Convenient route to water-sensitive sol–gel precursors using click chemistry†

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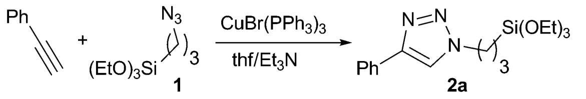
The CuAAC-'click' reaction under anhydrous conditions is reported as a new tool for the preparation of moisture-sensitive triethoxysilyl compounds that are obtained in 5 minutes in excellent yield with simple purification.

The copper catalyzed alkyne–azide cycloaddition reaction (CuAAC)[1] is receiving considerable interest owing to its excellent yield, functional group tolerance, and versatility. It is now commonly used in drug discovery programs, rotaxane and dendrimer synthesis and polymer chemistry. Recently, mesoporous 'click silicas' containing pendant azido groups have been designed to be functionalized *via* CuAAC with appropriate functional alkynes.[2] This new and simple methodology represents an important step towards the formation of functional hybrid materials by simple 'click'-grafting of dyes, ligands or catalysts for example.[3] However, it is often desirable to synthesize functional hybrid silicas directly from molecular precursors using the sol–gel process rather than by post-functionalization. Indeed, the hydrolysis–condensation of trialkoxysilylated molecules in the presence or absence of tetraethoxysilane is the most versatile method for preparing hybrid silica with controlled shape and porosity.[4] Several methodologies are commonly used to introduce the trialkoxysilyl groups, such as the hydrosilylation of olefins,[5] the Heck cross coupling between an aryl halide and vinyltriethoxysilane,[6] the rhodium-catalyzed silylation of the former,[7] the coupling of isocyanatopropyltriethoxysilane with amines[8] or nucleophilic substitutions on halogenopropyltriethoxysilanes.[9] However, the scope of each of these methods is limited, and severe limitations have been experienced, mainly for the synthesis of poly(trialkoxysilylated) molecules, precursors of bridged silsesquioxanes[10] and PMOs.[11] Moreover, the purification of these moisture-sensitive compounds is often a critical step for non-distillable or non-crystallizable compounds, as mixtures are often obtained. To extend the palette of synthetic tools available to obtain easily purified hybrid silica precursors, we envisaged a further development of the CuAAC methodology, to extend its applicability to reactions between functionalized alkynes and the readily available 3-azidopropyltriethoxysilane **1** (AzPTES).[2]

The CuAAC reaction has mainly been developed for hydrophilic compounds, and since alkoxysilanes are moisture sensitive, it was necessary to adapt the existing methods to allow this reaction to be performed in dry solvents. We present here our results concerning the very simple and fast functionalization of alkynes by CuAAC with AzPTES under alcohol- and water-free conditions yielding hybrid silica precursors in high yield and purity. This methodology should lead to significant improvements in the development of hybrid silicas for various applications.

Several catalytic systems have been reported for the CuAAC reaction: the most widely used methodology is based on a $CuSO_4$/sodium ascorbate system, but the reaction is carried out in a water/*tert*-butanol mixture; other catalytic systems are based on copper(I) salts, with triamine ligands[12] or using the $CuBr(PPh_3)_3$ complex.[13] The latter catalyst seems very promising, as it is very easily obtained on a multigram scale from cheap reactants. Thus, the benchmark reaction between AzPTES and phenylacetylene was tried under various conditions (Table 1). Using an equimolar amount of AzPTES and phenylacetylene in a dry thf/Et_3N solvent mixture (c = 2 mol L^{-1}) and a 1 mol% loading of copper catalyst under a nitrogen atmosphere at room temperature, coupling product **2a** was satisfactorily obtained as the sole reaction product with quantitative conversion after 15 hours (entry 1). The catalyst loading could be decreased to 0.5 mol% with a reaction time of 24 hours (entry 2), whereas further decrease of the catalyst amount to 0.3 mol% only yielded 67% of the desired compound (entry 3). Interestingly, the reaction could be carried out in only 3 hours using 0.5 mol% catalyst by increasing the temperature to 50 °C (entry 4). This reaction time could be decreased down to only 5 minutes using

Table 1 Optimization of the reaction conditions for the CuAAC of AzPTES and phenylacetylene[a]



Entry	Catalyst loading (%)	Temperature	Time	Conversion[b] (%)
1	1	rt	15 h	100
2	0.5	rt	24 h	100
3	0.3	rt	30 h	67
4	0.5	50 °C	3 h	100
5	0.5	100 °C[c]	5 min	100
6	0	100 °C[c]	5 min	0

[a] Reaction conditions: AzPTES (2.0 mmol), phenylacetylene (2.0 mmol), $[CuBr(PPh_3)_3]$ in thf/Et_3N 1 : 1 (1 mL) under nitrogen atmosphere. [b] Determined by ^1H NMR. [c] Microwave heating.

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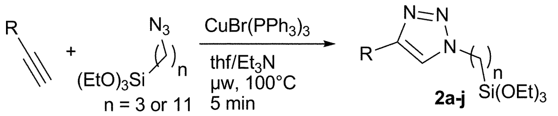
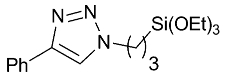
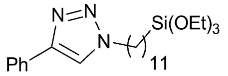
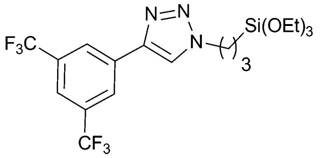
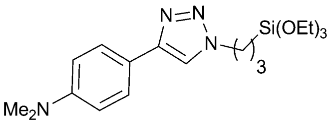
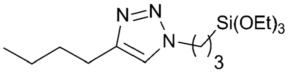
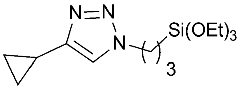
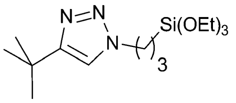
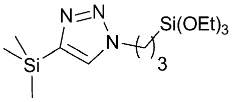
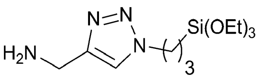
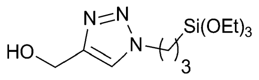
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of ^1H and ^{13}C NMR spectra of all new compounds; solid-state NMR spectra of the materials. See DOI: 10.1039/c0cc03417g

microwave irradiation at 100 °C with complete conversion (entry 5). The reaction occurs with complete regioselectivity and excellent selectivity since no byproducts are detected. Interestingly, no reaction occurs in the absence of copper catalyst. The 'click'-silylated product could be recovered in excellent yield (95%) after evaporation of the solvents and extraction with pentane. Notably, the only side-product that was evident is triphenylphosphine oxide (as evidenced by its ^{31}P NMR signal at 28.3 ppm), present at less than 1.5 mol%, as the remaining green copper salt is totally insoluble in pentane.

Table 2 Synthesis of monosubstituted organosilanes[a]



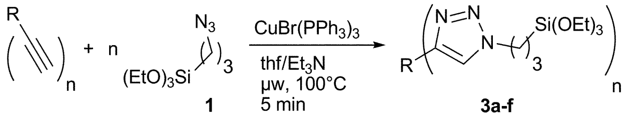
Entry	Product		Yield[b] (%)
1		**2a**	95
2		**2b**	97
3		**2c**	95
4		**2d**	90
5		**2e**	92
6[c]		**2f**	94
7[c]		**2g**	88
8[c]		**2h**	91
9		**2i**	93
10		**2j**	98

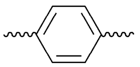
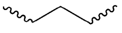
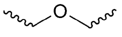
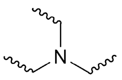
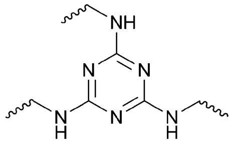
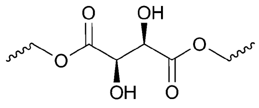
[a] Reaction conditions: alkyne (2.0 mmol), azide (2.0 mmol), $CuBr(PPh_3)_3$ (0.01 mmol), thf/Et_3N 1 : 1 (1 mL), 5 min, 100 °C under microwave irradiation. [b] Isolated yield. [c] Reaction carried out at room temperature for 48 h using 3 equiv. of alkyne.

The scope of this reaction was then examined on various types of substrates (Table 2): the use of a long alkyl chain (*e.g.* 11-azido-undecyltriethoxysilane, entry 2) did not affect the reactivity rate, while phenylacetylenes substituted with electron-donating or -withdrawing groups also react quantitatively with AzPTES under these conditions. In contrast, alkyl-substituted terminal acetylenes react slower: 10 minutes of microwave irradiation (100 °C) are necessary for the reaction of AzPTES with 1-hexyne; the cyclopropyl–*tert*-butyl or trimethylsilyl substituted compounds could not be reacted under these conditions, due to their high volatility. Instead, the reaction was performed at room temperature using 3 equivalents of the alkyne. The reaction was then evaluated with alkynes bearing functional and reactive groups. Interestingly, propargylamine and propargyl alcohol reacted very well under the standard reaction protocol with no side reaction. To our knowledge, this is the first time that a molecule containing both hydroxyl and triethoxysilyl functionalities has been isolated in a pure form, as the intra- or intermolecular transesterification reaction at the silicon site is known to readily occur. However, after one month at room temperature under nitrogen, the initially pure compound underwent almost complete degradation.

Furthermore, bridged organosilanes could be obtained by applying our standard method to molecules containing two or three ethynyl groups (Table 3): 1,4-diethynylbenzene and

Table 3 Synthesis of polysubstituted organosilanes[a]



Entry	Linker	Product[b]	Yield[c]
1		**3a**	87
2		**3b**	95
3		**3c**	94
4		**3d**	91
5		**3e**	92
6		**3f**	81

[a] Reaction conditions: alkyne (2.0 mmol), azide (n × 2.0 mmol), $CuBr(PPh_3)_3$ (n × 0.01 mmol), thf/Et_3N 1 : 1 (1 mL), 5 min, 100 °C under microwave irradiation. [b] Full structures are depicted in ESI.† [c] Isolated yield.

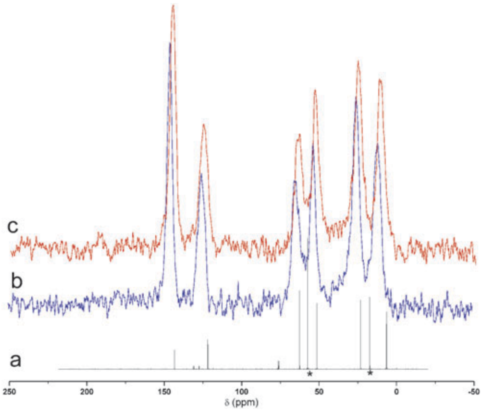


Fig. 1 ^{13}C NMR of **3c** in $CDCl_3$ (a), and CP-MAS solid-state ^{13}C NMR of materials derived from it (**M1** (c), **M2** (b)). The asterisks denote the ethoxy signals (δ 18 and 58 ppm).

1-6-heptadiyne could be easily functionalized, as well as propargyl ether or tripropargylamine. The latter examples represent challenging substrates, as the standard methods often fail for synthesizing 1,7-silylated flexible molecules due to competitive cyclizations that afford 5- or 6-membered rings. Also, melamine derivative **3e** could be easily obtained. This is an interesting new approach for synthesising such molecules, as compounds featuring NH and N-donor groups are known to poison hydrosilylation catalysts. Very interestingly, dipropargyl tartrate reacted very cleanly with AzPTES leaving the triethoxysilyl groups unaffected despite the presence of the 1,2-diol function. This single reaction demonstrates the high potential of our new methodology to synthesize and isolate products that were not conceivable before.

From bridged organosilane **3c**, materials could be obtained by the sol–gel process under acidic (**M1**, 4 equiv. HCl, pH 1) or nucleophilic conditions (**M2**). Their ^{13}C CP-MAS NMR spectra (Fig. 1) evidence the full preservation of both the C–Si bond and the triazole linker under the conditions used, thus validating the use of this linker to obtain functional hybrid materials.

In conclusion, we have developed a straightforward method to synthesize sol–gel precursors containing one or multiple triethoxysilyl groups using the CuAAC reaction under anhydrous conditions. This method is very promising thanks to its rate, high yield, selectivity and wide functional group tolerance. Indeed, unprecedently reported alkoxysilanes containing one or more hydroxyl groups could be isolated for the first time using this approach. Furthermore, the triazole linker has proven to be resistant under acidic or nucleophilic sol–gel conditions. Hence this new 'click-silylation' approach brings significant improvements in the synthesis of functional hybrid silica.

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