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COMMUNICATION

Zinc mediated allylations of chlorosilanes promoted by ultrasound: Synthesis of novel constrained sila amino acids†

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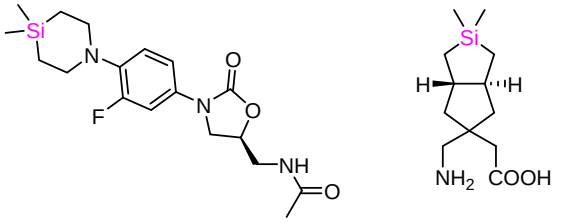
A simple, fast and efficient method for allylation and propargylation of chlorosilanes through zinc mediation and ultrasound promotion is reported. As a direct application of the resulting bis-allylsilanes, three novel, constrained sila amino acids have been prepared for the first time. The design and synthesis of the constrained sila analogue of GABA (γ-amino butyric acid) is a highlight of this work.

Organosilanes have wide applications in organic chemistry from the commonly used protecting groups to synthetic intermediates.[1] Compared to other organometallic reagents, they are stable in air and hence are easy to handle and store. Apart from their conventional use in organic synthesis and polymer chemistry,[2] organosilanes are being used in medicinal chemistry[3] as well. Since both carbon and silicon share the same group in the periodic table, medicinal chemists have used silicon as a bioisostere of carbon to improve the drug-like properties of the molecule, hence their use is becoming popular in recent times.[4] As a part of an ongoing program (Silicon-switch approach) in this group, we are interested in making novel silicon analogues of selected drug molecules to improve their desired properties. Some of the silicon analogues synthesized in this group have shown promising results (Figure 1).[5] Biological profiling and lead optimization are currently in progress with respect to the Silinezolid molecule. Along these lines, there is a need to explore simple and practical methods to access organosilicon building blocks which will be useful for the drug discovery programs based on "Silicon switch approach".[3]

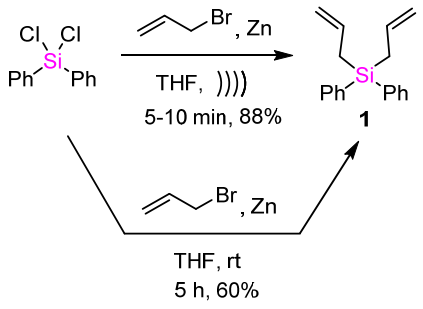
Allylsilanes are versatile reagents with very rich chemistry,[6] with a variety of methods known in the literature for their preparation. The reaction of Grignard reagents, prepared from allylhalides with chlorosilanes or alkoxysilanes, is the widely used method for their preparation.[7] Reactions mediated by other organometallic reagents using indium,[8] samarium[9] and zinc[10] are also known. However, there was no report in the literature for using sonication in preparing allylsilanes. The ultrasound waves disperse the metal and clean its surface, which makes it more reactive.[11] The experimental safety, simplicity, low-cost and the rapid reaction rate are the added advantages of this technique. Herein, organozinc mediated allylations and propargylations on a variety of chlorosilanes promoted by ultrasound waves are reported.



Silinezolid (WO2013/054275 A1) GABA analogue (present work)

Figure 1. Silicon analogues of known drugs from present group

The initial attempts started with diphenyldichlorosilane and allyl bromide using THF as the solvent. The chlorosilane, allyl bromide and zinc dust in THF solvent were sonicated by placing them in an ultrasound cleaning bath (37 KHz, 320 W). The reaction was complete within 10 minutes and the desired product diallyldiphenylsilane **1** was isolated in 88% yield. For the comparison purpose, the reaction was conducted without using ultrasonication and found that the present method is superior. After having this result in hand, the same conditions (2 eq. of allylbromide and 2 eq. of Zn per chloro) were applied to a variety of chlorosilanes, which include monochloro, dichloro as well as trichlorosilanes. All the results are compiled in Chart 1. In most of the cases the product was obtained in good to excellent yields.



Scheme 1. Allylation of chlorosilane using Zn mediation

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† Electronic Supplementary Information (ESI) available: Characterization data, NMR spectra and detailed experimental procedures. See DOI: 10.1039/b000000x/

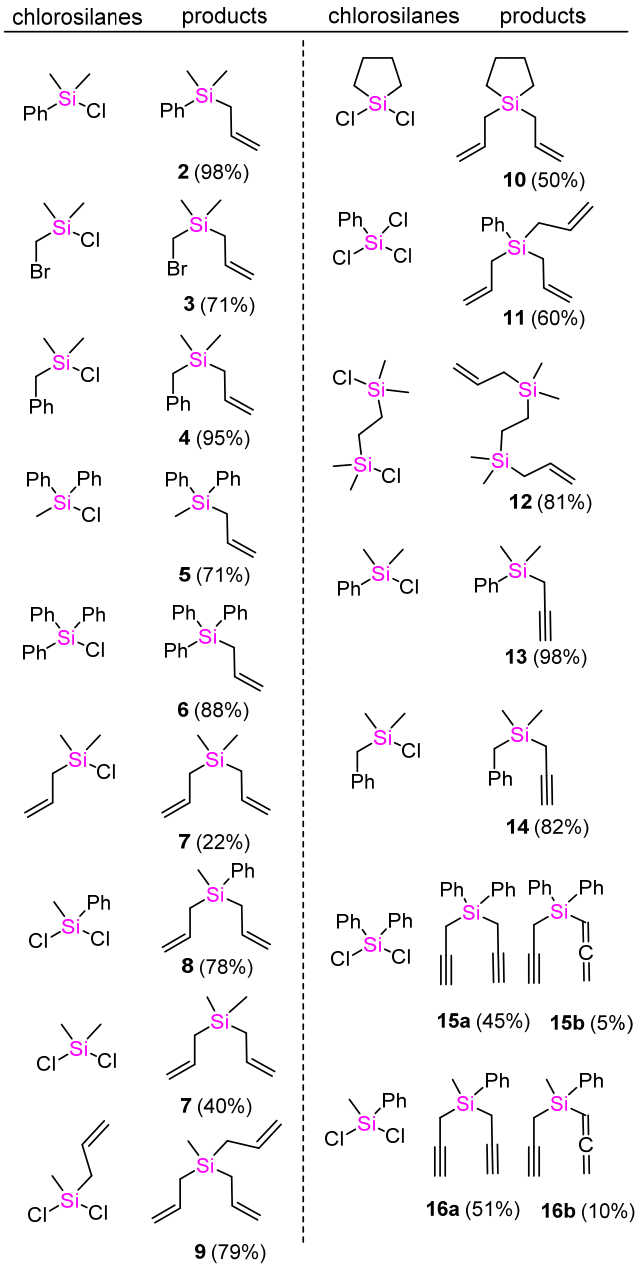
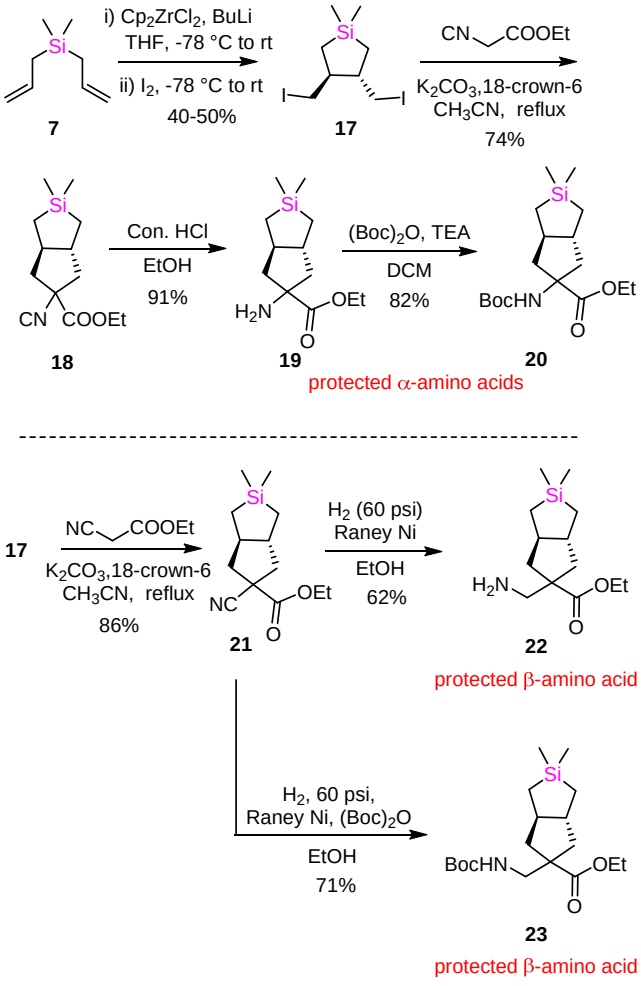


Chart 1. Scope of the method

In the case of monochlorosilanes, the products **2**, **3**, **4**, **5** and **6** were obtained in the range of 71-98% yield. However in the case of dimethylallylchlorosilane, the product **7** was isolated in poor yield due to its volatile nature. Addition of two and three allyl groups was also demonstrated using the same protocol to obtain products **7**, **8**, **9**, **10**, **11** and **12**. It is worth mentioning here that products like **9**, **11** and **12** are important building blocks in dendrimers and polymers. To expand the scope of the present method, the reaction of chlorosilanes with propargylbromide was also explored and the results are interesting. Propargylbromide reacted with dimethylphenylchlorosilane and dimethylbenzylchlorosilane under the same conditions to give exclusively the desired propargylcompounds **13** and **14**, respectively. In the case of dichlorosilanes, the propargylallenyl compound (**15b** and **16b**) were obtained as minor compounds in addition to the desired dipropargyl compounds (**15a** and **16a**). It is interesting to note that similar reaction mediated by indium metal as reported by Lai *et al*.[8] gives the allene derivative exclusively. The ^{1}H NMR data of all the known compounds were compared with the literature values and were found to be exactly matching.

As a direct application of the resulting allylsilanes, we envisaged the preparation of novel constrained unnatural silicon-containing amino acids which are interesting candidates in drug discovery as such or as part of the drug candidates. In addition, the synthetic unnatural aminoacids[12] can also be used for probing bioactive conformations in peptides of interest.[13] Synthesis and biological studies of silicon-containing amino acids, as well as peptides incorporating them, have been documented in literature.[14, 3d] However, they are still few in number with limited structural variation despite their attractive features. There is a need to find new routes to access novel and diverse silicon-containing amino acids. Along these lines, the crucial intermediate diiodo compound **17** was prepared from diallyldimethylsilane (**7**), by zirconacyclization followed by addition of iodine according to the literature protocol.[15] This intermediate **17** was used as a starting point to access various planned unnatural amino acids, particularly α–, β– and γ–amino acids with unusual 5,5-*trans* fusion.[16] Accordingly, compound **17**, on treatment with

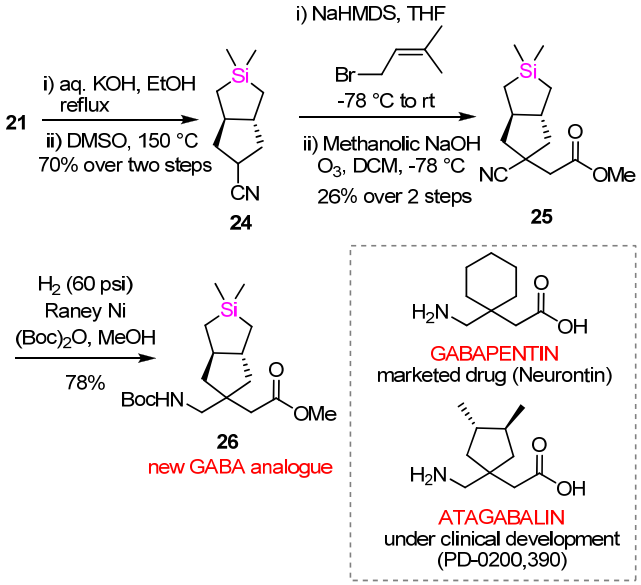


Scheme 2. Synthesis of constrained sila α–, β–amino acids

ethylisocyanoacetate in the presence of K_2CO_3 as base and a phase-transfer catalyst (18-crown-6), produced compound **18** as a sole product.[17] The ease of formation of such a strained system can be attributed to the larger Si-C bond length (189 pm as compared to 154 pm for an sp^3-sp^3 C-C bond),[18] which makes the reaction feasible under milder conditions. The isocyano group on hydrolysis (aq. HCl) gave the desired amino ester **19**, an unnatural α-amino acid in 91% yield. The free amine group was protected as the *t*-butyl carbamate to give orthogonally protected α-amino acid **20**. For the synthesis of the β-amino acid, compound **17** was treated with ethylcyanoacetate under the same conditions adopted for the synthesis of α-amino acid, to give α-cyanoester **21** in 86% isolated yield. The cyano group present in **21** was hydrogenated in the presence of Raney Nickel under 60 psi pressure, to furnish β-amino ester **22**. When the hydrogenation reaction was carried out in the presence of Boc anhydride, the Boc protected amino acid **23** was obtained with improved yield (Scheme 2). Both the α–, and β–amino acid derivatives **20** and **23** were well characterized using spectral data.[19]

After succeeding in the preparation of both α– and β–amino acids with an unprecedented core, the next task was to synthesize a GABA analogue with the same skeleton. GABA (γ-amino butyric acid) is the chief inhibitory neurotransmitter present in the mammalian central nervous system.[20] The deficiency of GABA is associated with several neurological disorders. For disease states associated with the deficiency of GABA, lipophilic GABA analogues have been synthesized.[20] The polar and flexible structure of GABA prevents it from crossing the blood brain barrier (BBB). Atagabalin[21] and Gabapentin[22] are pharmaceutically important, conformationally rigid GABA analogues. The incorporation of silicon is believed to increase the lipophilicity of a molecule which can be an attractive feature in the development of CNS drugs as it is expected to increase brain exposures. To our knowledge, Tacke's group, the pioneer of silicon switch approach, has claimed the sila-cyclohexyl and sila-cyclopentyl analogues of Gabapentin in a patent publication.[23] Therefore, we became interested in accessing novel, constrained sila analogues of GABA, which can be good starting points for the medicinal chemistry programs.

Synthesis of the newly designed GABA analogue began from the intermediate **21**. The compound **21** on selective ester hydrolysis, followed by thermal decarboxylation of resulting α-cyano carboxylic acid, gave the nitrile **24**. After a few attempts, alkylation of **24** with 3,3-dimethylallyl bromide gave the desired product in less yields.[24] The impure alkylated product was subjected to oxidative cleavage by ozonolysis in methanolic NaOH to furnish the desired compound **25**.[25] Although the ozonolysis reaction was clean, the alkylation needs further optimization. The compound **25** on reduction (Raney Ni, 60 psi) in the presence of Boc anhydride furnished the novel GABA analogue **26** in 78% yield (Scheme 3).[19] The new GABA analogue is structurally close to that of the marketed drug Gabapentin and a developmental candidate Atagabalin. Hence, compound **26** can serve as a starting point which needs more attention to profile in biological assays.



Scheme 3. Synthesis of silicon containing GABA analogue

In summary, a simple and rapid method for the preparation of allyl- and propargyl-silanes has been developed, which can be an addition to the existing toolbox to access these compounds. The unsaturated organosilanes are very good starting materials in the polymer industry, since they can undergo addition polymerization. Using allyl-silanes as starting material, silicon incorporated unnatural α–, β– and γ–amino acids with unusual 5,5-*trans* fusion have been prepared for the first time. The more lipophilic and conformationally rigid GABA analogue is expected to be an important compound, which may be useful for the modulation of various CNS disorders. Biological profiling, conformational studies and structure activity relationships (SARs) are the subject of future publications from this group.

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