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Facile syntheses of alkoxysilanated phosphorylcholines as surface modifiers: CuAAC and thiol-ene "click" reactions†

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Eight alkoxysilanated phosphorylcholine (PC) compounds were synthesized from CuAAC (copper-catalyzed azide/alkyne cycloaddition) and thiol-ene "click" reactions. This methodology will provide simple and efficient routes for the synthesis of alkoxysilanated PC modifiers. To demonstrate modification ability of these products, they were implanted onto silica beads, and the loading rates were quantified.

Phosphorylcholine (PC) has an ideal structure as described by the "fluid-mosaic model," a model of the bio-membrane structure proposed by Singer and Nicolson.[1] Phospholipids containing PC as a head group are major components of all eukaryotic cell membranes and make up at least 10% of all bacterial membranes.[2] Accordingly, PC derivatives show high affinity for living organs and tissues and have been widely used in the construction of bio-membranes and as excellent anti-fouling surface modifiers in various medical applications such as blood-contact devices,[3] bio-mimic membranes,[4] and surface treatments[5] to inhibit cell adhesion or decrease undesirable protein interactions.

One of the common methods for PC-related surface modification is to implant alkoxy- or halo-silyl functionalized PC compounds onto hydroxylated surfaces like medical devices,[6] metal alloys,[7] and glasses.[8] Formation of strong Si–O bonds without the need of a catalyst makes this method particularly useful for bridging functional groups and substrates. Efforts have been made to synthesize PC-containing macromolecules with methoxysilyl groups for modification of medical devices. For instance, copolymers of 2-methacryloyloxyethylphosphorylcholine (MPC) and 3-trimethoxysilylpropylmethacrylate (MPS) were used to promote adhesion on contact lenses.[6] Trimethoxysilyl groups ended poly(MPC) was synthesized to coat a Mg–Al–Zn alloy.[7] Besides macromolecules, the other PC-containing compounds were studied to modify not only large devices but also nano-sized particles. Chloro-silanated PC was first prepared to construct a bio-membrane on hydroxylated glasses.[8] However, with tedious processes requiring more than 5 steps, low total yields were obtained that restricted further applications. Although Yousuke, *et al.* obtained imine- and amide-bridged alkoxysilanated PCs, complicated synthetic routes and purification processes were not practical due to the moisture-sensitivity of alkoxysilyl groups.[9] A Pt/C-catalyzed hydrosilylation reaction of MPC with trimethoxysilane was carried out in methanol to synthesize methoxysilanated MPC for surface modification of medical alloys.[7] However, in our work, similar hydrosilylation reactions of MPC with trialkoxysilanes did not yield the expected products because trialkoxysilane reacted with alkyl alcohols to emit hydrogen gas in the presence of Pt/C or a Karstedt catalyst. Thus, it appears that Pt-catalyzed hydrosilylation is not suitable for the synthesis of alkoxysilanated PC. Therefore, the development of a simple and efficient method that combines alkoxysilyl groups with the PC moiety is urgently needed.

As is well known, the CuAAC reactions to give 1,2,3-triazoles show remarkably broad scope and exquisite selectivity.[10] As the most explored "click" reaction to date, CuAAC reaction has quickly found applications in polymer, biological and applied materials chemistry.[11] Precedents for this approach include several syntheses of functional alkoxysilanes,[12] graft-functionalization of polysiloxanes,[13] and preparation of poly-ferrocenylsilane block copolymers.[14] Especially, our group recently reported the syntheses and application of methallylsilanated PCs as surface modifiers *via* a CuAAC reaction.[15] These attributes led us to propose that the CuAAC reaction would be appropriate for the synthesis of alkoxysilanated PC. Besides CuAAC reaction, we found that the thiol-ene "click" reaction was widely used to synthesize dendrimers, functionalized bio-molecules, biomacromolecules, and new polymeric

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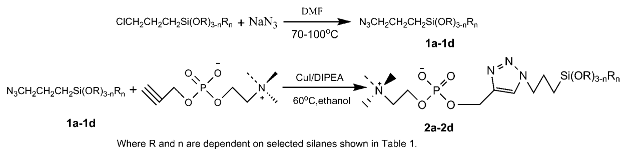
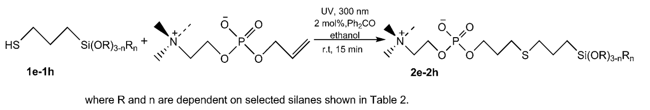
† Electronic supplementary information (ESI) available: (1) Syntheses and characterization of synthesized compounds. (2) XPS spectra of **2c-silica** and **2g-silica**. (3) NMR spectra of representive compounds. See DOI: 10.1039/c4ra15716h

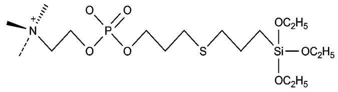
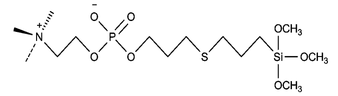
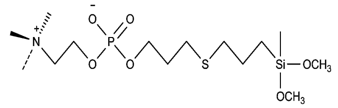
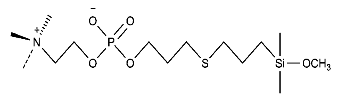


Scheme 1 Generic routes to synthesize **2a–d**.



Scheme 2 Generic routes to synthesize **2e–h**.

Table 2 Sulfur-bridged alkoxysilanated PCs (**2e–h**)

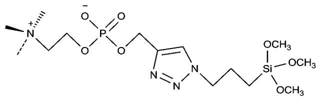
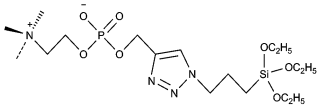
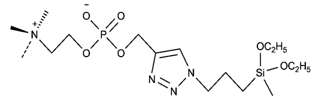
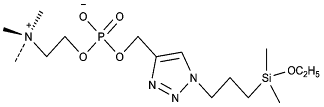
Entry	Silanes (**1e–h**)	Products (**2e–h**)
5	$(EtO)_3Si(CH_2)_3SH$	
6	$(MeO)_3Si(CH_2)_3SH$	
7	$(MeO)_2MeSi(CH_2)_3SH$	
8	$(MeO)Me_2Si(CH_2)_3SH$ **1h**[a]	

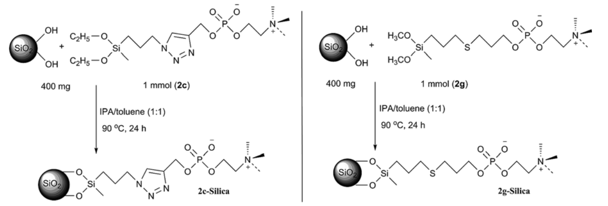
[a] **1e–g** are commercially available, **1h** was synthesized from **1f** according to the reported method.[22]

materials for applications ranging from lithography to porous microparticles.[11,16] In organo-silicon chemistry, this reaction has proven to be an efficient method to synthesize functionalized silanes,[17] silicon elastomeric materials[18] and oxide-free silicon surfaces.[19] Thus, it was envisioned that thiol-ene "click" reactions would be suitable for the synthesis of alkoxysilanated PCs.

Herein, we report the syntheses of alkoxysilanated PCs *via* CuAAC and thiol-ene "click" reactions. As shown in Scheme 1, the CuAAC reaction could be used to synthesize triazole-bridged alkoxysilanated PCs (**2a–d**). First, 3-azidopropylalkoxysilanes (**1a–d**, Table 1) were synthesized from 3-chloropropylalkoxysilanes using reported methods,[20] and propargylphosphorylcholine (PPC) was synthesized as reported in our previous work.[15] Equimolar amounts of 3-azidopropylalkoxysilane and PPC (1 mmol) were mixed in the presence of CuI/DIPEA (2 mmol/4 mmol). Then, these reactants were dissolved in ethanol under argon. Reactions could be run in ethanol (5 mL) and proceed smoothly at 60 °C for 12 h. Table 1 shows that azides (**1a–d**) smoothly coupled with PPC to produce alkoxysilanated PCs (**2a–d**) as light yellow powders in yields of 90–92%.

Table 1 Triazole-bridged alkoxysilanated PCs (**2a–d**)

Entry	Silanes (**1a–d**)	Products (**2a–d**)
1	$(MeO)_3Si(CH_2)_3N_3$	
2	$(EtO)_3Si(CH_2)_3N_3$	
3	$(EtO)_2MeSi(CH_2)_3N_3$	
4	$(EtO)Me_2Si(CH_2)_3N_3$	



Scheme 3 Representative silica surface modifications using **2c**, **2g**.

Testing the method of thiol-ene "click" reaction began with the preparation of allylphosphorylcholine (APC) as reported in our previous work.[21] Next, sulfur-bridged alkoxysilanated PCs (**2e–h**) were synthesized *via* the benzophenone initiated thiol-ene "click" reaction under a 300 nm UV lamp (Scheme 2). A slight excess of 3-mercaptopropyl alkoxysilane (**1e–h**, 1.10 mmol) and APC (1 mmol) were dissolved in 2 mL of EtOH in the presence of 2 mol% benzophenone. The reactions proceeded for 15 min under argon at room temperature. Table 2 shows that mercapto-silanes selectively participated in the thiol-ene reactions to result in pure α-addition products (**2e–h**) as light yellow powders in quantitative yields.

To verify that all of the alkoxysilanated PCs were useful as surface modifiers, they were implanted onto silica beads as shown in Scheme 3. The alkoxysilanated PC (1 mmol) and silica beads (400 mg) were dispersed in 20 mL of an IPA/toluene (10 mL/10 mL) mixture. After heating at 90 °C under N_2 for 24 h, the modified silica was filtered, washed with ethanol and toluene, and dried in a vacuum oven for 24 h. The loading rates were quantified as shown in Table 3.

Then, the resulting modified silica was characterized by elemental analysis. As shown in Table 3, the loading rates of alkoxysilanated PCs determined by nitrogen elemental analysis varied from 0.31–0.63 mmol g^{-1} demonstrated according to

Table 3 Loading rates of alkoxysilanated PCs (**2a–h**) onto silica beads

Products	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**[a]	**2g**	**2h**
Loading rate (mmol g^{-1})	0.44	0.38	0.31	0.34	0.55	0.63	0.42	0.43

[a] The loading rate for **2a–h** was based on the N value of modified silica determined by elemental analysis. For example: calculation of the loading rate of **2f** modified silica **2f-silica** (C (%) 9.0929, N (%) 0.8921) = (0.8921×10^{-2} g of N/1 g of compound PC-modified silica **2f-silica**) × (10^3 mmol of N/14 g of N) × (1 mmol of **2f**/1 mmol of N) = 0.63 mmol **2f**/1 g of compound PC-modified **2f-silica**.

Table 4 Surface elemental compositions of modified silica determined by XPS

	Surface elemental compositions (%)						Binding energy (eV)			
Modified silica	O	Si	C	N	P	S	C1s	N1s	P2p	S2s, S2p
2c-silica	54.11	30.21	12.37	2.62	0.59		286.7 (C–H) 286.2 (C–N) 285.5 (C–O)	399.9 (C–N=) 400.9 ((C)–N) 402.7 ($^+N(CH_3)_3$)	134.4	
2g-silica	50.79	27.78	17.65	1.32	1.15	1.32	289.1 (C–S) 286.7 (C–H) 286.2 (C–N) 285.5 (C–O)	403.1 ($^+N(CH_3)_3$)	134.5	228.1 (S2s), 163.8 (S2p)

reported method.[15] Methoxy-silanated modifiers were more active than ethoxy-silanated modifiers, and trimethoxysilanated PCs (**2a**, **2f**) gave the highest loading rates. Furthermore, loading rates were also affected by the steric effects of the PC tail-moiety. Compared with "sulfur-bridged PC" tail-group of **2e–h**, "triazole-bridged PC" tail-group of **2a–d** gave a greater steric effect. Thus, loading rates of **2e–h** were higher than these of **2a–d**.

To further evaluate the modified silica, the surface elemental compositions of two representative modified silica beads were determined by XPS as depicted in Table 4. The XPS C1s core-level spectrum of the **2c-silica** is comprised of three peak components. With binding energies (BEs) at about 286.7, 286.2 and 285.5 eV, they are attributed to the C–H, C–N, C–O species, respectively. The N1s core-level spectrum is splitting into three peaks. The peaks at the BEs of about 399.9 and 400.9 eV are attributed to imine nitrogen (C–N=) and amine nitrogen (C–N) of triazole rings, respectively. The peak at the BE of about 402.7 eV is associated with the positively charged nitrogen ($^+N(CH_3)_3$). The P2p core-level spectrum is at about 134.4 eV. For **2g-silica**, the XPS C1s core-level spectrum is comprised of four peak components. With BEs at about 289.1, 286.7, 286.2 and 285.5 eV, they are attributed to the C–S, C–H, C–N, C–O species, respectively. The N1s core-level spectrum is single peak with BE at about 403.1 eV ($^+N(CH_3)_3$). The peak of P2p core-level spectrum is also at about 134.5 eV. The S2s and S2p core-levels are observed at the BEs of about 228.1, and 163.8 eV, respectively. These results indicate that the PC was successfully implanted on silica beads.

Conclusions

In summary, it was shown that triazole- or sulfur-bridged alkoxysilanated PCs could be efficiently and simply synthesized *via* CuAAC and thiol-ene "click" reactions. These reactions proceeded smoothly in high yields, and a preliminary study showed that the reactions could be easily scaled-up. The synthesized alkoxysilanated PCs were demonstrated to be active surface modifiers by immobilization on silica beads. This methodology is suitable for the development of PC-containing silicon materials applicable to blood-contact conditions and bio-mimic systems.

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