **6c**	70	9.94	8.36
3d	 **5d**	90	10.28	8.55
4d	 **6d**	60	9.93	8.45
3e	 **6e**	80	10.14	8.16
3f	 **6f**	60	10.15	8.2
3g	 **6g**	75	10.11	8.08
4g	 **6g**	70	9.90	8.20

[a]Yields of isolated material

Desilylation of the 1-phenyl derivatives **3a** and **4a** to the corresponding previously reported carbaldehydes **5a** and **6a**[10] respectively was achieved by reaction with NaOH in ethanol (Scheme 2).[16,17] These reactions,



Scheme 2

besides confirming the regiochemical assignments, revealed a novel general entry to the barely explored class of formyl triazoles.

A wider investigation was then performed, in order to state the generality of this novel access to substituted formyltriazoles. Desilylation was found to occur smoothly with all the acylsilane substrates used. The results are summarized in Table 2.

In conclusion, the reaction of acetylenic silyl ketone **1** with azides of different nature affords a direct entry to disubstituted triazoles, thus showing a simple access to a wide variety of 1-functionalized-4-formyl-1,2,3-triazoles.

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11) *General procedure*. A solution of 30 mg (0.096 mmol) of acetylenic silyl ketone **1** in 1 mL of toluene was treated with 11 mg (0.096 mmol) of phenyl azide. The reaction was stirred at 110°C in the dark for 12 h and monitored by TLC. Removal of the solvent under vacuum afforded the crude product, which was purified by TLC (petroleum ether : ethyl acetate 5 : 1) to obtain 21 mg of **3a** and 7 mg of **4a**. **3a**: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.3-7.8 (m, 20 H), 8.18 (s, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 120.5, 121.5, 128.0, 129.3, 129.8, 130.2, 131.2, 136.3, 136.7, 153.1, 223.0. MS (m/e): 431 (M^+,10), 402 (45), 326 (56), 259 (100), 181 (48), 105 (27), 77 (20). **4a**: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.3-7.8 (m, 21 H).

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15) ^{1}H-NMR δ (ppm) for H-5 protons: 8.18 (**3a**), 8.13 (**3b**), 8.10 (**3c**), 8.19 (**3d**), 7.82 (**3e**), 7.80 (**3f**), 7. 72 (**3g**).

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17) A solution of 28 mg (0.065 mmol) of compound **3a** in 1 mL of ethanol was treated with two drops of a 10% NaOH solution, stirred at room temperature in the dark for 5 min, then treated with water and brine. Drying and removal of the solvent under vacuum afforded the crude product which was purified by TLC (petroleum ether : ethyl acetate 5 : 1) to obtain 21.5 mg of pure **5a**.(77%) ^{1}H NMR ($CDCl_3$) δ (ppm): 7.3-7.8 (m, 5 H), 8.53 (s, 1H), 10.24 (s, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 120.9, 123.3, 129.7, 129.9, 136.1, 148.0, 185.0. MS (m/e): 173 (M^+, 6), 144 (33), 117 (21), 84 (100), 77 (68), 69 (11), 57 (21), 51 (46), 47 (24).

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