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Allylsilanes Derived from Aminoacids in the Synthesis of Piperidine and Pyrrolidine Derivatives

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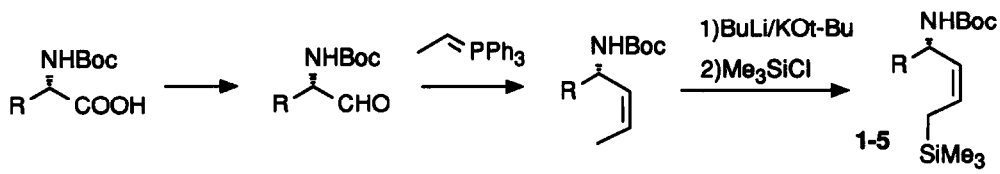
Abstract: *Allylsilanes preapared from α-aminoacids react with acyl chlorides in the presence of $TiCl_4$ to give unsaturated amino ketones, easily transformed into pyrrolidine derivatives, whereas addition to aldehydes gave 2,6-disubstituted tetrahydropyridines.*

Naturally occurring α-aminoacids can be easily transformed into optically active allylsilanes.[1] This transformation is based on the reduction of NBoc-aminoacids into NBoc-amino aldehydes, Wittig reaction with ethylidentriphenylphosphorane and silylation of the corresponding NBoc-allyl amines after metallation with the Schlosser base BuLi/KOt-Bu (scheme 1).



1 R = CH_3 . **2** R = $C_6H_5CH_2$. **3** R = $(CH_3)_2CHCH_2$. **4** R= $C_2H_5(CH_3)CH$. **5** R = $TBDMSOCH_2$.

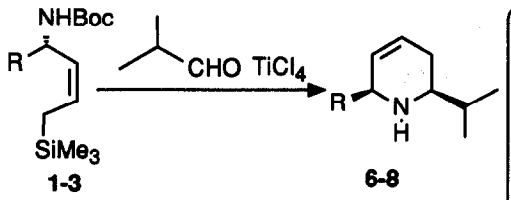
Scheme 1

Products **1-5** present a stereocentre directly bonded to the nucleophilic double bond of the allylsilane, and this stereocentre is expected to have a stereodirecting effect on the reactions taking place on the double bond.[2]

The most typical reaction of allylsilanes is the Lewis acid mediated addition to aldehydes to give homo allylic alcohols.[3] This reaction requires the use of strong Lewis acids (as $TiCl_4$ or $SnCl_4$) in chlorinated solvents, conditions which are somehow incompatible with the presence of the Boc protection of the amino group, as revealed by the reaction of allylsilanes **1** and **3** with aliphatic aldehydes such as acetaldehyde or 2-methylpropanal in the presence of $TiCl_4$. At -78°C the expected products were not formed (in the reaction mixture the starting materials remained unchanged) and after warming the reaction to room temperature we obtained a complex mixture of by-products, generally characterized by the loss of the Boc protecting group.

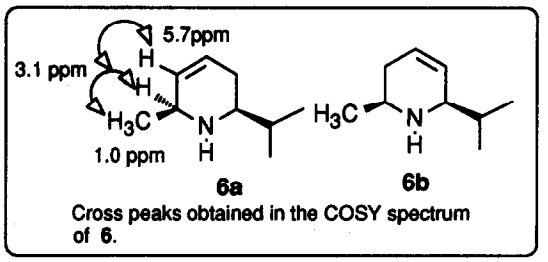
Attempts to change the Lewis acid ($BF_3{\cdot}OEt_2$, $SnCl_4$, $CF_3SO_3SiMe_3$, $YbCl_3$ or $ZnCl_2$) did not give any

success, whereas better results were obtained changing the mode of the reaction. Addition of allylsilanes **1-3** to a solution of 2-methylpropanal and $TiCl_4$ in CH_2Cl_2 at room temperature followed after 3 minutes by aqueous work-up gave directly the piperidine derivatives **6-8** (scheme 2).



1-3 **6-8**

6 R = CH_3 (45%). **7** R = $(CH_3)_2CHCH_2$ (51%).
8 R = $C_2H_5(CH_3)CH$ (45%).



6a **6b**

Cross peaks obtained in the COSY spectrum of **6**.

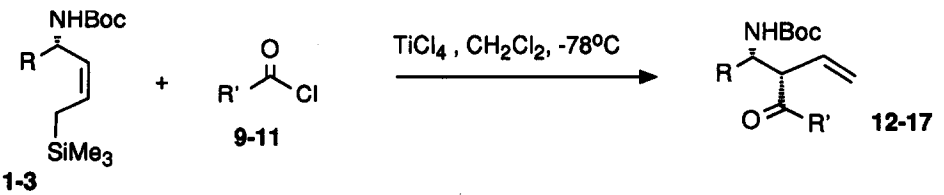
Scheme 2

The structures of products **6-8** were investigated using a ^1H COSY spectrum. The correlations described in scheme 2 are consistent with structure **6a** and the formation of a product with the hypothetical structure **6b** could be excluded. The stereochemical assignment of products **6-8** was based on the 200 mHz ^1H NMR spectrum which showed the position of the substituents at C-6 (axial-axial coupling constant H(C-6)-H(C-5) : 11 Hz).[4] Although the coupling constant H(C-2)-H(C-3) is not diagnostic, the observed value of 7 Hz is consistent with the value obtained after a conformational analysis of the structure **6a** using a program for molecular mechanics.

Compounds **6-8** could be formed "via" an intermediate imminium ion obtained by nucleophilic attack of the nitrogen of products **1-3** to the aldehyde in the presence of the Lewis acid, followed by intramolecular attack to the allylic carbon close to the silicon.[5] The acidic medium where the reaction was carried out accounts for the loss of the *tert*-butoxycarbonyl protection of the nitrogen.[6]

The above mentioned results showed a lower reactivity of allylsilanes **1-5** with respect to other allylsilanes, probably because of the steric hindrance around the double bond.[7]

The electrophilic substitution of the trimethylsilyl group of **1-3** was only accomplished using the stronger electrophiles acyl chlorides **9-11** (scheme 3).



1-3 **9-11** **12-17**

9 R = CH_3 . **10** R = $C_6H_5CH_2$. **11** R = C_6H_{13}

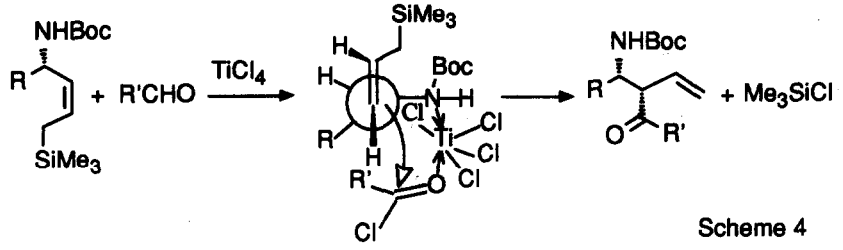
12 R = CH_3 ; R' = CH_3 . **13** R = $(CH_3)_2CHCH_2$; R' = CH_3 . **14** R = $(CH_3)_2CHCH_2$; R' = $C_6H_5CH_2$.
15 R = $(CH_3)_2CHCH_2$; R' = C_6H_{13}. **16** R = $C_6H_5CH_2$; R' = CH_3 . **17** R = $C_6H_5CH_2$; R' = $C_6H_5CH_2$.

Scheme 3

Slow addition of allylsilanes **1-3** (1.2 mmol) to a mixture of acyl chlorides **9-11** (1 mmol) and $TiCl_4$ (1 mmol) in CH_2Cl_2 (2 mL) at -78°C followed, after 2-3 h at this temperature, by quench with a saturated solution of NH_4Cl, gave products **12-17** (yields: **12**: 60%; **13**: 51%; **14**; 65%; **15**: 45%; **16**: 49%; **17**: 50%). All the products were isomerically pure, we found no trace of the other isomer by tlc, glc and ^1H NMR analysis.

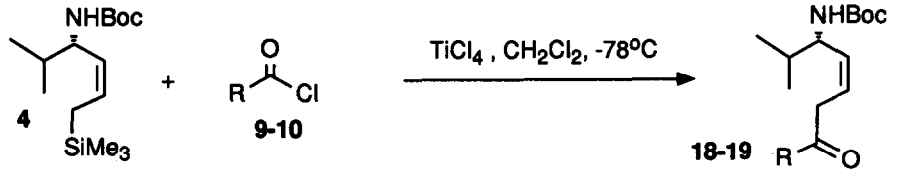
The stereochemistry of products **12-17** was 3(S), 4(S) as revealed by ^1H NMR analysis[1] and NOE experiments on product **21**. This result can be interpreted with an intermolecular chelation of the $TiCl_4$ to the

acyl and the NBoc groups as illustrated in scheme 4.



Scheme 4

The regiochemistry of this reaction was very sensitive to the steric hindrance of the allylsilane. When the reaction was tried on product **4**, we obtained substitution of the trimethylsilyl group without allylic shift[8] giving compounds **18** and **19** (see scheme 5), optically active γ-amino- α,β-unsaturated ketones, which can be considered as versatile building blocks in organic synthesis.[9]

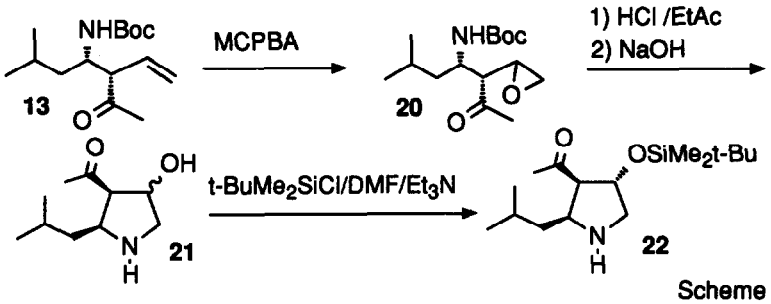


18 R= CH_3 (69%). **19** R = $C_6H_5CH_2$ (75%).

Scheme 5

The Z stereochemistry of products **18-19** was assigned by the determination of the J_{cis} which was 14 Hz and resulted the same the starting materials. The isolation of products **18** and **19** confirmed the well precedented [10] tendency of hindered allylsilanes to react at the C-sp^3 of the allylic system.

Compound **13** was transformed into the pyrrolidine derivative **22** through the sequence of reactions described in scheme 6.



Scheme 6

Oxidation of **13** with MCPBA/Na_2CO_3 in CH_2Cl_2 gave epoxide **20** as a mixture of diastereoisomers (60% yields, relative amounts not determined) and subsequent deprotection of the NBoc group, followed by neutralization, gave the pyrrolidine derivative **21** in a 63% yield as a mixture of diastereoisomers (6:1), from which, after protection with t-$BuMe_2SiCl$ (DMF /Et_3N /60°C/ 36 h) we obtained compound **22** (61 % yield, isolated as the oxalate, m.p. 136-139°C dec.) as the 2(S), 3(R), 4(S) isomer, which can be considered a potential intermediate for the synthesis of pyrrolidine alkaloids.[11]

Acknowledgements. *This work was financially supported by Ministero della Ricerca Scientifica e Tecnologica (Rome) Fondi MURST-40%. We thank one referee of this paper for the helpful suggestions on the mechanism of the reactions described in scheme 2 and 5.*

References and Notes.

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3. Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. Nativi, C.; Ricci, A.; Taddei, M. in *Frontiers of Organosilicon Chemistry*, Bassindale, A-R., Gaspar, P.P. Ed., The Royal Society of Chemistry, London, 1991, 332.
4. Arseniyadis, S.; Sartoretti, J. *Tetrahedron Lett.* **1985**, *26*, 729.
5. The same result could be obtained by protodesilylation of the starting material and intramolecular "ene" reaction of the so formed terminal alkene.
6. **Typical procedure**: 2-Methyl-propanal (42 mg, 0.57 mmol) was dissolved under Argon in dry CH_2Cl_2 (0.5 mL) and cooled to 0°C. Titanium tetrachloride (108 mg, 0.57 mmol) was added with a syringe and the bright yellow mixture warmed to room temperature. Allylsilane **1** (150 mg, 0.58 mmol) in CH_2Cl_2 (0.25 mL) was added. After stirring for 3 min, the mixture was cooled to 0°C and a saturated solution of NH_4Cl (0.5 mL) added with a syringe followed by Et_2O (2 mL). The ethereal layer was separeted, washed with brine and dried over anhydrous Na_2SO_4. Product **6** was isolated by column chromatography on silica gel: 37 mg, 55% yield. ^1H NMR (200 mHz/$CDCl_3$) δ 0.90-1.10 (m, 9H), 1.13 (m, 1H), 1.66 (m, 2H), 1.70 (bm, 1H, NH), 2.85 (m, 1H), 3.15 (m, 1H), 5.54 (m, 1H), 5.74 (m, 1H). MS m/z 139 (M^+), 76, 46 (base).
7. Additional substituents of the developing carbenium centre causes generally a strong reactivity increase: Mayr, H.; Hagen, G. *J. Chem. Soc. Chem. Commun.* **1989**, 91.
8. Products **18-19** may be obtained also through desilylation followed by acylation of the terminal double bond which takes place intramolecularly from an acyl-titanium complex assembled on the nitrogen atom as illustrated in scheme 4.
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