## SILYLAMINES IN ORGANIC SYNTHESIS : A NEW ACCESS TO FUNCTIONAL PYRROLES VIA ORGANOCUPRATES ADDITION ON METHYL-BIS(TRIMETHYLSILYL)AMINOMETHYLPROPIOLATE

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Summary : Organocuprate addition reactions on methyl-bis(trimethylsilyl)aminomethylpropiolate lead to the formation of a Z-vinyl cuprate with a high stereoselectivity. Upon reaction of acid chloride, pyrroles are formed by a spontaneous intramolecular cyclisation of the intermediate Z-silylamino enone. Various functional substituted pyrroles can be obtained in one step by this route.

We previously reported a simple synthesis of functional silyl protected «-acetylenic amines by use of lithium N,N-bis(trimethylsilyl)aminomethylacetylide 1 (eq-1)<sup>1</sup>.

$$\begin{array}{c} \text{HC} \equiv \text{C}-\text{CH}_2-\text{Br} & \xrightarrow{(\text{Me}_3\text{Si})_2\text{NLi}} \\ 1 & \text{SiMe}_3 & \xrightarrow{\text{E}^+} \text{E}-\text{C} \equiv \text{C}-\text{CH}_2-\text{N} \begin{pmatrix} \text{SiMe}_3 \\ \text{SiMe}_3 \end{pmatrix} \begin{pmatrix} 1 \\ 1 \end{pmatrix} \\ \end{array}$$

Compounds of type 2 are potential precursors of nitrogen heterocycles. Stereospecific addition reactions on the carbon-carbon triple bond will provide functional alkenylamines from which cyclisation reactions to nitrogen heterocycles can be envisaged. For example the reaction of butyl copper on the methyl-bis(trimethylsilyl)aminomethylpropiolate 3 followed by acid hydrolysis offered a one-step conversion to lactames 5  $(eq-2)^2$ .



We wish to report here that the reaction of organocuprate reagents with the amino ester 3 led to the intermediate formation of a Z-vinylcuprate which upon treatment with acid chlorides provided a one step preparation of substituted pyrroles. Whereas the reaction of butyl copper with ester 3 provided almost stereoselectively the Z-alkenyl amino ester 6, the addition of lithium dibutyl cuprate was found to afford the Eadduct 7 with a high stereoselectivity (eq-3). Of interest is the addition of the mixed cuprate : Me(Hexynyl)CuLi, which yields the adducts in a 24 to 1 E/Z ratio.



The stereochemistry of the organocuprate addition reactions on propiolic acid esters has been found to be a function of reaction temperature, time and also of the nature of the reagents, solvent and ligand present 3-5. An intermediate enolate is responsible for the stereochemical outcome of the reaction 6-8. Isomerisation of the initially formed cisaddition product 8 can be accounted for by the intervention of the allenolate species 9 (Scheme 1).

Scheme 1



However the selective obtention of the E-adduct 7 after protonolysis cannot be accomodated by an electrophilic attack on the intermediates 8 or 9, which should lead to the exclusive or predominant formation of the Z-adduct 6. The formation of 7 seems to arise from protonation of the trans-addition product 10. The reason for the stability of this isomer may lie in an intramolecular coordination of the nitrogen atom. An intramolecular stabilisation has been shown for example to reverse the regioselectivity of organocuprates addition, on propargylic dialkylamines<sup>9</sup>. An isomerisation favoring one steroisomer by intramolecular chelation was also observed in the carbometallation of functionalized silylalkynes by Grignard reagents <sup>10</sup>. In the present case, owing to the low nucleophilicity of the (Me<sub>3</sub>Si)<sub>2</sub>N group an intramolecular coordination is less favorable <sup>2</sup>. Nevertheless, a lithium-nitrogen interaction in 10 can account for the change in stereochemistry between butyl copper and organocuprate reagents and for the observed high stereoselectivity.

From a synthetic point of view, the reaction of the vinyl cuprate 10 offers the possibility to introduce a new functional group in a cis position with respect to the aminomethyl substituent opening new possibilities of cyclisation reactions to nitrogen heterocycles.

We found that acid chlorides readily reacted to give functionally substituted pyrroles (Scheme 2).

## Scheme 2



The formation of the pyrrole ring certainly arises from an intramolecular reaction of the cisorientated silylamino group and carbonyl function in the initially formed enone 11. The cyclic intermediate 12 then undergoes a spontaneous elimination of siloxane to give after treatment with silicic acid pyrroles 13 in 44 to 66 % non optimized yields. According to this method functional pyrroles are obtained in one step from the readily avalaible starting materials. In addition, it is interesting to note that this new route leads to pyrroles unsubstituted in position 5 and therefore, particularly relevant to the porphyrin field<sup>11</sup>.

The synthetic interest of this pyrrole synthesis was illustrated in a short preparation of bicyclic molecules (Scheme 3). The reaction of vinylcuprate 6 with bromo-alkyl acid chlorides led to the expected 2-bromo alkyl pyrroles 14-16. Treatment of the crude reaction product with solid KOH in the presence of  $TDA_1$  as phase transfer catalyst<sup>12</sup>, resulted

in the obtention of the bicyclic compounds 17-19 in 36 to 65 % yield with respect to the starting aminopropiolate 3. Such ring system is well represented as a structural subfeature in many alkaloīds<sup>13</sup>.

Scheme 3



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(Received in France 9 March 1987)